ACTIVE SURVEILLANCE IN LOCALIZED PROSTATE CANCER

Hong Seok Park, Korea University Hospital
The great disparity between cancer incidence and mortality indicates that many men may not benefit from definitive treatment of localized prostate cancer.

Autopsy studies have shown that 60% to 70% of older men have some areas of cancer within the prostate. This can be compared with the 15% to 20% of men diagnosed with prostate cancer during their lifetime and with the 3% lifetime risk of death from prostate cancer.

Men who choose not to undergo immediate therapy may opt for continued follow-up under a program of watchful waiting or active surveillance.
Contents

- True Prevalence of Prostate Cancer
- Natural History of Prostate Cancer
- Guideline of Active Surveillance (by EAU, NCCN)
- Conclusion
## The Burden of Prostate Cancer in the United States

<table>
<thead>
<tr>
<th></th>
<th>Whites</th>
<th>African Americans</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td>164.3</td>
<td>272.1</td>
<td>170.1</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>30.2</td>
<td>73.0</td>
<td>32.9</td>
</tr>
<tr>
<td>New cases in 2005</td>
<td>201,320</td>
<td>30,770</td>
<td>232,090</td>
</tr>
<tr>
<td>Mortality in 2005</td>
<td>25,300</td>
<td>5,050</td>
<td>30,350</td>
</tr>
<tr>
<td>Lifetime risk of disease</td>
<td>17.6%</td>
<td>20.6%</td>
<td>NA</td>
</tr>
<tr>
<td>Lifetime risk of death from disease</td>
<td>2.8%</td>
<td>4.7%</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Age standardized per 100,000 population, 1996–2000.

*Data from* Ries et al, 2004; Jemal et al, 2004; and American Cancer Society, 2005.*
Prostate Cancer Detection as a Function of Serum Prostate-Specific Antigen (PSA) Level and Digital Rectal Examination (DRE) Findings in Contemporary Series

<table>
<thead>
<tr>
<th>PSA Level (ng/mL)</th>
<th>DRE Findings[^1]</th>
<th>Cancer Detection Rate (%)[^2]</th>
<th>Cancer Yield on Biopsy (%)[^3]</th>
<th>Rate of High-Grade Cancer on Biopsy (%)[^4]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>-</td>
<td>8.8</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>-</td>
<td>17.0</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>-</td>
<td>12</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>0.7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td>-</td>
<td>15-25</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>2</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>4-10</td>
<td>-</td>
<td>11</td>
<td>17-32</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>11-27</td>
<td>45-51</td>
<td>11.7</td>
</tr>
<tr>
<td>&gt;10</td>
<td>-</td>
<td>41</td>
<td>43-65</td>
<td>19.4</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>31-76</td>
<td>70-90</td>
<td>50.5</td>
</tr>
<tr>
<td>&lt;4</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>1-3</td>
<td>13-17</td>
<td></td>
</tr>
<tr>
<td>&gt;4</td>
<td>-</td>
<td>14</td>
<td>23-38</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>14-38</td>
<td>55-63</td>
<td>20.6</td>
</tr>
</tbody>
</table>

The Study Design of PCPT

- 18,882 men 55 years of age or older
- Normal DRE
- PSA level of 3.0 ng per milliliter or lower
- DB-RCT: Treat finasteride (5 mg per day) or placebo for seven years
The Result of PCPT

<table>
<thead>
<tr>
<th></th>
<th>Finasteride</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dx of PCa</td>
<td>803 / 4368 (18.4%)</td>
<td>1147 / 4692 (24.8%)</td>
</tr>
<tr>
<td>For Cause Biopsy</td>
<td>435 / 1639 (26.5%)</td>
<td>571 / 1934 (29.5%)</td>
</tr>
<tr>
<td>End of Study Biopsy</td>
<td>368 / 3652 (75) (10.1%)</td>
<td>576 / 3820 (99) (15.1%)</td>
</tr>
</tbody>
</table>

NEJM 2003
The Result of PCPT (Age)

<table>
<thead>
<tr>
<th>Age</th>
<th>Finasteride</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>55–59</td>
<td>205 / 1380 (14.9%)</td>
<td>309 / 1492 (20.7%)</td>
</tr>
<tr>
<td>60–64</td>
<td>254 / 1442 (17.9%)</td>
<td>357/1477 (24.2%)</td>
</tr>
<tr>
<td>65–</td>
<td>344 / 1546 (22.3%)</td>
<td>481/1722 (27.9%)</td>
</tr>
</tbody>
</table>

NEJM 2003
The Result of PCPT (PSA)

<table>
<thead>
<tr>
<th>PSA (ng/ml)</th>
<th>Finasteride</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0–1.0</td>
<td>212 / 1975 (10.7%)</td>
<td>357 / 2196 (16.3%)</td>
</tr>
<tr>
<td>1.1–2.0</td>
<td>344 / 1616 (21.3%)</td>
<td>457 / 1647 (27.7%)</td>
</tr>
<tr>
<td>2.1–3.0</td>
<td>247 / 777 (31.8%)</td>
<td>332 / 848 (39.2%)</td>
</tr>
</tbody>
</table>

NEJM 2003
OBJECTIVE: To describe the natural history of initially untreated early-stage prostate cancer. A key secondary objective was to calculate long-term survival rates by stage, grade, and age at diagnosis.

DESIGN: Prospective cohort study.

SETTING: Population-based in 1 county of Sweden, without screening for prostate cancer.

PATIENTS: A group of 642 patients with prostate cancer of any stage, consecutively diagnosed between 1977 and 1984 at a mean age of 72 years with complete follow-up to 1994.

MAIN OUTCOME MEASURES: Proportion of patients who died from prostate cancer, and 15-year survival (with 95% confidence interval [CI]), corrected for causes of death other than prostate cancer.

Progression-Free Survival  Disease-Specific Survival

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>No. of Patients</th>
<th>%</th>
<th>95% CI (%)</th>
<th>%</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-T2</td>
<td>300</td>
<td>48</td>
<td>37-59</td>
<td>81</td>
<td>74-88</td>
</tr>
<tr>
<td>T3-T4</td>
<td>183</td>
<td>47</td>
<td>33-61</td>
<td>57</td>
<td>45-68</td>
</tr>
<tr>
<td>M+</td>
<td>159</td>
<td>6</td>
<td>0.8-11</td>
<td>6</td>
<td>-0.1-12</td>
</tr>
</tbody>
</table>


Patients with localized prostate cancer have a favorable outlook following watchful waiting, and the number of deaths potentially avoidable by radical initial treatment is limited. Without reliable prognostic indicators, an aggressive approach to all patients with early disease would entail substantial overtreatment.

In contrast, patients with locally advanced or metastatic disease need trials of aggressive therapy to improve their poor prognosis.
Natural history of early, localized prostate cancer.
A prospective, population-based study in Sweden. : 20 yrs study

Johansson, JAMA. 2004;291:2713-2719
Cause-Specific Survival by Stage of Disease and Tumor Grade at Diagnosis

Johansson, JAMA. 2004;291:2713-2719
Although most prostate cancers diagnosed at an early stage have an indolent course, local tumor progression and aggressive metastatic disease may develop in the long term. These findings would support early radical treatment, notably among patients with an estimated life expectancy exceeding 15 years.
Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer.

Connecticut Tumor Registry. Retrospective cohort study. A total of 767 men with localized prostate cancer diagnosed between 1971 and 1984, aged 55 to 74 years at diagnosis, either not treated or treated with immediate or delayed hormonal therapy, and followed up for 10 to 20 years after diagnosis.

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>the probability of dying from prostate cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to 4</td>
<td>4% to 7%</td>
</tr>
<tr>
<td>5</td>
<td>6% to 11%</td>
</tr>
<tr>
<td>6</td>
<td>18% to 30%</td>
</tr>
<tr>
<td>7</td>
<td>42% to 70%</td>
</tr>
<tr>
<td>8 to 10</td>
<td>60% to 87%</td>
</tr>
</tbody>
</table>

Survival and Cumulative Mortality From Prostate Cancer and Other Causes Up to 20 Years After Diagnosis, Stratified by Age at Diagnosis and Gleason Score

## Life Table 2009, Man in Korea

<table>
<thead>
<tr>
<th>Age</th>
<th>Expected Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>25.11</td>
</tr>
<tr>
<td>60</td>
<td>20.98</td>
</tr>
<tr>
<td>65</td>
<td>17.05</td>
</tr>
<tr>
<td>70</td>
<td>13.43</td>
</tr>
<tr>
<td>75</td>
<td>10.24</td>
</tr>
<tr>
<td>80</td>
<td>7.55</td>
</tr>
</tbody>
</table>
Localized Prostate Cancer

**T1 Clinically inapparent tumour not palpable or visible by imaging**
- T1a Tumour incidental histological finding in 5% or less of tissue resected
- T1b Tumour incidental histological finding in more than 5% of tissue resected
- T1c Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA] level)

**T2 Tumour confined within the prostate**
- T2a Tumour involves one half of one lobe or less
- T2b Tumour involves more than half of one lobe, but not both lobes
- T2c Tumour involves both lobes
Watchful waiting vs Active surveillance

Watchful waiting (WW)
- the conservative management of PCa until the development of local or systemic progression, at which point the patient would be treated palliatively with transurethral resection of the prostate (TURP) or other procedures for urinary tract obstruction and hormonal therapy or radiotherapy for the palliation of metastatic lesions.

Active surveillance (AS)
- an active decision not to treat the patient immediately and to follow him with close surveillance and treat at pre-defined thresholds that classify progression (i.e. short PSA doubling time and deteriorating histopathological factors on repeat biopsy). In these cases, the treatment options are intended to be curative.
Goals of active surveillance

- provide definitive treatment for men with localized cancers that are likely to progress

- reduce the risk of treatment-related complications for men with cancers that are not likely to progress
Which patients are suitable candidates for active surveillance?

- Patients with lower risk tumors (low Gleason score, PSA level, and clinical stage) with a shorter than 10~15 life expectancy.

- In case of a longer life expectancy, patients with very small areas of cancer in their biopsy or patients who, at the time of diagnosis, are reluctant to accept the side effects of potentially curative therapies.
Active Surveillance by EAU guideline

- T1a

- Standard treatment for well-, and moderately, differentiated tumours and < 10-year life expectancy. In patients with > 10-year life expectancy, re-staging with TURP and biopsy is advised
Active Surveillance by EAU guideline

- cT1c-cT2a
- Treatment option in patients with PSA < 10 ng/mL, biopsy, Gleason score < 6, < 2 biopsies positive, < 50% cancer involvement of each biopsy.
- Patients with a life expectancy < 10 years.
- Patients who do not accept treatment-related complications
Candidate for Active Surveillance according to NCCN guideline

- low-risk prostate cancer who have a life expectancy of less than 10 years
  Tumor stage: T1-T2a, Tumor grade: Gleason score 2-6,
  PSA level: <10 ng/mL

- very-low risk, or clinically insignificant prostate cancer who have a life expectancy of up to 20 years
  Tumor stage: T1c, Tumor grade: Gleason score \( \leq 6 \)
  PSA level <10 ng/mL, PSA density < 0.15 ng/mL per gram
  < 3 positive biopsy cores, \( \leq 50\% \) cancer in each core
Low risk Prostate Cancer Patients

**Life expectancy < 10 years**

*Active Surveillance*
- PSA as often as every 6 months
- DRE as often as every 12 months

**Life expectancy \( \geq 10 \) years**

*Active Surveillance*
- PSA as often as every 6 months
- DRE as often as every 12 months
- Prostate biopsy as every 12 months

*Radiation Therapy*

*Radical Prostatectomy*
Very Low risk Prostate Cancer Patients

**Life expectancy <20 years**

- Active Surveillance
  - PSA as often as every 6 months
  - DRE as often as every 12 months
  - Prostate biopsy as every 12 months

**Life expectancy ≥20 years**

- Active Surveillance
  - PSA as often as every 6 months
  - DRE as often as every 12 months
  - Prostate biopsy as every 12 months

- Radiation Therapy
- Radical Prostatectomy
What is the Definitive Clue of Malignancy?

Death due to Cancer Progression

- Morphology
- Molecular Tumor Marker
- Biologic Behavior
What is the Definitive Clue of Malignancy?

Death due to Cancer Progression

- Morphology
- Molecular Tumor Marker
- Biologic Behavior

Metastasis
Goal of Radical Surgery for Cancer patients

- **Cure**
  - **Necessity**: Sufficient malignant potential
  - **Success**: Complete removal of cancer tissue from patients
Usefulness of Radical Surgery for Cancer Patients

- Low Grade & Stage
  - T1: Success
  - T2: Necessity
  - T3: Success

- High Grade & Stage
  - T1: Success
  - T2: Necessity
  - T3: Necessity
Active surveillance is a solution to the widely acknowledged problem of overdiagnosis and overtreatment of clinically insignificant disease which accompanies early detection of prostate cancer using prostate-specific antigen (PSA) and biopsy.

This approach is supported by data demonstrating that patients who fall into the category of clinically insignificant disease can be identified with reasonable accuracy, and that patients who are initially classified as low risk who reclassify over time as higher risk and are then treated more aggressively are in most cases still cured.