Pathological Findings at Radical Prostatectomy in Japanese Prospective Active Surveillance Cohort

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Objectives: The present study was carried out to analyze pathological features of prostatectomy specimens performed at different timing and trigger during active surveillance.

Methods: One hundred and thirty-four patients that fit a selection condition similar to the so-called Hopkins’ criteria were enrolled into the present study between January 2002 and December 2003. Patients were recommended to start curable treatment when they showed prostate-specific antigen-doubling time of 2 years or shorter or pathological progression at 1-year re-biopsy. Median observation period was 61 months.

Results: Fourteen patients underwent radical prostatectomy immediately after enrollment (Group A) whereas 28 patients underwent radical prostatectomy after substantial periods of active surveillance (Group B). Of the 28 Group B, trigger of radical prostatectomy was on protocol in 17 patients (Group B1) whereas 11 patients underwent radical prostatectomy by their preference (Group B2). Upgrade from initial biopsy was observed in 43% of Group A and 68% of Group B. Upgrade was more frequently observed in Group B1 than B2 with border line significance ($P = 0.075$). Perineural infiltration and positive surgical margin rates of Group B1 were significantly higher than those of B2 ($P < 0.05$).

Conclusions: Unfavorable pathological features of surgical specimens were more frequently observed in patients who underwent radical prostatectomy due to short prostate-specific antigen-doubling time or biopsy findings than those who underwent radical prostatectomy because of other reasons including patients’ preference. Rates of unfavorable pathological features at radical prostatectomy that deviate initial selection criteria was high enough to support integration of frequent biopsies into active surveillance program.

Key words: prostate cancer — active surveillance — prostatectomy — pathological findings

INTRODUCTION

Few studies so far has assessed pathological findings of radical prostatectomy (RP) specimens in patients who initially opted active surveillance (AS) and underwent RP thereafter with special relevance to timing and trigger of leaving AS.

Also in Japan was seen in as many Western countries, early stage, low-risk prostate cancer are increasing especially in younger generations due to the prevalence of prostate-specific antigen (PSA) screening. However, the actuarial exposure rate of PSA testing in Japanese men is quite lower than that in American (1).
AS focused on men for whom therapy in delayed until the tumor becomes progressive and curative treatment can be offered. It was appeared that annual mortality rate in low-risk prostate cancer appears to remain stable after 15 years from diagnosis, which does not support aggressive treatment for localized low-risk prostate cancer (2). In USA, the use of AS has started to increase again after an apparent nadir of 6.2% in 2000 (3). However, it is suggested that AS may be underused in the management of very low-risk prostate cancer (4). One of the reasons for this underuse is uncertainty of long time natural history of prostate cancer or fear for the underestimation of its malignant potential. How can we select accurately and safely the true low risk or insignificant prostate cancer within the curative window?

Physicians try to select the low risk for life-threatening cancer or attempt to detect the sign of progression within curative window by using various patients’ selection criteria or follow-up programs of AS. Unfortunately, there are few randomized studies for low-risk prostate cancer between definitive radical treatment and AS. The Scandinavian randomized study of watchful waiting versus RP showed a survival benefit from surgery (5). However, patient population of this study consisted of substantial intermediate or high-risk patients. Only 5% were diagnosed based on PSA screening and median PSA was 12.8 ng/dl. Substantial rate of patients were not suitable for AS.

Moreover, few studies have examined pathological findings of RP specimens in Japanese patients eligible for AS program. For avoiding the morbidity in radical treatment, i.e. overtreatment, and guarantee the safety for delayed treatment, selection criteria of AS is needed to be standardized. For AS selection criteria, pathological findings of biopsy at initial diagnosis play the most important role. On the other hand, we know that there is discrepancy between the findings of biopsy and RP specimens (6–10). Even with small cancer foci in biopsy specimen, significant disease is presented in substantial ratio of RP specimen. Recently, many studies about AS were reported, but they do not clearly tell us who should be offered this option, how to do it, and how to define success and failure. Some will lose the window of opportunity on curative treatment and will pay a price in term of quality of life.

It is most important to clarify whether delayed intervention in AS program is as safe as immediate treatment. The present study was carried out to analyze pathological features of prostatectomy specimens performed at different timing and trigger during AS.

PATIENTS AND METHODS

This was a multicenter prospective one-arm cohort study. Seven cancer center hospitals and six university hospitals in Japan participated in this study. The institutional review board of each participating institution approved the study protocol and all the patients gave written informed consent.

PATIENTS

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. Mean age of patients was 69.3 years old ranging between 54 and 80. Initial PSA was ranged from 2.2 to 17 ng/ml (mean = 6.4ng/ml). The patients’ characteristics at enrollment are shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Patients’ characteristics at enrollment</th>
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<tr>
<td>Initial treatment</td>
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<td>Age</td>
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<td>50–59</td>
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<td>Core No. at biopsy</td>
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<td>9–10</td>
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<td>11–12</td>
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<td>Positive core No.</td>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
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<td>Gleason sum</td>
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AS, Active surveillance; RP, Radical prostatectomy.
stage T1cN0M0, (ii) age 50–80, (iii) serum PSA < 20 ng/ml, (iv) one or two positive cores per 6–12 systematic biopsy cores, (v) Gleason score ≤6 and (vi) maximum cancer involvement in positive core <50%. Candidate patients in whom the biopsy criteria of (iv), (v) and (vi) were confirmed by the central pathologist (T.S.) were asked to give their written consent to participate in this study.

**Follow-up Protocol**

In patients who opted for the AS program, serum PSA was monitored every 2 months for 6 months and every 3 months thereafter as shown in Fig. 1. Those who showed PSA doubling time (PSADT) of ≤2 years after 6 months were recommended to start aggressive treatment. Patients undergoing AS were recommended to start treatment either when PSADT assessed with all PSA measurements or that assessed with current six measurements per 1 year was 2 years or less. 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.

**Histopathological Review**

For RP specimens, stepwise serial sections were made and subjected to thorough pathological review by the central pathologist. Pathological T-stage was described according to the UICC TNM-classification 1997 (11).

**Statistics**

We assessed differences in pathological findings between groups with the use of generalized $\chi^2$ and non-parametric Wilcoxon’s rank-sum tests. $P$ value < 0.05 was considered to be statistical significant.

**RESULTS**

**Choice of Treatment, Timing and Reasons for RP**

Follow-up periods ranged from 1 to 78 months, a median observation period was 61 months. The Choices of treatment after enrollment, timing and reasons for RP are shown in Fig. 2. Among 16 patients who chose immediate treatment (within 3 months after diagnosis), 14 patients (defined as Group A) underwent RP. One chose external beam radiotherapy and the other chose androgen deprivation therapy. Of 117 patients who chose AS as a initial treatment, 34 remained on AS for maximal observation of 78 months with 5-year actuarial AS-remaining rate being 41.4% (Fig. 3). Twenty-eight patients (defined as Group B) underwent RP in the course of AS program due to varied reasons. Group B was subclassified into Group B1 and B2. The Group B1 included the patients who underwent RP by the trigger of PSA-kinetics or re-biopsy findings (17 cases). The Group B2 ($n = 11$) included the patients who underwent RP without recommendation of the AS protocol, patient’s preference and difficult voiding. A median duration from diagnosis till RP in Group B was 16 months.

**Reasons for Leaving AS Program**

Seventy patients out of 117 ceased AS program in the present study. Reasons for leaving AS program are followed; Pathological progression by re-biopsy findings were in 16, PSADT <2 years were in 23, difficult voiding due to the concomitant benign prostate hypertrophy (BPH) in 11 and patients preference were in 13.

**Pathological Features of RP Specimens**

Histopathological features of RP specimens are summarized in Table 2. Of 42 patients who underwent RP (Group A and

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**Figure 1.** Follow-up protocol of the present AS cohort. Serum PSA was monitored every 2 months for 6 months and every 3 months thereafter. Those who showed PSA doubling time (PSADT) of ≤2 years after 6 months were recommended to start aggressive treatment. Patients undergoing AS were recommended to start treatment when PSADT assessed with all PSA measurements was ≤2 years. The patients who remained on AS for 1 year were recommended to undergo re-biopsy.
Group B), 25 (59.5%) were upgraded from the initial biopsy (Gleason score; 3 + 4: 17, 4 + 3: 6, 4 + 4: 2). Upgrade was observed in 43% of Group A and 68% of Group B. Capsular invasion were found in five patients (Group A: 1, Group B: 4), but there was no vascular and seminal vesicle invasion. There was no statistical difference in pathological findings between Group A and Group B.

In comparison between Group B1 and B2, upgrade was more frequently observed in Group B1 than B2 with borderline significance (P = 0.075). Perineural infiltration and positive surgical margin rates in Group B1 were significantly higher than those in B2 (P < 0.05). Capsular invasion was presented in Group B1 but not in B2. The findings of Group B1 revealed worse pathological findings than that of B2.

Life-threatening cancer defined as ≥pT3 or ≥8 GS was found 1 out of 14 in Group A and 6 out of 28 in Group B.

**PSA Recurrence After RP**

PSA recurrence was found 3 out of 14 in Group A (21.4%), 7 out of 28 in Group B (25%). Among Group B, recurrence occurred 7 out of 17 in Group B1, on the other hand, no recurrence was observed in Group B2. Elapsed time from operation to recurrence was 8–17 month (median 13 month) in Group A and 5–38 month (median 18 month) in Group B.

**DISCUSSION**

Early stage and low-risk prostate cancer is increasing in Japan as was seen in Western countries. According to a recent report, 49% of screening-detected cancer will be defined as the indolent cancer (defined as organ-confined cancer of <0.5 ml and with no Gleason pattern 4 or 5) by using updating nomogram (12). Despite the increasing number of men with very favorable disease characteristics, the pattern of prostate cancer treatment appears to be more aggressive for one or two decades, and the rates of AS applications did not increased, even among low-risk patients aged ≥75 years (13). This is suggesting that not only patients but also physicians overestimate the seriousness of these low-risk cancers and lack the confidence in the accuracy of grading and staging. Because little is known about the natural history of prostate cancer stratified by risk, less
aggressive management has been resisted in many constituencies. Within this context, overdiagnosis and overtreatment is focusing nowadays. Klotz (14) has estimated that if all the patients who have good-risk and low-volume disease were offered RP compared with the strategy AS, the number-needed-to-treat would be $\approx 100$ for each patient who avoids a prostate cancer death. And also, it will be concluded that the proportion of those who die of disease is not likely to be significantly different from the proportion dying in spite of aggressive treatment of all good-risk patients at the time of diagnosis. To be prevalent of AS and to decrease the overdiagnosis or overtreatment, it is important to clarify whether delayed intervention in AS program is as safe as immediate treatment. Under these circumstance, some prospective studies are now in progress for clarifying the feasibility of AS [PRIAS, PIVOT (15), START (16) (17), ProtecT (18)].

For avoiding being missed opportunity for cure, prospective protocol-based AS programs are needed to optimize selection criteria and to find the appropriate trigger points for switching to active therapy. Among the triggers, pathological findings of prostate biopsy play a most valuable roll in selecting patients appropriate for AS. It is very important issue that the result of systematic prostate biopsy is usually underestimated. We previously reported that the pathological biopsy findings in patients who are eligible for our AS program were upgraded pathologically in 37% at re-biopsy in 1 year after enrollment (19). We know that there are substantial discrepancies between biopsy findings and RP specimens. A recent study evaluated the pathological outcomes of men meeting published criteria for AS who elected immediate RP to assess the risk of under grading and under staging in candidates for AS (20). Overall, 28% of the men experienced a Gleason upgrade, 21% had extracapsular extension and 11% had seminal vesicle involvement. It is estimated that in men qualifying based on published AS inclusion criteria, rates of upgrading varied between 23 and 35%, the incidence of extracapsular extension ranged from 7 to 19% and seminal vesicle involvement ranged from 2 to 9%. In the present study, 25 out of 42 (59.5%) were upgraded and 5 out of 42 (11.9%) were upstaged; however, there was no seminal vesicle invasion. These information as to the possibility of underestimation of biopsy is to be provided to patients at decision-making.

The results of this study show that the issue of underestimation in initial prostate biopsy was considerable problem. Some patients who initially classified into favorable risk actually harbor more aggressive disease that can be cured by
immediate radical treatment. A recent study (21) reported that the pathologic features and outcomes of patients treated at low PSA levels are favorable and similar for patients with PSA ≤2.5 versus 2.6–4.0. However, >50% of the former have potentially biologically unimportant cancer. More strict inclusion criteria in PSA threshold might be beneficial for detecting favorable cancer. On the contrary, Chun et al. (22) mentioned that despite highly favorable biopsy features, between 11 and 33% of men had unfavorable prostate cancer at RP and only a minority (13.4%) had pathologically confirmed insignificant prostate cancer. Neither clinically insignificant nor pathologically unfavorable features could be predicted with sufficient accuracy at clinical decision-making. Another group (23) also evaluated the ability of PSA density (PSAD) and biopsy features to predict pathologic outcomes, i.e. ‘insignificant’ prostate cancer in a contemporary RP population. Two hundred and seventy-four men underwent RP and had the required data for analysis, overall, by these criteria, 24.5% of patients were considered to have potentially ‘insignificant’ cancer preoperatively; whereas, only 2.6% had a so-called ‘insignificant’ tumor in the RP specimen. They concluded that a model including Gleason grade, PSAD and number of positive biopsy cores did not provide an accurate means of selecting patients for active monitoring in their patient cohort.

One of the solutions for underestimation in initial prostate biopsy is immediate repeat biopsy after initial diagnosis (24). Berglund et al. (6) showed that immediate repeat biopsy in cases of AS with selective delayed intervention resulted in 27% being upgraded or upstaged and those were more likely to show higher grade and stage disease at RP. The repeat biopsy has been recommended because it improved the discrimination of who are the best candidates for AS with selective delayed intervention.

Another potential solution is to increase the number of biopsy cores. The effect the number of biopsy cores taken has on the rate of clinically significant Gleason sum upgrading (GSU) in patients with low-risk prostate cancer is examined (25). Patients with low-risk prostate cancer assessed with fewer biopsy cores were at a substantially greater risk of GSU. It was concluded that the number of biopsy cores taken represents one of the foremost predictors of GSU and should be taken into consideration during clinical decision-making in patients who are candidates for watchful waiting, AS or brachytherapy.

Another problem beside inclusion criteria, how can we detect or predict clinical progression in AS program patients within curative window. PSA-kinetics, especially PSADT or prostate re-biopsy seem to be relevant [PRIAS (26)]. We previously reported that PSADT is varied in patients on AS program in Japan (19), the threshold of PSADT is varied between AS program. About the value of PSADT, Khatami et al. (27) reported that PSA relapse was observed in 9 of 70 patients who received RP during a mean follow-up of 37 months, and none of the 37 operated patients with a PSADT > 4 years had a PSA relapse. It seems that the threshold of PSADT might be reconsidered to discriminate aggressive cancer from moderate one.

In the present study, it was evaluated whether there are the differences in pathological findings between that of immediate RP group (Group A) and that of delayed RP group (Group B). But there were no pathological differences between two groups.

On the other hand, unfavorable pathological features of surgical specimens were more frequently observed in patients who underwent RP due to short PSADT or biopsy findings (B1) than those who underwent RP because of other reasons including patients’ preference (B2). Interestingly, among Group B, PSA recurrence occurred 7 out of 17 in Group B1 and no recurrence was observed in Group B2. From these results, our AS program could distinguish aggressive cancer from non-aggressive cancer to some extent by re-biopsy and PSADT measurement in the course of AS.

Concerning about the issue of dedifferentiation, from the results of current study, 16 out of 117 patients showed progression by repeat biopsy, and 19 out of 28 patients in Group B showed more than seven Gleason score in RP specimen. Although underestimation of initial biopsy might be one reason, there is the possibility that some of them had dedifferentiation during AS.

Five year AS-remaining rate in our study is 41.4%. This is relative lower rate than we expected. It is supposed that one of the reasons of low remaining rate is the low exposure rate of PSA screening in Japan. Because we have few dates about natural history or prognosis of the patients in AS program in the Japanese low-risk prostate cancer, not only patients but also physicians feel anxiety unnecessarily.

One limitation of our analysis is that the patients who underwent palliative surgery for difficult voiding, e.g. Holmium laser enucleation of prostate (HoLEP), trans urethral resection of prostate were excluded from our AS program at the point of operation. We have to follow-up the patients who underwent such a palliative intervention. Anyhow, it is revealed that patients suffering from difficult voiding due to the concomitant BPH are not small population.

CONCLUSION

Unfavorable pathological features of surgical specimens and PSA recurrence after operation were more frequently observed in patients who underwent RP due to on protocol triggers including short PSADT and re-biopsy findings than those who underwent RP because of off protocol reasons including patients’ preference and voiding difficulty due to lower urinary tract symptoms/BPH. Rates of unfavorable pathological features at RP that deviate initial selection criteria was high enough to support integration of frequent biopsies into AS program. Patient selection criteria and follow-up program should be established and be confirmed the safety of delayed intervention on AS program not only from the perspective of the patients but also physicians.
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Conflict of interest statement

None declared.

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