Indication for active surveillance

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Active Surveillance in Low Risk Disease: Who Doesn’t Need Treatment?

Rationale for active surveillance

Results of active surveillance
‘prostate cancer is the only human cancer that is curable, but which commonly does not need to be cured’

Parker, Lancet Oncol 5:101-106, 2004
AS vs radical therapy: weighing the benefits and risks

Active treatment

Active surveillance

OVERTREATMENT

- Probability of survival benefit very low in low-risk patients
- Treatment-related morbidity: incontinence, impotence

UNDERTREATMENT

- Disease progression is possible → small chance to lose opportunity for cure
- “Treatment-”related morbidity: anxiety, infection (related to multiple re-biopsies)

AS versus WW

- **Goals active surveillance (AS)**
  - Provide definitive treatment for men that are likely to progress
  - Reduce the risk of treatment-related complications

- **Watchful waiting (WW)**
  - Policy of observation with the use of palliative treatment for symptomatic progression
Gleason Score 6 Adenocarcinoma: Should It Be Labeled As Cancer?

H. Ballentine Carter, Alan W. Partin, Patrick C. Walsh, Bruce J. Trock, Robert W. Veltri, William G. Nelson, and Donald S. Coffey, The Johns Hopkins University and Johns Hopkins Hospital, Baltimore, MD

Eric A. Singer, National Cancer Institute, National Institutes of Health, Bethesda, MD

Jonathan I. Epstein, The Johns Hopkins University and Johns Hopkins Hospital, Baltimore, MD
Do Adenocarcinomas of the Prostate With Gleason Score (GS) ≤ 6 Have the Potential to Metastasize to Lymph Nodes?

Hillary M. Ross,* Oleksandr N. Kryvenko,† Janet E. Cowan,‡ Jeffry P. Simko,‡§ Thomas M. Wheeler,‖ and Jonathan I. Epstein, MD*¶‖
**Table 1.** Gleason 3 lacks the hallmarks of cancer

<table>
<thead>
<tr>
<th>Characteristic of cancer</th>
<th>Gleason 3</th>
<th>Gleason 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expression of pro-proliferation embryonic, neuronal, hematopoietic stem cell genes, EGF, EGFR [4]</td>
<td>No</td>
<td>Overexpressed</td>
</tr>
<tr>
<td>AKT pathway [4]</td>
<td>No</td>
<td>Aberrant</td>
</tr>
<tr>
<td>HER2/neu [5]</td>
<td>No</td>
<td>Amplified</td>
</tr>
<tr>
<td>Insensitivity to antigrowth signals [Cyclin D2 methylation, CKDN1β] [6–8]</td>
<td>Expressed</td>
<td>Absent</td>
</tr>
<tr>
<td>Resistance to apoptosis: DAD1 [8]</td>
<td>Negative</td>
<td>Strong expression</td>
</tr>
<tr>
<td>BCL2 [9]</td>
<td>Mostly negative</td>
<td>Upregulated</td>
</tr>
<tr>
<td>Absence of senescence: TMPRSS2-ERG [10–13]</td>
<td>ERG normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Sustained angiogenesis: VEGF [14,15]</td>
<td>Expression low</td>
<td>Increased</td>
</tr>
<tr>
<td>Other pro-angiogenic factors, microvessel density [16]</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Tissue invasion/metastasis markers (CXCR4, others) [17]</td>
<td>Normal</td>
<td>Overexpressed</td>
</tr>
<tr>
<td>Clinical evidence of metastasis/mortality [18**,19]</td>
<td>Virtually absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.
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
20-Year Outcomes Following Conservative Management of Clinically Localized Prostate Cancer

Albertsen et al JAMA 293:2095-2101, 2005

Conclusion  The annual overall survival appears to remain stable after 15 years from diagnosis, independent of prostate-specific antigen (PSA) levels and Gleason score.

Department of Urology, Academic Medical Center Amsterdam
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% p0.52
### 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>no. of events</td>
<td>% (95% CI)</td>
<td>no. of events</td>
<td>% (95% CI)</td>
</tr>
</tbody>
</table>

#### Death from prostate cancer

<table>
<thead>
<tr>
<th></th>
<th>Radical Prostatectomy (N=347)</th>
<th>Watchful Waiting (N=348)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>63 17.7 (14.0 to 22.4)</td>
<td>99 28.7 (24.2 to 34.2)</td>
<td>11.0 (4.5 to 17.5) 0.56 (0.41 to 0.77) 0.001</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>31 18.3 (13.1 to 25.7)</td>
<td>58 34.1 (27.3 to 42.5)</td>
<td>15.8 (6.0 to 25.5) 0.45 (0.29 to 0.69) 0.002</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>32 17.3 (12.5 to 24.0)</td>
<td>41 23.9 (18.2 to 31.5)</td>
<td>6.6 (−2.1 to 15.2) 0.75 (0.47 to 1.19) 0.19</td>
</tr>
<tr>
<td>Tumor risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>11 10.2 (5.8 to 18.0)</td>
<td>20 14.0 (9.1 to 21.5)</td>
<td>3.8 (−4.6 to 12.2) 0.54 (0.26 to 1.13) 0.17</td>
</tr>
<tr>
<td>Intermediate</td>
<td>24 15.1 (10.2 to 22.2)</td>
<td>50 39.3 (31.3 to 49.3)</td>
<td>24.2 (13.6 to 34.9) 0.38 (0.23 to 0.62) &lt;0.001</td>
</tr>
<tr>
<td>High</td>
<td>28 33.1 (24.0 to 45.7)</td>
<td>29 35.7 (26.3 to 48.5)</td>
<td>2.6 (−12.7 to 17.8) 0.87 (0.52 to 1.46) 0.84</td>
</tr>
</tbody>
</table>
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

Watchful Waiting vs. Radical Prostatectomy in distress from urinary leakage, protective aids against leakage, and erectile dysfunction.
Prostate cancer is not what it used to be!

US prostate cancer incidence
Radical Prostatectomy versus Observation for Localized Prostate Cancer

PIVOT trial, comment

- Original design: 2000 patients
- Modified to 740 patients; in trial only 731 patients
- One fifth of patients did not adhere to the assigned treatment which further reduces the ability to discern a treatment effect
- Study was underpowered
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 ≤3+3)

• **How?**
  – Regular PSA/clinical assessment
  – Repeat biopsy
  – MRIs
Results of active surveillance of localised prostate cancer
Which patients are the best candidates for AS?

- Eligibility criteria for AS in prospective cohort studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>PSA (ng/mL)</th>
<th>PSA density (ng/mL/g)</th>
<th>Gleason sum</th>
<th>Amount PCa on biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johns Hopkins¹</td>
<td>T1c</td>
<td>-</td>
<td>&lt; 0.15</td>
<td>≤ 6</td>
<td>≤ 2 cores; ≤ 50% PCa in any core</td>
</tr>
<tr>
<td>PRIAS²</td>
<td>T1c-2</td>
<td>≤ 10</td>
<td>&lt; 0.2</td>
<td>≤ 6</td>
<td>≤ 2 cores</td>
</tr>
<tr>
<td>Toronto³</td>
<td></td>
<td>≤ 10</td>
<td>-</td>
<td>≤ 6</td>
<td></td>
</tr>
<tr>
<td>UCFS⁴</td>
<td>T1-2a</td>
<td>&lt; 10</td>
<td>-</td>
<td>≤ 6</td>
<td>&lt; 33% of cores</td>
</tr>
<tr>
<td>Miami⁵</td>
<td>T1a-2</td>
<td>≤ 10</td>
<td>-</td>
<td>≤ 6</td>
<td>≤ 2 cores; ≤ 20% PCa in any core</td>
</tr>
<tr>
<td>MSKCC⁶</td>
<td>T1-2a</td>
<td>&lt; 10</td>
<td>-</td>
<td>No pattern 4 or 5</td>
<td>≤ 3/10 cores; ≤ 50% PCa in any core</td>
</tr>
<tr>
<td>SAMS⁷</td>
<td>T1c-2a</td>
<td>&lt; 13</td>
<td>&lt; 0.2</td>
<td>≤ 6</td>
<td>≤ 33% of cores; ≤ 6 mm in any core</td>
</tr>
</tbody>
</table>

What do the guidelines say?

- **EAU, NCCN**: AS is a treatment option for men with the lowest risk of PCa progression:

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Very) low-risk PCa</td>
<td>Very-low risk PCa</td>
</tr>
<tr>
<td>Life expectancy (yr)</td>
<td>&gt; 10</td>
<td>≥ 10</td>
</tr>
<tr>
<td>Clinical stage</td>
<td>T1-2</td>
<td>T1c</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>≤ 10</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Biopsy Gleason sum</td>
<td>≤ 6</td>
<td>≤ 6</td>
</tr>
<tr>
<td>Positive biopsy cores</td>
<td>≤ 2</td>
<td>&lt;3</td>
</tr>
<tr>
<td>% cancer per core</td>
<td>≤ 50</td>
<td>≤ 50</td>
</tr>
<tr>
<td>PSA density (ng/mL/g)</td>
<td>-</td>
<td>&lt; 0.15</td>
</tr>
</tbody>
</table>
Is AS a valid treatment option for men with localised PCa?

Prospective cohort studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Median FU (yr)</th>
<th>% pts treated</th>
<th>CSS (%)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johns Hopkins¹</td>
<td>769</td>
<td>2.7</td>
<td>33</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>PRIAS²</td>
<td>2,494</td>
<td>1.6</td>
<td>21</td>
<td>100</td>
<td>2 yr: 97</td>
</tr>
<tr>
<td>Toronto³</td>
<td>450</td>
<td>6.8</td>
<td>30</td>
<td>5 yr: 99.7</td>
<td>10 yr: 97.2</td>
</tr>
<tr>
<td>UCFS⁴</td>
<td>321</td>
<td>3.6</td>
<td>24</td>
<td>100</td>
<td>5 yr: 100</td>
</tr>
<tr>
<td>Miami⁵</td>
<td>230</td>
<td>2.7</td>
<td>14</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Göteborg⁶</td>
<td>439</td>
<td>6.0</td>
<td>37</td>
<td>99</td>
<td>10 yr: 81</td>
</tr>
</tbody>
</table>

CS : cancer-specific survival; FU: follow-up; NR: not reported; OS: overall survival; pts: patients

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


Conclusion
Active surveillance for favorable-risk prostate cancer is feasible and seems safe in the 15-year time frame. In our cohort, 2.8% of patients have developed metastatic disease, and 1.5% have died of prostate cancer. This mortality rate is consistent with expected mortality in favorable-risk patients managed with initial definitive intervention.
Medium-term Outcomes of Active Surveillance for Localised Prostate Cancer


Results: 471 patients 2002-2011 median FU 5 years

93% Gleason 3+3
median PSA 6.4

Conclusions: This study demonstrates satisfactory medium-term outcomes for AS in selected men with localised prostate cancer.
<table>
<thead>
<tr>
<th>Condition</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>
<tr>
<td>Variable</td>
<td>P value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>----------------</td>
<td>-----------</td>
<td>---------------------</td>
</tr>
<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>

Medium-term Outcomes of Active Surveillance for Localised Prostate Cancer

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.
## Guidelines on Prostate Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Median follow-up (months)</th>
<th>Progression</th>
<th>RP (%)</th>
<th>Survival (%)</th>
<th>Remaining on active surveillance* (PFS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dall’Era, et al. (24)</td>
<td>47</td>
<td>35</td>
<td>5</td>
<td>8</td>
<td>97 100 54</td>
</tr>
<tr>
<td>van As, et al. (25)</td>
<td>22</td>
<td>13</td>
<td>18</td>
<td>2</td>
<td>98 100 73</td>
</tr>
<tr>
<td>Soloway, et al. (26)</td>
<td>32</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>100 100 86</td>
</tr>
<tr>
<td>Klotz et al. (17)</td>
<td>82</td>
<td>9</td>
<td>14</td>
<td>3</td>
<td>78.6 97.2 70</td>
</tr>
<tr>
<td>Tosoain, et al. (27)</td>
<td>32</td>
<td>14</td>
<td>-</td>
<td>9</td>
<td>98 100 54</td>
</tr>
<tr>
<td>Adamy, et al. (28)</td>
<td>22</td>
<td>13</td>
<td>14</td>
<td>11</td>
<td>- - -</td>
</tr>
<tr>
<td>Bul, et al. (29)</td>
<td>19</td>
<td>27</td>
<td>21</td>
<td>10</td>
<td>97 100 76 (2 y)</td>
</tr>
</tbody>
</table>

*OS = Overall Survival, CSS = Cancer-Specific Survival, PFS = Progression-Free Survival*
# Guidelines on Prostate Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Median follow-up (mo)</th>
<th>pT3 in RP patients</th>
<th>OS</th>
<th>CSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>van As, et al. (25)</td>
<td>326</td>
<td>22</td>
<td>8/18 (44%)</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>Carter, et al. (73)</td>
<td>407</td>
<td>41</td>
<td>10/49 (20%)</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>Bul, et al. (28)</td>
<td>533-1,000</td>
<td>48</td>
<td>4/24 (17%)</td>
<td>90</td>
<td>99</td>
</tr>
<tr>
<td>Soloway, et al. (26)</td>
<td>99</td>
<td>45</td>
<td>0/2</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Roemeling, et al. (74)</td>
<td>278</td>
<td>41</td>
<td></td>
<td>89</td>
<td>100</td>
</tr>
<tr>
<td>Khatami, et al. (75)</td>
<td>270</td>
<td>63</td>
<td>Not stated</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Klotz, et al. (17)</td>
<td>452</td>
<td>73</td>
<td>14/* (58%)</td>
<td>82</td>
<td>97 at 10 y</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2,130-3,000</strong></td>
<td><strong>43</strong></td>
<td></td>
<td><strong>90</strong></td>
<td><strong>99.7</strong></td>
</tr>
</tbody>
</table>
**Guidelines on Prostate Cancer**

### Recommendations - active surveillance

<table>
<thead>
<tr>
<th>Description</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active surveillance is an option in patients with the lowest risk of cancer progression: over 10 years of life-expectancy, cT1-2, PSA ≤ 10 ng/mL, biopsy Gleason score ≤ 6 (at least 10 scores), ≤ 2 positive biopsies, minimal biopsy core involvement (≤ 50% cancer per biopsy).</td>
<td>2a</td>
<td>A</td>
</tr>
<tr>
<td>Follow-up should be based on DRE, PSA and repeated biopsies. The optimal timing for follow-up is still unclear.</td>
<td>2a</td>
<td>A</td>
</tr>
<tr>
<td>Patients with biopsy progressions should be recommended to undergo active treatment.</td>
<td>2a</td>
<td>A</td>
</tr>
</tbody>
</table>
## Guidelines on Prostate Cancer

<table>
<thead>
<tr>
<th>Recommendations - watchful waiting</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watchful waiting may be offered to all patients not willing to accept the side-effects of active treatment, particularly patients with a short life-expectancy.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>When on watchful waiting, the decision to start any non-curative treatment should be based on symptoms and disease progression (see Chapter 12).</td>
<td>1a</td>
<td>B</td>
</tr>
</tbody>
</table>
The diagnostic triad in prostate cancer diagnosis
PSA production and action

- **T**, testosterone
- **DHT**, dihydrotestosterone
- **5α-R**, 5α-reductase

**Epithelial cell**

- **Nucleus**
- **Transcription**
- **Translation**
- **mRNA**
- **PSA** (neutral serine protease)
- **PSA secreted into gland lumen and blood stream**

**Testosterone**

- **5α-R**

**Diagram:**

- PSA secreted into gland lumen and blood stream
- PSA (neutral serine protease)
- Translation
- mRNA
- Transcription
- 5α-R, 5α-reductase
- DHT
- Epithelial cell
- Nucleus
- Testosterone
- PSA
Prostate cancer – Diagnosis by Bx
Is MR-guided biopsy needed?

Biopsy-device with TRUS – MRI fusion
# Biological and clinical implications of the transitional and clonal hypotheses

<table>
<thead>
<tr>
<th>Transitional Hypothesis</th>
<th>Clonal Hypothesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason score progresses from 3 to 4 over time</td>
<td>Gleason score remains relatively unchanged over time</td>
</tr>
<tr>
<td>Gleason 3 is precursor to 4</td>
<td>Gleason 3 and 4 are different entities</td>
</tr>
<tr>
<td>Patients with pure Gleason 6 tumors at risk of developing</td>
<td>Patients without Gleason 4 component may never develop it</td>
</tr>
<tr>
<td>Gleason 4 component</td>
<td></td>
</tr>
<tr>
<td>Gleason 3 is malignant or premalignant</td>
<td>Gleason 3 is a neoplasm of low malignant potential</td>
</tr>
<tr>
<td>Pure Gleason 6 tumors need early treatment to prevent</td>
<td>Pure Gleason 6 tumors do not need treatment</td>
</tr>
<tr>
<td>progression</td>
<td></td>
</tr>
<tr>
<td>All foci of prostate cancer must be treated</td>
<td>Only “index lesion” containing Gleason 4 component needs to be treated</td>
</tr>
<tr>
<td>Serial biopsy necessary in patients on active surveillance</td>
<td>After accurate initial grading/staging is completed, serial biopsies are unnecessary</td>
</tr>
<tr>
<td>to assess for Gleason progression</td>
<td></td>
</tr>
</tbody>
</table>
Inclusion criteria:
1) Histologically proven adenocarcinoma of the prostate.
2) Men should be fit for curative treatment.
3) PSA-level at diagnosis ≤ 10 ng/mL.
4) PSA density (PSA D) less than 0.2 ng/ml/ml.
5) Clinical stage T1C or T2.
6) Gleason score 3+3=6.
7) One or 2 biopsy cores invaded with prostate cancer.
   a. If an MRI, including targeted biopsies on positive lesions, is done at inclusion, there is no limit in the number of positive cores (that is, more than two, and no limit in the % of cancer present in the cores).
   b. If saturation biopsies (either transperineal or transrectal) are done 15% of the cores can be positive with a maximum of 4. (i.e. <20 cores 2 cores can be positive (standard), 20-26 cores 3 cores can be positive, >26 cores 4 cores can be positive) (all other inclusion criteria still apply).
8) Participants must be willing to attend the follow-up visits.
9) Adequate biopsy sampling:

<table>
<thead>
<tr>
<th>Prostatic volume (cc)</th>
<th>Number of biopsy cores</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-40</td>
<td>8</td>
</tr>
<tr>
<td>40-60</td>
<td>10</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>12</td>
</tr>
</tbody>
</table>

Exclusion criteria:
1) Men who cannot or do not want to be radiated or operated.
2) A former therapy for prostate cancer.
Active Surveillance

PSA < 20 ng/ml

Clinical stage < cT3

Repeat biopsy indicated by time path?

PSA-DT > 10 year

Repeat biopsy: Maximum 2 cores with PCa AND Gleason 3+3

Definitive therapy

Metastases on bone scan?

End of study

Continue Active Surveillance

Time table

<table>
<thead>
<tr>
<th>Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month</td>
<td>0**</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>12</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>PSA-test</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>DRE</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Biopsy*</td>
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<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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</tr>
<tr>
<td>Evaluation</td>
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<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

* Repeat biopsy: Standard after 1, 4, 7 and 10 year and subsequently every 6 years.
If PSA-DT is 0-10 years repeat biopsy every year is advised. No more than 1 biopsy per year should be performed.
** Time of diagnosis.
Fig. 1 - Participants in the observational Prostate Cancer Research International: Active Surveillance (PRIAS) database during 2006–2013 per continent [6]. (a) Absolute number of men included in the PRIAS study. (b) Annual increase in number of men included in the PRIAS study, reflecting growth.
PIVOT Recruitment and Enrollment

Eligible Men
N=5023

Declined randomization
N=4292

Randomized
N=731

Radical prostatectomy
N=364
RP: N=281 (77%)

Observation
N=367
RP: N=35 (10%)
ProtecT
Prostate testing for cancer and Treatment

218,966 men aged 50-69 years were invited to participate
122,502 responded
22,058 did not attend
5,954 declined to participate
16,104 did not attend appointment
100,644 attended appointment
18,015 not recruited
766 not eligible
10,350 declined to participate
82,629 were recruited
73,863 ineligible PSA results
73,158 <3.0 ng/mL
7,598 >30.0 ng/mL
46 results not given
8,566 had an eligible PSA result
1,152 did not receive biopsy
7,414 received prostate biopsies
5,468 single biopsy
1,946 more than one biopsies
4,518 biopsy negative or other
3,064 biopsy negative or mild atypia
756 high grade PIN
255 A-SAP
3 inadequate specimen
2,896 had a positive biopsy result for prostate cancer
470 ineligible
270 advanced disease
200 locally but excluded
2,417 eligible for randomisation (localised prostate cancer)

2,664 participants were eligible
2,417 recruited in main trial
247 recruited in pilot study

1,021 were not randomly assigned
997 selected treatment
24 were randomly assigned to two groups

1,643 participants were randomly assigned
1,497 from main trial
146 from pilot study

545 allocated to active monitoring
545 allocated to radiotherapy
553 allocated to surgery
Platinum Priority – Review – Prostate Cancer

Editorial by XXX on pp. x–y of this issue

How Does Active Surveillance for Prostate Cancer Affect Quality of Life? A Systematic Review

Lara Bellardita a,*, Riccardo Valdagni a,b, Roderick van den Bergh c, Hans Ransdorp e, Claudia Repetto a, Lionne D.F. Venderbos d, J. Athene Lane f,l, Ida J. Korfage g,l

Conclusions: Patients undergoing AS reported good QoL and did not appear to suffer major negative psychological impacts. Longer follow-up is required as well as investigation into which patients are predisposed to negative impact and leaving AS prematurely.
A longitudinal study on the impact of active surveillance for prostate cancer on anxiety and distress levels

Venderbos et al *Psycho-Oncology* 24:348-354, 2015

*Conclusions:* When men with low-risk PC are managed with AS, fear of disease progression and general anxiety decreased, and only few may discontinue AS because of anxiety and distress. This suggests that negative QoL effects are limited in men with favourable clinical characteristics who opted for AS. (Registered trial number, NTR1718)
Compliance Rates with the Prostate Cancer Research
International Active Surveillance (PRIAS) Protocol and Disease Reclassification in Noncompliers


*Patient summary:* We looked at compliance with an active surveillance protocol for low-risk prostate cancer in a large active surveillance study. We observed reluctance to undergo yearly biopsies because of fast rising prostate-specific antigen, despite a higher risk of disease progression. Further research should aim to safely reduce the number of repeat biopsies in men on active surveillance to increase protocol adherence.
Urological consultation 2
Previously screened, no biopsy

Transrectal ultrasound (TRUS) (0/1) 0
Rectal examination (DRE) (0/1) 0
Prostate volume (ml) 45
PSA (ng/ml) 3.7

Calculate
KEY POINTS

• Gleason pattern 3 (or Gleason 3 + 3 = 6) lacks the hallmarks of cancer, as defined in terms of abnormalities in gene expression and function, and clinical experience. Gleason 4, in contrast, exhibits most of the molecular characteristics of cancer.

• Overdiagnosis and overtreatment of clinically insignificant prostate cancer has been largely responsible for many organizations rejecting PSA screening.

• Active surveillance, characterized by close monitoring, periodic biopsy, and serial PSA, is a well tolerated and effective means to manage low-risk prostate cancer while avoiding the overtreatment problem.

• Multiparametric MRI represents a major step forward in early identification of high-grade disease in patients diagnosed with Gleason 6 cancer.

• Focal therapy is an alternative to surveillance for selected patients with intermediate-risk unilateral disease.
Conclusions

- Not all prostate cancers need immediate treatment
- AS is ‘a’ standard of care in low risk PCa
- AS is safe in intermediate time frame
- HR Other Cause to PCa Mortality 9.2 at 15 years
- Increasing acceptance
- An evolving strategy (need of MRI and biomarkers)
Review

Screening for Prostate Cancer: A Review of the Evidence for the U.S. Preventive Services Task Force

Roger Chou, MD;
Jennifer M. Croswell, MD, MPH;
Tracy Dana, MLS;
Christina Bougatsos, BS;
Ian Elswick, MD;
Ron Ronco, MD;
Ken Sickmann, MD, MPH;
Helen C. Koenig, MD, MPH;
Clarence Lam, MD, MPH;
Ashley Maltz, MD, MPH;
J. Bruin Rugge, MD, MPH; and
Kenneth Lin, MD

Published on-line Annals of Internal Medicine Oct 2011

Conclusion: Prostate-specific antigen–based screening results in small or no Reduction in prostate cancer–specific mortality and is associated with harms related to subsequent evaluation and treatments, some of which may be unnecessary.

EAU 2014
Result
The chance of having a positive biopsy is 18%