Prospective Evaluation of Selection Criteria for Active Surveillance in Japanese Patients with Stage T1cN0M0 Prostate Cancer

Yoshiyuki Kakehi¹, Toshiyuki Kamoto², Taizou Shiraiishi³, Osamu Ogawa², Yoshimi Suzukamo⁴, Shunichi Fukuhara⁴, Yuko Saito⁵, Ken-ichi Tobisu⁵, Tadao Kakizoe⁶, Haruhiko Fukuda⁶, Koichiro Akakura⁷, Hiroyoshi Suzuki⁸, Nobuo Shinozaki⁹, Shin Egawa¹⁰, Akira Irie¹¹, Takefumi Sato¹¹, Osamu Maeda¹², Norio Meguro¹², Yoshiteru Sumiyoshi¹³, Takanori Suzuki¹⁴, Nobuaki Shimizu¹⁵, Yoichi Arai¹⁶, Akito Terai¹⁷, Tetsuro Kato¹⁸, Tomonori Habuchi¹⁸, Hiroyuki Fujimoto¹⁹ and Masashi Niwakawa²⁰

¹Department of Urology, Faculty of Medicine, Kagawa University, Kagawa, ²Department of Urology, Kyoto University Graduate School of Medicine, Kyoto, ³Department of Second Pathology, Mie University School of Medicine, Tsu, ⁴Department of Epidemiology and Healthcare Research, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, ⁵Clinical Trial Coordination Office and Department of Urology, Shizuoka Cancer Center, Nagaizumi, Shizuoka, ⁶Clinical Trials and Practice Support Division, Center for Cancer Control and Information Services and Department of Urology, National Cancer Center, Tokyo, ⁷Department of Urology, Tokyo Kosei Nenkin Hospital, Tokyo, ⁸Department of Urology, Chiba University Graduate School of Medicine, Chiba, ⁹Department of Urology, Hokkaido University Graduate School of Medicine, Sapporo, ¹⁰Department of Urology, The Jikei University School of Medicine, Tokyo, ¹¹Department of Urology, Kitasato University School of Medicine, Sagamihara, Kanagawa, ¹²Department of Urology, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka, ¹³Department of Urology, Shikoku Cancer Center, Ehime, ¹⁴Department of Urology, National Cancer Center Hospital East, Chiba, ¹⁵Department of Urology, Gunma Cancer Center, Gunma, ¹⁶Department of Urology, Tohoku University Graduate School of Medicine, Miyagi, ¹⁷Department of Urology, Kurashiki Central Hospital, Okayama, ¹⁸Department of Urology, Akita University School of Medicine, Akita, ¹⁹Department of Urology, National Cancer Center Central Hospital Tokyo and ²⁰Department of Urology, Shizuoka Cancer Center, Shizuoka, Japan

Received August 22, 2007; accepted November 18, 2007; published online February 12, 2008

Objective: Selection criteria for active surveillance (AS) program of localized prostate cancer remain to be standardized. The purpose was to evaluate the validity of selection criteria and investigate the feasibility of this AS program.

Methods: Patients meeting the criteria (i) stage T1cN0M0, (ii) age 50–80, (iii) serum prostate-specific antigen (PSA) ≤ 20 ng/ml, (iv) one or two positive cores per 6–12 systematic biopsy cores, (v) Gleason score ≤ 6, and (vi) cancer involvement in positive core ≤ 50% were enrolled and encouraged to start AS for at least 6 months during the period between January 2002 and December 2003. PSA was measured bimonthly for 6 months and every 3 months thereafter. Trigger of treatment recommendation was PSA-doubling time (PSADT) of ≤ 2 years or pathological progression at re-biopsy. Primary endpoint was %PSADT > 2y’, which was defined as the proportion of patients who showed PSADT assessed at 6 months > 2 years out of all the patients who chose AS. Point estimate of %PSADT > 2y’ was expected to be > 80%.

Results: One hundred and eighteen patients opted for AS and 16 chose immediate treatment at enrollment. PSADT for the initial 6 months based on four measurements could be assessed in 106 patients. Intent-to-treat analysis of %PSADT > 2y’ was 71.2% (84/118, 95% CI: 62.1–79.2). Pathological progression rate at 1-year re-biopsy was 33%. Fifty-four (46%) patients remained on AS for maximal observation of 54 months. General health-related QOL in patients undergoing AS was not impaired.

Conclusions: The primary endpoint, ‘%PSADT > 2y’, did not meet the pre-specified decision criteria. Further prospective study with revised program and endpoint is needed.

Key words: active surveillance — prostate cancer — PSA-doubling time

For reprints and all correspondence: Yoshiyuki Kakehi, Department of Urology, Faculty of Medicine, Kagawa University, 1750-1 Ikenobe, Miki-cho, Kita-ku, Kagawa 761-0793, Japan. E-mail: kakehi@med.kagawa-u.ac.jp

© The Author (2008). Published by Oxford University Press. All rights reserved.
INTRODUCTION
Widespread use of prostate-specific antigen (PSA) testing in Japan has resulted in a marked increase in the incidence of ‘favorable risk’ cancer, as has been seen in Western countries. Subsets of prostate cancers detected by PSA screening, however, might not have adversely affected patients’ life span if they were to remain undetected. Etzioni et al. (1) estimated over-diagnosis rates under PSA screening in Caucasian and African-American men as 18–44%, but the rate still remains unclear in Japanese men. Minimal cancer (tumor volume <0.5 ml, organ-confined, no Gleason pattern 4 or 5) was found in 31.6% in the first round and 42.6% in the second round (4-year interval) in the screening arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC), Section Rotterdam (2). In contrast, Loeb et al. (3) detected only 5–10% of clinically insignificant cancer in their longitudinal prostate-cancer screening study. To avoid over-treatment without compromising lifetime, active surveillance (AS) with selective delayed intervention seems a practical treatment option for favorable risk patients, although selection criteria remain to be standardized.

Selection criteria so far published were based on biopsy features and PSA levels at diagnosis, although they have not yet been validated in a prospective trial (4,5). Organ-confined cancers with tumor volume >0.5 ml of Gleason score ≤6 have been considered as indolent or clinically unimportant. This standard, however, was arbitrarily defined (6). What is clinically more important is tumor growth velocity. The only way so far applicable for the prediction of tumor growth velocity is to utilize PSA kinetics. In men with untreated prostate cancer, serum PSA appears to increase exponentially over time (7). Therefore, PSA-doubling time (PSADT), calculated using log-linear regression, may be an appropriate measure of cancer growth.

In this study, we have prospectively evaluated the selection criteria for AS with selective delayed intervention in patients with favorable risk prostate cancer using PSADT that was calculated with four consecutive PSA points for 6 months as a primary endpoint.

PATIENTS AND METHODS
This was a multi-center prospective non-randomized study. Seven cancer center hospitals and six university hospitals participated in this study. The institutional review board of each participating institution approved the study protocol and all the patients gave written informed consent.

STUDY POPULATION AND ENROLLMENT CRITERIA
Patients with newly detected stage T1cN0M0 prostate cancer harboring the biopsy features described subsequently were enrolled during the period between January 2002 and December 2003. In order to be eligible for the study, participants should have met the following criteria: (i) age ranging between 50 and 80, (ii) initial serum PSA being ≤20 ng/ml, (iii) number of positive core being one or two per 6–12 systematic biopsy cores, (iv) Gleason score being ≤6 and (v) ≤50% cancer involvement in any of the positive cores. Patients who had past history of cerebral infarction, unstable angina, diabetes uncontrollable with insulin, severe hypertension or suffered myocardial infarction within 6 months were excluded from this study. In the first step, candidate patients in whom the biopsy criteria of (iii), (iv) and (v) were confirmed by the central pathologist were asked to give their written consent to participate in this study. Then the patients were encouraged to start AS for at least 6 months according to the program described subsequently. Those who did not want to opt for AS immediately started treatments including radical prostatectomy (RP), external beam radiation (EBRT) and androgen-deprivation therapy (ADT).

THE AS PROGRAM
In patients who opted for the AS program, serum PSA was monitored every 2 months for 6 months and every 3 months thereafter. Those who showed PSADT of ≤2 years (y) after 6 months were recommended to start aggressive treatment. After the initial checkpoint, patients undergoing AS were recommended to start treatment when either PSADT assessed with all PSA measurements or PSADT assessed with PSA points measured within 1 year was ≤2 years. The patients who remained on AS for 1 year were recommended to undergo re-biopsy and those who did not fit the initial pathology criteria were also recommended to start aggressive treatment.

PSA ASSAY AND PSADT
All PSA determinations were made centrally using the Tandem-R monoclonal immuno-radiometric assay (Hybritech Inc., San Diego, CA, USA). PSADT was assessed with the assumption that PSA changed with time in simple exponential fashion, which was precisely described elsewhere (8). PSADT was calculated as the natural log of 2 divided by the slope, if PSA values were distributed on the y-axis of a scatter plot and time on the x-axis. It was a line function that fitted the PSA values over time and the PSA slope was calculated using least-squared regression. Outlier of PSA values was excluded from regression calculation when clinical manifestation of prostate inflammation was apparent. These calculations were performed with the software specifically developed for this study.

When an unnatural increase in serum PSA was found during AS, re-measurement of PSA was allowed within 3 months. Then, the principal investigator, the secretary of the study office and the duty doctor discussed whether the pending PSA value could be omitted from the PSADT evaluation.
HISTOPATHOLOGICAL REVIEW
In addition to the eligibility criteria (iii), (iv) and (v) described earlier, the maximal tumor length was recorded for all positive cores by the central pathologist. For radical prostatectomy specimens, stepwise serial sections were made and subjected to thorough pathological review. Pathological T-stage was described according to the UICC TNM-classification 1997 (9).

QOL ASSESSMENT
The patient-reported health-related quality of life (HRQOL) was assessed at the time of registration and 1 year later. General HRQOL was evaluated with the Japanese version RAND SF-36 (10), and disease-related QOL was assessed with the Japanese version UCLA Prostate Cancer Index (UCLA PCI) (11). Each scale of SF-36 was standardized to the Japanese population normative values, with a mean score of 50 and an SD of 10. The function and bother scores of urinary, bowel and sexual domains of UCLA PCI were calculated according to the scoring instructions (12).

ENDPOINTS AND SAMPLE SIZE
Primary endpoint was ‘%PSADT > 2y’ defined as a proportion (%) of AS patients showing PSADT >2 years at the initial 6-month assessment out of all the patients who opted for AS at registration. The secondary endpoints were defined as follows: (i) proportion (%) of AS patients who met the initial pathology criteria at the time of re-biopsy, (ii) proportion (%) of the non-organ-confined rate in patients who chose radical prostatectomy as an initial strategy, (iii) adverse events in patients who chose aggressive treatment as an initial strategy, (iv) impairment of HRQOL in AS patients and other treatment patients, (v) overall survival of AS patients and other treatment patients and (vi) metastasis-free survival of AS patients and other treatment patients. The planned sample size was 100 patients who opted for AS, which was determined based on the precision of estimate to give the width of 95% confidence intervals for ‘%PSADT > 2y’ within 10%.

FOLLOW-UP
The local progression in AS patient was examined with digital rectal examination (DRE) and transrectal ultrasonography at least twice per year and at the suspicion because of rising PSA. Chest X-ray, CT scan or MRI for abdominal/pelvic cavity and bone scintigraphy were performed at least once every two years to rule out the presence of metastasis.

STATISTICAL ANALYSIS
This study was designed to evaluate the validity of our selection criteria for AS. Point estimate of the primary endpoint was expected to be >80% for validating the selection criteria. The point estimates and 95% confidence intervals calculated by the exact method were carried out for proportions. For QOL analysis, subscale scores were compared with the Japanese population normative values and differences of subscale scores within patients were assessed. The Student’s t-test and paired t-test were carried out accordingly in QOL analysis for exploratory purpose.

RESULTS
PARTICIPANTS
One hundred and thirty-four patients were enrolled into this study, and 118 chose the AS program and 13 chose RP, 2 chose EBRT and 1 chose ADT as an initial treatment. Table 1 shows clinical and pathological characteristics of each treatment group.

PSADT IN AS PATIENTS AND PRIMARY ENDPOINT
Among 118 patients who chose the AS program, 7 changed the treatment strategy immediately after registration and 5 patients missed at least 1 PSA determination during the first 6 months. Therefore, PSADT at 6 months was completely calculated in 106 AS patients. Fortunately, there was no unnatural increase in PSA possibly due to prostate inflammation during the initial 6-month evaluation, although it was found in 11 patients thereafter. Distribution of PSADT at 6 months in the 106 patients is shown in Fig. 1. Twenty-two patients showed PSADT to be <2 years, whereas 59 patients showed PSADT to be >10 years or negative PSA slope. On the basis of the intent-to-treat analysis, the primary endpoint, ‘%PSADT > 2y’ at 6 months, was 71.2% (95% CI: 62.1–79.2%).

PREDICTION OF ‘RAPID RISER’
Among 106 AS patients in whom PSADT at 6 months was completely calculated, 22 (20.8%) patients were so-called rapid risers (PSADT ≤2 years) as described earlier. In order to analyse the proportion of rapid riser in the setting of more stringent criteria, one more condition could be added to the original criteria. Either one of following conditions could be added: (i) PSA density <0.15, (ii) maximum tumor length <3 mm, (iii) initial PSA <10 ng/ml or (iv) only one positive core per 6–12 systematic cores. Distribution of PSADT ≤2 years, 2 years <PSADT <10 years and PSADT ≥10 years under the four sets of criteria was compared (Table 2). Distribution of PSADT, however, did not prove to be statistically different between any of the subgroups and the original AS cohort, and the proportion of rapid risers under more stringent condition was not reduced.
THE 6-MONTH PSADT VERSUS THE 12-MONTH PSADT

For 99 patients undergoing AS for ≥1 year including 12 patients who wanted to remain on AS in spite of short PSADT at 6 months (<2 years), the initial 6-month PSADT was compared with the 12-month PSADT that was assessed using all PSA determinations for 1 year after registration, as shown in Fig. 2. Eight of the 12 patients who wanted to remain on AS in spite of short PSADT (PSADT ≤2 years) at 6 months showed the 12-month PSADT to be >2 years.

RE-BIOPSY

As a rule of the present study, re-biopsy was recommended to the patients who remained on AS for 1 year and showed PSADT >2 years at the 12-month evaluation, although a few wanted to continue AS in spite of short PSADT. Sixty-six out of 99 patients who remained on AS at least for 1 year agreed to undergo re-biopsy. Among the 66 patients, four patients wanted to continue AS in spite of PSADT >2 years. The pathological evaluation revealed that 44 out of 66 patients (66.7%, 95% CI: 54.0–77.8) were eligible for the pathological selection criteria again, including 25 patients in whom the second-round biopsy turned negative. Among the 22 patients who did not meet the criteria, three or more positive cores were found in 15 patients, Gleason score ≥7 was observed in 13 and >50% cancer occupation in a positive core was found in 7 as shown in Table 3. There was no association of PSADT with the aggressive findings. Two of four who had PSADT <2 years showed the aggressive findings and the remaining two met the pathological criteria again. After confirmation of deviation from the pathological criteria at re-biopsy, 15 of 22 patients immediately underwent treatment (10: RP; 3: EBRT with or without ADT; 1: seed implantation; 1: ADT) and showed no clinical recurrence until 31 October 2006. In contrast, seven patients wanted to continue AS despite the aggressive pathological findings at re-biopsy. Six remained on AS uneventfully, whereas one patient who started ADT 1 year later showed re-elevation of PSA on 31 October 2006.

PROSTATECTOMY SPECIMENS

Thirteen patients chose RP as the initial treatment and one patient who chose EBRT at registration underwent RP soon after registration.

<table>
<thead>
<tr>
<th>Component</th>
<th>AS</th>
<th>RP</th>
<th>EBRT</th>
<th>ADT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>60–69</td>
<td>61</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>67</td>
</tr>
<tr>
<td>70–74</td>
<td>44</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>51</td>
</tr>
<tr>
<td>75–80</td>
<td>18</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Initial PSA (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>95</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>108</td>
</tr>
<tr>
<td>≥10</td>
<td>23</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>7.2</td>
<td>7.1</td>
<td>11.2</td>
<td>4.6</td>
</tr>
<tr>
<td>Core no. at biopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>37</td>
<td>5</td>
<td>0</td>
<td>42</td>
</tr>
<tr>
<td>7–8</td>
<td>33</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>9–10</td>
<td>21</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>11–12</td>
<td>27</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Positive core no.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>91</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>103</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>Gleason sum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>105</td>
<td>11</td>
<td>2</td>
<td>1</td>
<td>119</td>
</tr>
<tr>
<td>Max. % cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>13.6</td>
<td>9.4</td>
<td>16.8</td>
<td>11.1</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>11.2</td>
<td>9.0</td>
<td>16.8</td>
<td>11.1</td>
</tr>
<tr>
<td>Max. % cancer</td>
<td></td>
<td>46.7</td>
<td>35</td>
<td>23.3</td>
<td>11.1</td>
</tr>
<tr>
<td>Max. tumor length (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>103</td>
<td>12</td>
<td>1</td>
<td>1</td>
<td>117</td>
</tr>
<tr>
<td>≥3</td>
<td>15</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>1.6</td>
<td>1.5</td>
<td>2.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>1.4</td>
<td>1.5</td>
<td>2.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Max. % cancer</td>
<td></td>
<td>5.8</td>
<td>3.5</td>
<td>3.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

One patient who chose EBRT at registration underwent RP soon after registration.

ADT: androgen-deprivation therapy
AS: active surveillance
PSA: prostate-specific antigen
RP: radical prostatectomy
EBRT: external beam radiation

Table 1. Baseline data in each treatment group

One patient who chose EBRT at registration underwent RP soon after registration.

ADT: androgen-deprivation therapy
AS: active surveillance
PSA: prostate-specific antigen
RP: radical prostatectomy
EBRT: external beam radiation

Figure 1. Distribution of the initial 6-month prostate-specific antigen doubling time (PSADT). PSADT >10 years or those which showed negative slope is categorized as PSADT >10 years.

In contrast, among 58 patients with PSADT estimated at 6 months being >10 years (‘stable PSA’), only two patients showed PSADT <2 years at 12 months.
immediately after enrollment. Non-organ-confined cancer, positive surgical margins and peri-neural invasion were found in 1, 3 and 4 patients, respectively. There was no lymphatic, vascular and seminal vesicle invasion. Invasion to the bladder wall, the urethral mucosa and the rectal wall were also not found (data not shown).

HRQOL IN AS PATIENTS

Baseline HRQOL was measured in 128 patients (AS: 114; RP: 11; EBRT: 2; ADT: 1). As to the general HRQOL measured with SF-36, the physical functioning, bodily pain and vitality scores in patients who chose the AS program were better than the age-adjusted Japanese population normative values ($P < 0.05$, Student’s $t$-test) as shown in Fig. 3A. There was no difference in the baseline scores of both SF-36 and UCLA-PCI between those who remained on AS and those who started other treatment within 1 year. HRQOL of 1 year after AS was measured in 95 patients, and the subscale scores of SF-36 were not statistically different from the baseline scores. Bodily pain, vitality and mental health scales in patients remaining on AS for 1 year were better than the age-adjusted Japanese population normative values ($P < 0.05$, Student’s $t$-test), as shown in Fig. 3B. In AS patients, however, the urinary function, sexual function and bowel bother scores measured with UCLA-PCI were worse than the baseline scores ($P < 0.05$, paired $t$-test).

FOLLOW-UP AFTER REGISTRATION

Of all participants, neither manifestation of metastasis nor cancer death was observed until 31 October 2006, and three died of other disease and five did not turn up for follow-up. Of the 118 patients who chose AS, 54 (46%) remained on AS for maximal observation of 54 months, with 3-year actuarial AS-remaining rate being 48.9%. The reasons for

### Table 2. Distribution of the initial 6-month PSADT in subgroups that fit the original selection criteria or that with one additional restriction

<table>
<thead>
<tr>
<th>PSADT at 6 months</th>
<th>Original criteria (%)</th>
<th>Additional restriction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSADT &lt; 10</td>
<td>PSADT &gt; 0.15</td>
</tr>
<tr>
<td>Rapid</td>
<td>22 (20.8)</td>
<td>18 (21.7)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>25 (23.5)</td>
<td>23 (27.7)</td>
</tr>
<tr>
<td>Stable</td>
<td>59 (55.7)</td>
<td>42 (50.6)</td>
</tr>
<tr>
<td>Patient number</td>
<td>106</td>
<td>83</td>
</tr>
</tbody>
</table>

Rapid: PSADT was ≤2 years; intermediate: PSADT was between 2 years and 10 years; stable: PSADT was ≥10 years.

PSADT: prostate-specific antigen doubling time

### Table 3. Pathological findings of re-biopsy at 1 year after AS and deviation rates from the selection criteria

<table>
<thead>
<tr>
<th>Pathological criteria</th>
<th>Deviation rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of positive core</td>
<td>0 1 2 3 4 or more</td>
</tr>
<tr>
<td>Patient number</td>
<td>25 13 13 12 3</td>
</tr>
<tr>
<td>% Cancer/positive core</td>
<td>0 1–25 25–50 50–75 75–100</td>
</tr>
<tr>
<td>Patient number</td>
<td>25 28 6 5 2</td>
</tr>
<tr>
<td>Gleason score</td>
<td>No score 5 6 7 8–10</td>
</tr>
<tr>
<td>Patient number</td>
<td>25 2 28 9 4</td>
</tr>
</tbody>
</table>

Number of patients who deviated each pathology criterion was divided with number of AS patients who agreed with re-biopsy ($n = 66$).

Fig. 3A. There was no difference in the baseline scores of both SF-36 and UCLA-PCI between those who remained on AS and those who started other treatment within 1 year. HRQOL of 1 year after AS was measured in 95 patients, and the subscale scores of SF-36 were not statistically different from the baseline scores. Bodily pain, vitality and mental health scales in patients remaining on AS for 1 year were better than the age-adjusted Japanese population normative values ($P < 0.05$, Student’s $t$-test), as shown in Fig. 3B. In AS patients, however, the urinary function, sexual function and bowel bother scores measured with UCLA-PCI were worse than the baseline scores ($P < 0.05$, paired $t$-test).
leaving AS in the 64 patients were as follows: PSADT ≤ 2 years in 17, pathology progression in 16 and change in T-stage (T1c–T2a) in one. The remaining 30 patients have had co-morbidities (n = 8) or for some unknown reason (n = 7). Among the 15 patients who wanted to leave the AS program without PSA rise or progression, eight complained of aggravating difficulty in urinary voiding due to accompanying benign prostate hyperplasia (BPH), resulting in undergoing cancer treatment (RP: 4; EBRT: 1; ADT: 1) or transurethral resection of BPH (n = 2). Of 16 patients who chose immediate treatment, 15 have been alive without metastasis and one died of lung cancer. Through the observation period, no serious adverse event has been observed in both the AS program group and those who chose immediate treatment.

DISCUSSION

This is the first prospective study on AS in Japanese patients with prostate cancer detected only with PSA elevation. Until the time we started this study, AS had not yet been generally accepted treatment option in Japan, where a randomized study comparing AS with non-AS could hardly been accepted. We therefore designed this study as a phase II setting to assess the validity and feasibility of our AS program. We enrolled 118 AS patients from 13 institutions, which was fewer than the expectation from viewpoint of the most current urology practice. In the early 2000s, however, the annual average number of stage T1cN0M0 patients newly treated at a university hospital or a cancer center hospital in Japan was estimated to be 20–40. Among them, 10–20% of stage T1c might have met the Hopkins pathology criteria for indolent cancer. Under these circumstances, the number of enrollment and those opting for AS suggests high motivation of participants in this study.

PSADT assessed with four serial measurements for 6 months was used as the primary endpoint in this study, although it was a surrogate for survival endpoint. In the calculating PSADT, one critical issue to be solved is how we should handle unnatural surges possibly due to prostate inflammation. Particularly, the number of PSA determinants was relatively small; the influence of measurement error upon estimation of PSADT would be strong. In this study, there was fortunately no unnatural increase in PSA during the initial 6-month evaluation, which might have influence on the primary endpoint. As to the point estimate of ‘%PSADT > 2y’, it was expected to be > 80% when this study was designed under the following backgrounds. In 43 untreated cases including 15 non-organ-confined cancers at Stanford University series, 79% showed PSADT to be > 2 years (7). In 48 Japanese untreated localized cancers (T1-3N0M0 including 40% of Gleason score ≥ 7), 71% showed PSADT to be > 2 years (13). Our previous retrospective study in 78 Japanese untreated patients (T1N0M0: 53, T2-3N0M0: 25) found that 91% showed PSADT > 2 years (14). On the basis of these retrospective studies, although all were small in size, we expected ‘%PSADT > 2 y’ to be ≥ 80% for the validation of the selection criteria because candidate patients with this selection criteria harbored more favorable biopsy features than those described earlier.

‘%PSADT > 2 y’ did not reach 80%, and the selection criteria were not validated. We, however, do not consider that major revision of the selection criteria is needed. In the next study, we rather consider that the primary endpoint should be assessed after a longer period (≥ 1 year) of observation. Comparison of the 6-month PSADT with the 12-month PSADT in the present AS patients strongly suggests the possibility of overestimation as to PSADT estimated at 6 months. The Toronto AS experience demonstrated that the optimal time to determine whether to start a definitive treatment was 2.3 years after starting AS in most of the cases (15, 16). In D’Amico et al.’s (17) PSA velocity study, most of the cohort were followed for median of > 5 years prior to prostatectomy, but cancer-death rate at 7 years was only 1.75% in Gleason score ≤ 6 patients. These data warrant a prospective study of AS in which 1–2 years are allowed for observing PSA kinetics. It also remains undetermined whether the critical point of recommendation to start treatment should be PSADT ≤ 2 years or PSADT ≤ 3 years. The Toronto AS program has recently revised the timing of
treatment recommendation from PSADT ≤2 years to PSADT ≤3 years (16).

The present study demonstrates the limitation of the current systematic biopsy with regard to select low-risk cancers. The upgrading rate (19.7%) was slightly higher than that (12.9%) seen in the Johns Hopkins series (18). Under-estimation of biopsy has also been demonstrated in the patients who chose RP immediately after registration. These results indicate the necessity to incorporate re-biopsy into AS program, although patients who opt for AS seem to be reluctant to undergo re-biopsy.

The Scandinavian randomized trial did not indicate any significant impairment of HR-QOL at 5 years in the watchful waiting arm (19). Similarly, in the present study, any of the SF-36 subscales was not impaired after 1 year of AS. Although 54% of the patients left the AS program and started therapy to the prostate with maximal observation of 4.5 years, 14% stopped AS due to aggravation of physical condition unrelated to prostate cancer. In particular, it should be noted that 7% of AS patients left AS due to voiding difficulty caused by accompanying BPH.

In conclusion, the results obtained here together with those in similar AS programs being conducted in North America and Europe warrant a prospective analysis of AS program in Japanese patients with modified protocol in which selection criteria and primary endpoint are revised.

Funding

This work was supported by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare of Japan (11–10), the Research Grant from the Foundation for Promotion of Cancer Research, Japan (2006) and the Research Grant from the Japanese Urological Association (2004). 

Acknowledgment

We thank Dr Takayoshi Demura, Sapporo Kosei Hospital, for his great contribution to this study.

Conflict of interest statement

None declared.

References

4. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA 1994;271:368–74.