Cancer Prostate - Role of Watchful waiting and Active Surveillance.

Evidence for deferred treatment option

Dr Azhar bin Amir Hamzah
HUSM, Kubang Kerian
CONTENT

• Incidence vs mortality
• Natural history
• WW vs AS (Indication, drawbacks)
• Evidence of deferred therapy in
  – Localized Pca
  – Locally Advanced
  – Metastatic
  – Ongoing trials
### Leading cancer types for new cases by sex (USA, 2007)

<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostate</strong></td>
<td><strong>Breast</strong></td>
</tr>
<tr>
<td>29%</td>
<td>26%</td>
</tr>
<tr>
<td>Lung and Bronchus</td>
<td>Lung and Bronchus</td>
</tr>
<tr>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>Colon and Rectum</td>
<td>Colon and Rectum</td>
</tr>
<tr>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>Urinary Bladder</td>
<td>Urinary Corpus</td>
</tr>
<tr>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Melanoma of the Skin</td>
<td>Melanoma of the Skin</td>
</tr>
<tr>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Kidney &amp; Renal pelvis</td>
<td></td>
</tr>
<tr>
<td>4%</td>
<td></td>
</tr>
</tbody>
</table>
International Comparison of Age-Standardized Incidence Rates for Prostate Cancer in Selected Registries, Males, 1993-1996

Note: Rates are per 100,000 standardized to the World population. Sites are ranked in decreasing order.
Source: Surveillance and Risk Assessment Division, CCDPC, Health Canada

(Courtesy of Dr Ito, Gunma University, Japan)
The incidence of prostate cancer in Japanese males

Incidence rate per 100,000 standardized to the World population

(Center for Cancer Control and Information Services, National Cancer Center, Japan)
Predictive numbers of male cancer in Japan

(Courtesy of Dr Ito, Gunma University, Japan)
Prostate cancer incidence rate in Korea

Reference; MOHW 2008

(Courtesy of Korean Prostate Cancer Working Group)
In Malaysia – 4th common ca
Prostate Cancer incidence: Singapore

(Singapore Cancer Registry)

(Courtesy of Dr Christopher Cheng, Singapore)
SINGAPORE TEN MOST FREQUENT CANCERS IN MALES, 2002-2006

(Courtesy of Dr Christopher Cheng, Singapore)
Incidence rates of prostate cancer in Indonesia were unavailable. This data is from 2 tertiary care hospitals in Jakarta (1995-2008) (Courtesy of Professor Rainy Umbas, Indonesia)
Incidence and death

• **BUT**, there is a **great difference between the incidence of PCa and deaths from PCa.**
  
  – In USA, 240,890 new cases with only 33,720 deaths (1 in 8)
  – Autopsy studies of people dying from different causes- 2/3 of older men have histological Pca

• A large proportion of these tumours **will not progress.**

• The incidence of small, localised, well-differentiated PCa is increasing, **d/t - PSA screening and ‘multicore’ schemes of prostate biopsy.**

Prostate Cancer

• 232,000 new cases in 2005
  – 40% more than compared to 1985
  – 50% are low risk
• “Stage Migration”
  – PSA Screening has led to dramatic reduction in metastases at diagnosis
• Lifetime risk of being diagnosed with prostate cancer has increased from 10% in the pre-PSA era to 17%
• Lifetime risk of dying from PCa remains at 3%

Incidence and mortality: USA versus England & Wales
The influence of PSA

Oliver et al Lancet 2000 355 1788
Incidence rate

PSA era in 1988

Death rate

35% reduction in Pca death from 1993
Natural history of localized prostate cancer managed with no initial treatment

<table>
<thead>
<tr>
<th>Biopsy grade</th>
<th>% risk of metastasis (10 yrs)</th>
<th>% risk of prostate cancer death (15 yrs)</th>
<th>Estimated lost years of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td>19</td>
<td>4-7</td>
<td>&lt;1 year</td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>6-11</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>6-11</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>42</td>
<td>42-70</td>
<td>5</td>
</tr>
<tr>
<td>8-10</td>
<td>74</td>
<td>56-87</td>
<td>6-8</td>
</tr>
</tbody>
</table>

20-Year Outcomes Following Conservative Management of Clinically Localized Prostate Cancer

- Retrospective population-based cohort study
  - Connecticut Tumor registry, 1971-1984
- 767 men, ages 55-74, observation 24 years
- Mortality rate: 3.3% per year during first 15 years, then 1.8% per year thereafter.
- Low grade (GS 2-4) 0.6% per year, high grade (GS 8-10) 12% per year

20-YEAR OUTCOMES FOLLOWING CONSERVATIVE MANAGEMENT OF PCA

Survival and cumulative mortality from Pca and other causes up to 20 yrs after diagnosis, stratified by age at diagnosis and Gleason score.

Albertsen et al. JAMA 2005; 293: 2095–101
**Conclusion** The annual mortality rate from prostate cancer appears to remain stable after 15 years from diagnosis, which does not support aggressive treatment for localized low-grade prostate cancer.

*JAMA. 2005;293:2095-2101*
Localized prostate cancer

• Conservative
  • Active surveillance
  • Watchful waiting
• Radical prostatectomy
  • Open
  • Laparoscopic
  • Robotic
• Radiotherapy
  • External Beam Radiotherapy (EBRT)
  • Brachytherapy
• Cryoablation, Radiofrequency Interstitial Tumor ablation, High Intensity Focused Ultrasound (HIFU)
• Many men with localised PCa would not actually benefit from definitive treatment.
• With the aim of **reducing the risk of overtreatment** in this subgroup of patients, two conservative management strategies of ‘watchful waiting’ and ‘active surveillance’ have been proposed.

**Watchful waiting (WW)**
- WW aka = ‘deferred treatment’ / ‘symptom-guided treatment’.
- Terminology coined in the pre-PSA screening era (before 1990) and referred to the conservative management of PCa.
- Rationale: PCa often progresses slowly, dx in older men, in whom there is a high incidence of co-morbidity mortality.

**Active surveillance (AS)**
- AS aka=‘active monitoring’.
- It includes an active decision not to treat the patient immediately.
- Instead, the patient is followed up under close surveillance.
Watchful waiting

• Is the conscious decision to avoid treatment in a patient until it is required, usually when symptoms of progressive disease develop or the PSA rise above an arbitrary cut off value.

• Indications:
  1. Live expectancy is less than 10-15 yrs
  2. Low grade and low stage cancer
  3. Significant co-morbidities
Active Surveillance (AS)

• First formally described by Richard Choo in 2001
• Is a management option for men who have potentially curable Pca, but wish to avoid the cx associated with intervention
• Approach to low risk prostate cancer
  – Close monitoring of PSA kinetics and serial biopsies
  – If progression is detected, definitive radical treatments are offered
• May avoid radical intervention in up to 60-80% of pts
Indications for AS:

**Royal Marsden criteria**
- Age 50-80 yrs
- Fit for radical treatment
- PSA < 15 ng/mL
- Stage T1-2
- Gleason score of ≤3+4
- < 50% positive cores

**NICE guideline (based on Epstein)**
- Fit for radical intervention
- PSA < 6
- PSAD < 0.15ng/mL/cc
- Stage T1c- T2b
- Gleason score <6
- Less than 3 positive cores and no core more than 50% positive or over 10mm

**D’ Amico criteria**

<table>
<thead>
<tr>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psa ≤= 10</td>
<td>T2b</td>
<td>Psa &gt; 20</td>
</tr>
<tr>
<td>G ≤= 6</td>
<td></td>
<td>G &gt; = 8</td>
</tr>
</tbody>
</table>
# AS vs. WW

## Contrasts between active surveillance and watchful waiting

<table>
<thead>
<tr>
<th></th>
<th>Active surveillance</th>
<th>Watchful waiting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aim</strong></td>
<td>To individualise treatment</td>
<td>To avoid treatment</td>
</tr>
<tr>
<td><strong>Patient characteristics</strong></td>
<td>Fit for radical treatment</td>
<td>Age &gt;70 or life expectancy &lt;15 yrs</td>
</tr>
<tr>
<td></td>
<td>Age 50–80</td>
<td></td>
</tr>
<tr>
<td><strong>Tumour characteristics</strong></td>
<td>T1–T2 GS ≤7 Initial PSA &lt;15</td>
<td>Any T stage GS ≤7 Any PSA</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Frequent PSA testing</td>
<td>PSA testing unimportant</td>
</tr>
<tr>
<td></td>
<td>Repeat biopsies</td>
<td>No repeat biopsies</td>
</tr>
<tr>
<td><strong>Indications for treatment</strong></td>
<td>Short PSADT</td>
<td>Symptomatic progression</td>
</tr>
<tr>
<td></td>
<td>Upgrading on biopsy</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment timing</strong></td>
<td>Early</td>
<td>Delayed</td>
</tr>
<tr>
<td><strong>Treatment intent</strong></td>
<td>Radical</td>
<td>Palliative</td>
</tr>
</tbody>
</table>

Follow up regimes in AS

Royal Marsden regime:

- PSA monthly for 1\textsuperscript{st} year, 3monthly – 2\textsuperscript{nd} year, 6 monthly thereafter
- Repeat TRUS biopsy at 18-24 months, and 2 yearly thereafter
- Imaging – only if disease progression develops

AUA recommendation

- PSA and DRE every 3 monthly x 2 yrs, then 6 monthly
- 10-12 core biopsy at 1 yr, then every 3-5 yrs till 80 yrs

Van NJ, Cancer J, 2007
Drawbacks of AS

• A valid treatment options, but no long term data
• Young men with long life expectancy may miss the chance for curative intervention.
• Lack of consensus on the ideal follow-up regime
• Compliance of pt on follow-up regime
• 25% can have progression without PSA increase
• 24-27% of the patient have aggressive tumour

Indicators for disease progression

• 1. PSADT < 2 years (20% patients)
• 2. Grade progression on repeat biopsy – Gleason score > 7 (4+3); or more than 50% positive core biopsy (about 15% pts)
• Patient anxiety harboring untreated cancer (10% pts)

What is the Outcome of AS?

- **Evidence for AS:** Klotz (J of Clin Onco 2005)

- Entry criteria: \( \leq T2b, G\leq 7, \text{PSA} \leq 15 \)
- Follow up protocol: PSA and DRE = 3/12 for 2 years then 6/12ly
  - TRUS Bx at 1 year, then every 3-5 years till 80 yr

- Intervention: PSADT 2-3 yrs
  - Gleason 7 or higher
  - primary grade 4/5
  - >50% positive cores
  - pt anxiety
Clinical Results of Long-Term Follow-Up of a Large, Active Surveillance Cohort With Localized Prostate Cancer

Laurence Klotz, Liying Zhang, Adam Lam, Robert Nam, Alexandre Mamedov, and Andrew Loblaw

450 Patients
6.8 year F/U
97% Actuarial CaP Survival
78% Overall Survival
30% Failure
50% BPR at 5 yrs in Failures

J Clin Oncology, Jan 2010
• **Klotz results on AS**: 
  
  • 8 year f/u :- OS = 85%,
  
  • Disease specific survival (CSS)=99%, only 2 pts died from CaP

  • 34% came off AS to Rx = 15% rising PSA, 12% pt preference, 4% Gleason rise, 3% clinical progression

  • 10 year f/u :- 72% still on AS , CSS = 98.5%

  • - chance of upgrading from G3→4 is 1%/year
  
  • - chance of dying from other dx is 19X cf CaP
Role of deferred treatment

• Localised PCa (stage T1-T2, Nx-N0, M0)
• Locally advanced PCa (stage T3-T4, Nx-N0, M0)
• Metastatic PCa (stage M1)
Can Localized Prostate Cancer Be Managed Conservatively?

What is the evidence?
Evidence for deferred treatment

**Watchful waiting**

- **Cohort Studies**
  - Connecticut Tumor Registry (1971-84)
  - Karolinska; 1997

- **Watchful waiting vs. Radical Treatment**

- **Watchful Waiting vs. Prostatectomy**
  - VACURG (1967-1975)

**Active Surveillance**

- **4.1 Strategies**
  - START Trial, NCIC PR.11 (2007-ongoing)

- **4.2 Trials**
  - Dutch PRIAS trial
  - U.S. Multi-Institutional; 2009
  - Johns Hopkins (1995-ongoing)
  - UCSF; 2008 (1991-)
  - University of Miami; 2008
  - Royal Marsden (1993-2002)
  - European Randomized Study of Prostate Cancer; 2007
Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4)

• First prospective randomized trial to show benefit of radical prostatectomy

• Initially by Holmberg et al (2002), and most recently by Anna Bill Axelson

• 695 patients (surgery 347 vs. ww 348)
  – 1989 to 1999, 14 centers Sweden, Finland, Iceland
  – Age <75, T1-T2(5%T1c, 75% T2), PSA <50
  – Median follow-up 10.8 years, Median PSA 12.8
  – 1 endpoint = CaP death, 2 endpoints= mets, dx progression, death from other causes
  – 5% diagnosed based on PSA screening

Radical prostatectomy *versus* WW
6.2 years follow-up

Probability of death from any cause (n=695)

Relative risk 0.83 (0.57, 1.20); p=0.31

Holmberg *et al.* NEJM 2002; 347: 781–9
Radical prostatectomy *versus* WW
8.2 years follow-up

Probability of death from any cause (n=695)

Cumulative incidence of death from any cause (%)

Relative risk 0.74 (0.56, 0.99); *p*=0.04

No. at risk
Radical prostatectomy 347 343 332 284 210 118
Watchful waiting 348 341 326 279 198 104

### Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4)

<table>
<thead>
<tr>
<th>Absolute risk reduction of Surgery vs. WW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
</tr>
<tr>
<td>Distant Metastases</td>
</tr>
<tr>
<td>Cancer-specific mortality</td>
</tr>
<tr>
<td>Overall mortality</td>
</tr>
</tbody>
</table>

- **Gleason 2-6**: 60%
- **Gleason 7-10**: 26%
- **Age < 65**: Overall Mortality ARR 18.3 (P =0.004)
- **Age > 65**: no benefit

• Evidence for RP vs WW:
  
  • Death were reported in 83 pts in the RP gp and 106 pts in WW gp.
  
  • Specific Prostate cancer deaths accounts 30 (8.6%) in RP gp vs 50 (14.4%) in WW gp.
  
  • Result showed RP gp has 44% Relative risk Reduction (RRR) in men < 65yo (8.6% RP vs 14.4% WW) at 10 yrs, and improvement of disease specific, overall survival and met progression (LE: 1b)

• Bill-Axelson et al. NEJM, 2011 (15 yrs report)
  
  – The no need to treat (NNT) to prevent one death: 15 overall and 7 for men < 65

• In pt underwent RP – 7x higher risk of death if had extracapsular tumour growth
RP vs WW in Early PCa  Bill-Axelson A, Holmberg L NEJM 364;18, May 5 2011

- NNT 15; 7 for men < 65 yrs
Pitfalls of SPCG-4

- Only 5% of pts had T1c tumour (PSA detected), whereas 75% were T2 tumours (in contrast to present day practice, whereby only 15% of cases are T2 tumours. (May not be applicable in today’s population due to lead time effects afforded by PSA screening.)
- Study excluded high grade disease
- Pathological data were limited, so it is not known how many were up-staged secondary to positive margin.
- Overall number of deaths in the study was small
- Cancer specific survival was only improved in men < 65 yrs of age
PIVOT trial
Objective: RCT comparing RP vs observation in localized PCa pts.

 METHODS
From November 1994 through January 2002, we randomly assigned 731 men with localized prostate cancer (mean age, 67 years; median PSA value, 7.8 ng per milliliter) to radical prostatectomy or observation and followed them through January 2010. The primary outcome was all-cause mortality; the secondary outcome was prostate-cancer mortality.
Evidence against RP:

- All cause mortality = 47% RP vs 49.9% obs (ARR 2.9%) p = 0.22
- CaP mortality = 5.8% RP vs 8.4% obs (ARR 2.6%), p = 0.09
Adverse events post RP within 30 days = 21% (1 death)

Table 1. Adverse Events Occurring within 30 Days after Surgery.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients (N = 280)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>60 (21.4)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>12 (4.3)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Renal failure or dialysis</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Bowel injury requiring surgical repair</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Additional surgical repair</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td>Bleeding requiring transfusion</td>
<td>6 (2.1)</td>
</tr>
<tr>
<td>Urinary catheter present &gt;30 days after surgery</td>
<td>6 (2.1)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Other</td>
<td>28 (10.0)</td>
</tr>
</tbody>
</table>

* Of the 364 men randomly assigned to the radical-prostatectomy group, radical prostatectomy was completed in 230. Multiple events may have occurred in a single patient.

Table 2. Patient-Reported Urinary, Erectile, and Bowel Dysfunction at 2 Years, According to Study Group.*

<table>
<thead>
<tr>
<th>Dysfunction</th>
<th>Radical Prostatectomy</th>
<th>Observation</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary incontinence†</td>
<td>49/287 (17.1)</td>
<td>18/284 (6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Erectile dysfunction‡</td>
<td>231/285 (81.1)</td>
<td>124/281 (44.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bowel dysfunction¶</td>
<td>35/286 (12.2)</td>
<td>32/282 (11.3)</td>
<td>0.74</td>
</tr>
</tbody>
</table>
• Age, race, PS, comorbidities, histology = all no effect on 1/2 outcomes
• RP → reduction in all cause mortality in PSA >10 (p=0.04) and int/high risk groups (p=0.07)
• Less bone mets in RP group.

CONCLUSIONS

Among men with localized prostate cancer detected during the early era of PSA testing, radical prostatectomy did not significantly reduce all-cause or prostate-cancer mortality, as compared with observation, through at least 12 years of follow-up. Absolute differences were less than 3 percentage points. (Funded by the Department of Veterans Affairs Cooperative Studies Program and others; PIVOT ClinicalTrials.gov number, NCT00007644.)
Does active surveillance for men with localized prostate cancer carry psychological morbidity?

- Assessed anxiety and depression in 764 consecutive outpatients with prostate cancer
  - Royal Marsden NHS Foundation Trust, UK
  - HADS survey (Hospital Anxiety and Depression Scale)
    - 14-item self-reported scale
  - Patients
    - AS (100)
    - On-treatment (81)
    - After treatment (148)

Does active surveillance for men with localized prostate cancer carry psychological morbidity?

Active surveillance was not associated with greater psychological distress than more immediate treatment for prostate cancer.
Ongoing landmark trials on deferred treatment

• The Prostate Testing for Cancer and Treatment (ProtecT)
• Standard Treatment Against Restricted Treatment (START) trials.
• Both studies are attempting to compare early interventions to active surveillance but use different inclusion criteria and intervention approaches.
The ProtecT study
(*Prostate testing for cancer and Treatment*)

- **233,000 Invitations**
  - Men 50-69 years

- **116,500 (50%) attendees**
  - Prostate check clinic

- **12,815 (11%) Raised PSA**

- **2,050 (16%) Localised**

- **Randomisation min 60%**

- **Advanced cancer**

- **Active Monitoring 410-683**
- **Radical Prostatectomy 410-683**
- **Radical Radiotherapy 410-683**
- **Preference 0-830**

- **Annual research follow-up**
The ProtecT study
(*Prostate testing for cancer and Treatment*)

- ProtecT, begun in the United Kingdom in 2001, will soon complete enrollment of more than 1500 men aged 50–69 with clinically localized prostate cancer detected through a PSA testing program.

- ProtecT is randomly assigning patients into one of three treatment arms: conformal radiotherapy, prostatectomy, or active monitoring following a treatment plan.
START trial

• The START trial is in its feasibility phase in Canada, will enroll 2130 men in Canada, US and UK (low-risk localized prostate cancer defined by PSA 10 ng/mL or less and Gleason score 6 or less.)

• START will compare early interventions (surgery, external beam radiation, or brachytherapy) to active surveillance.
Deferred treatment for locally advanced PCa (stage T3-T4, Nx-N0, M0)

- The literature reporting - sparse.
- There are no randomised studies that compare more aggressive rx with deferred rx.
- Most patients whose disease progresses after deferred treatment of locally advanced PCa will be candidates for hormone therapy.
- There are reports showing that hormone treatment may safely be delayed until metastatic progression occurs, as no survival advantage was noted.
• 50 selected asymptomatic patients (mean age 71 years) with highly or moderately differentiated stage T3 M0 PCa were followed up for 169 months.
• The 5- and 10-year cancer-specific survival rates were 90% and 74%, respectively.
• The authors concluded that WW might be a treatment option for selected patients with non poorly differentiated T3 tumours and a life expectancy of less than 10 years (LE: 3).

Deferred treatment for metastatic PCa (stage M1)

- very sparse data
- Candidates for such treatment should be:
  - asymptomatic patients with a strong wish to avoid treatment-related side-effects (LE: 4).
    - As the median survival time is about 2 years, the time without any treatment (before symptoms occur) is very short in most cases.
- close follow-up must be possible.
Summary – EUA 2013

<table>
<thead>
<tr>
<th>Active surveillance</th>
<th>2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with the lowest risk of cancer progression: cT1-2a, PSA ≤ 10 ng/mL, biopsy Gleason score ≤ 6 (at least 10 cores), ≤ 2 positive biopsies, minimal biopsy core involvement (≤ 50% cancer per biopsy).</td>
<td></td>
</tr>
<tr>
<td>Active surveillance selection is based on confirmatory biopsies.</td>
<td></td>
</tr>
<tr>
<td>Follow-up is based on DRE, PSA and repeated biopsies. The optimal timing for follow-up is still unclear (yearly or every 2 years).</td>
<td></td>
</tr>
<tr>
<td>The trigger for patients being moved off active treatment is based mainly on grade progression on repeated biopsies or at the patient’s request.</td>
<td></td>
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</tbody>
</table>
### Summary

<table>
<thead>
<tr>
<th><strong>8.5.2 Options</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In presumed localised PCa (Nx-N0, M0):</strong></td>
<td></td>
</tr>
<tr>
<td>Stage T1b-T2b patients who are well informed and have well-differentiated PCa and a life expectancy of 10-15 years.</td>
<td></td>
</tr>
<tr>
<td>All patients not willing to accept side-effects of active treatment.</td>
<td></td>
</tr>
<tr>
<td>Well-informed, asymptomatic patients with high PSA levels for whom cure is unlikely.</td>
<td>3</td>
</tr>
<tr>
<td><strong>In locally advanced disease (stage T3-T4):</strong></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic patients with well or moderately differentiated cancer, PCa and a short life expectancy.</td>
<td>3</td>
</tr>
<tr>
<td>PSA &lt; 50 ng/mL and PSA doubling time &gt; 12 months.</td>
<td>1</td>
</tr>
<tr>
<td><strong>In metastatic disease (M1):</strong></td>
<td></td>
</tr>
<tr>
<td>A very rare patient without any symptoms and the possibility of close follow-up.</td>
<td>4</td>
</tr>
</tbody>
</table>
Thank you

Selamat Hari Kebangsaan