

Current status of active surveillance in prostate cancer

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Active surveillance (AS) is a management strategy involving close monitoring the course of disease with the expectation to intervene if the cancer progress, in a super-selected group of low-risk prostate cancer (PCa) patients. Determining AS candidates should be based on careful individualized weighing of numerous factors: life expectancy, general health condition, disease characteristics, potential side effects of treatment, and patient preference. Several protocols have been developed to determine insignificant PCa for choosing ideal AS candidates. Results regarding disease reclassification during AS have been also reported. In an effort to enhance accuracy during selection of AS candidate, there were several reports on using magnetic resonance imaging for prediction of insignificant PCa. Currently, there is an urgent need for further clinical studies regarding the criteria for recommending AS, the criteria for reclassification on AS, and the schedule for AS. Considering the racial differences in behavior of PCa between Western and Asian populations, more stringent AS protocols for Asian patients should be established from additional, well-designed, large clinical studies.

Keywords: Prostatectomy; Prostatic neoplasms; Watchful waiting

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ACTIVE SURVEILLANCE: BACKGROUND AND RATIONALE

Active surveillance (AS) is a management strategy in a superselect group of low-risk prostate cancer (PCa) patients involving close monitoring of the course of disease with the expectation to intervene if cancer progresses. By delaying intervention for indolent tumors and treating only when more clinically-significant PCa is detected, AS minimizes overtreatment. Compared with watchful waiting, which involves monitoring the course of PCa with the expectation of delivering palliative therapy for development

of symptoms, change in exam, or prostate specific antigen (PSA) that suggests symptoms are imminent, AS is mainly applicable to younger men with seemingly indolent cancer, with the goal of deferring treatment and its potential side effects (Table 1). Because such patients have a longer life expectancy, they should be followed closely, and treatment should start promptly before the cancer progresses so as not to miss the chance for cure.

Such a unique concept of treatment is based on concerns about overdiagnosis and overtreatment related to the increased diagnosis of PCa due to the widespread use of PSA for early detection or screening. The debate

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Table 1. Active surveillance versus watchful waiting

	Active surveillance	Watchful waiting
Treatment intent	Curative	Palliative
Follow-up	Predefined schedule	Patient-specific
Assessment/markers used	DRE, PSA, rebiopsy, optional MRI	Not predefined
Life-expectancy	>10 y	<10 y
Aim	Minimize treatment-related toxicity without compromising survival	Minimize treatment-related toxicity
Comments	Only for low-risk patients	Can apply to patients at all stages

DRE, digital rectal examination; PSA, prostate-specific antigen; MRI, magnetic resonance imaging.

regarding the need to diagnose and treat every man with PCa is originated from: the high prevalence of PCa on prostate autopsy and the discrepancy between incidence and mortality rates of PCa [1-4]. The controversy regarding the value of PSA screening for early detection of PCa [3-9] was emphasized by the Goteborg study, a subset of the European Randomized Study for Screening of Prostate Cancer (ERSPC) [10]. Although the study showed a 40% absolute cumulative risk reduction of PCa mortality (compared to ERSPC 20% and PLCO [Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial] 0%), 293 men needed to obtain screening visits and 12 needed to be diagnosed in order to prevent one PCa death. Moreover, the estimated probability of overtreatment ranged from 23% to 42% of all screen-detected cancers [11], and cancer detection was responsible for up to 12.3 years of lead-time bias [12].

CURRENT AS PROTOCOLS

In the 2015 National Comprehensive Cancer Network (NCCN) guidelines, AS is recommended in men with very-low-risk PCa (T1c, Gleason score [GS]≤6, PSA<10 ng/mL, fewer than three biopsy cores positive, ≤50% cancer in any core, PSA density [PSAD]<0.15 ng/mL/g) and life expectancy ≤20 years. The European Association of Urology guidelines [13] are similar: clinically confined PCa (T1–T2), GS≤6, three or fewer biopsies involved with cancer, ≤50% of each biopsy involved with cancer, and PSA<10 ng/mL.

The NCCN recommendation for follow-up schedule during AS includes PSA no more often than every 6 months unless clinically indicated, digital rectal examination (DRE) no more often than every 12 months unless clinically indicated, and repeat prostate biopsy considered annually to assess for disease progression (Biopsy should be repeated within 6 months of diagnosis if initial biopsy was <10 cores or assessment discordant; for example, palpable tumor contralateral to the side of positive biopsy). A repeat prostate biopsy is indicated when DRE change or PSA increase, although neither parameter is very reliable for detecting

PCa progression.

The panel recommends starting intervention when GS 4 or 5 cancer is found upon repeat prostate biopsy, when PCa is found in a greater number of prostate biopsies, or when PCa occupies a greater extent of the prostate biopsy, as these findings are regarded as cancer progression. Different criteria have been applied to define cancer progression [14], although most groups used the following criteria: PSA-doubling time (DT) with a cutoff ranging between ≤2 and ≤4 years, GS progression to ≥7 at rebiopsy (at intervals ranging from 1 to 4 years), PSA progression >10 ng/mL, although the role of PSA-DT in identifying the need for intervention has recently been challenged [15-17].

AS: ADVANTAGES AND DISADVANTAGES

The advantages of AS include: (1) avoiding the side effects of definitive therapy that may not be necessary; (2) maintaining quality of life and normal activities; (3) minimizing the risk of unnecessary treatment for small, indolent cancers; and (4) low initial costs. The disadvantages of AS include: (1) possibility of missing an opportunity for cure; (2) possibility of progression or metastasis of the cancer before treatment; (3) increased difficulty in the treatment of more aggressive cancer with greater side effects; (4) increased difficulty of the nerve-sparing technique during radical prostatectomy; (5) increased anxiety of living with untreated cancer; (6) need to examine and undergo frequent prostate biopsies; (7) uncertain long-term natural history of untreated PCa; and (8) undetermined timing and value of periodic imaging studies.

“INSIGNIFICANT PROSTATE CANCER”: APPLICATIONS

Patients with insignificant PCa might be ideal AS candidates, considering its indolent nature. Currently, there are no biological markers to clearly differentiate tumors that will progress or be indolent. Hence, statistical models

have been developed to predict tumor aggressiveness. Epstein et al. [18,19] suggested a model using preoperative clinical and pathologic features that can predict “insignificant PCa” (tumor volume <0.2 mL, GS <7, and organ-confined tumor). The preoperative parameters used in this model include no GS 4 or 5 in biopsy pathology, PSAD ≤ 0.1 ng/mL/g, less than three involved biopsy cores (with a minimum of six total cores being obtained), no core with >50% involvement or PSAD of 0.1 to 0.15 ng/mL/g, and cancer <3 mm in only one prostate biopsy core specimen. Stamey et al. [20] proposed that tumors <0.5 mL could probably be regarded as insignificant with respect to the long DT. Recently, Wolters et al. [21] challenged this widely accepted definition of insignificant PCa. The authors reported that clinically insignificant PCa might include index GS 6 and pT2 disease with index volume ≤ 1.3 mL and total volume ≤ 2.5 mL.

An appropriate, reliable definition of “insignificant PCa” is crucial for the following reasons. If the definition is too stringent, a significant proportion of insignificant PCa patients would be ineligible for AS and become the object of unnecessary intervention [22]. Conversely, without a stringent definition, treatment of low-risk PCa could probably be suboptimal, especially in this era of robotic surgery and focal therapies with relatively low morbidities.

However, there are numerous studies reporting the risks of unfavorable pathological features such as upgrading of GS and pathologic upstaging in prostatectomy specimens from patients who were initially regarded as having insignificant PCa according to preoperative Epstein criteria; the frequency of such features ranged from 16% to 42% [23]. The risk of GS upgrading was approximately 30% in a previous meta-analysis [24]. Other series [25,26] have shown that up to 8% of cancers that qualified as being insignificant according to the Epstein criteria were not organ-confined in the postoperative pathologic reports.

These findings suggested the need for caution against using this protocol as it is, and many variations regarding

this definition have been suggested (reviewed by Bastian et al. [27]).

VARIOUS AS PROTOCOLS

Several contemporary AS protocols are shown in Table 2 from Johns Hopkins Medical Institution (JHMI) [28], Memorial Sloan-Kettering Cancer Center (MSKCC) [29], University of California at San Francisco (UCSF) [30], Prostate Cancer Research International: Active Surveillance (PRIAS) [31], University of Miami (UM) [32], and One Asian protocol [33].

DISEASE RECLASSIFICATION

During AS, some of patients in the favorable-risk group are at risk, owing to pre-existing higher-risk disease that was not obvious at initial diagnosis or to disease progression over time. These patients can be detected by close monitoring such as serial measurement of PSA value or prostate biopsy and reclassified into the higher-risk group.

The Toronto group, JHMI group, and UCSF group recently reported the follow-up results of their AS patients (Table 3). Approximately one-third of these patients were reclassified as higher-risk and treated over time. The PCa mortality was quite low in an intermediate time frame (5–10 years). As for the active treatments during AS, radical prostatectomy or radiation therapy +/- androgen deprivation therapy was performed. In the Toronto group, the 5-year biochemical recurrence-free survival rates in the surgery and radiation treatment groups were only 62% and 43%, respectively. However, in the Johns Hopkins group [31], the 5-year biochemical recurrence-free survival rates were 96% and 75% for the surgery and radiation treatment groups, respectively. In addition, Ha et al. [36] reported their early experience with AS. They concluded PSA-DT was not associated with cancer progression, suggesting the need to

Table 2. Contemporary active surveillance protocols

Institution	Clinical stage	Gleason score	PSA (ng/mL)	PSAD	No. of positive cores	Single core involvement (%)
JHMI [28]	T1c	≤6	-	≤0.15	≤2	≤50
MSKCC [29]	T1c–T2a	≤6	≤10	-	≤3	≤50
UCSF [30]	T1c–T2	≤6	≤10	-	≤33% (at least 6)	≤50
PRIAS [31]	T1c–T2	≤6	≤10	≤0.2	≤2	-
UM [32]	T1c–T2	≤6	≤15	-	≤2	≤20
Takehi [33]	T1c	≤6	≤20	-	≤2	≤50

PSA, prostate specific antigen; PSAD, PSA density; JHMI, Johns Hopkins Medical Institution; MSKCC, Memorial Sloan-Kettering Cancer Center; UCSF, University of California at San Francisco; PRIAS, Prostate Cancer Research International: Active Surveillance; UM, University of Miami.

Table 3. Reports on disease reclassification during active surveillance

Variable	University of Toronto [34]	JHMI [28]	UCSF [35]
Median age (y)	70	66	63
No. of patients	450	769	513
Median follow-up (mo)	6.8	2.7	3.6
Conversion to intervention (%)	30	33	24
Median time to treatment (y)	-	2.2	3.5
Overall survival	68	98	98
Cancer-specific survival	97	100	100
Primary reason for treatment			
PSA increase	14 ^a	-	26 ^b
GS change	8	14	38
Anxiety	3	9	8

JHMI, Johns Hopkins Medical Institution; UCSF, University of California at San Francisco; PSA, prostate specific antigen; GS, Gleason score.

^a:PSA doubling time <3 y. ^b:PSA velocity >0.75 ng/mL/y.

perform regular prostate biopsy. They also emphasized that application of AS strategy to Korean patients should carry very careful considerations.

AS PROTOCOL IN AN ASIAN POPULATION

Considering the clinicopathological differences in PCa between Western and Korean populations [37], there have been concerns about the validity of Western AS protocols in Korean PCa patients [38,39]. Kim et al. [38] evaluated several Western AS protocols by applying these protocols to their RP series and compared the pre- and postoperative pathologic characteristics. Of 1,006 patients, GS upgrading occurred in 41.6% to 50.6%, extracapsular extension in 4.1% to 8.5%, seminal vesicle invasion in 0.5% to 1.6%, pathologic upstaging in 4.5% to 9.3%, and misclassification in 44.5% to 54.8% of patients. These data suggest the possibility of underestimation of Korean PCa by current Western AS protocols.

Several studies have compared the current Western AS protocols to determine their reliability [22,40-44]. Lee et al. [44] analyzed several contemporary AS protocols (from JHMI, UCSF, MSKCC, UM, and PRIAS) with regard to sensitivity, specificity, and accuracy in order to determine the validity of these criteria for Korean PCa patients. According to their analysis, the PRIAS protocol was most appropriate among five Western protocol for Korean men to determine AS candidates.

In 2013, Lim et al. [45] suggested new AS criteria for Korean patients: cT1-cT2, GS≤6, PSA≤10 ng/mL, ≤1 positive biopsy core, and ≤50% core involvement. KaKehi et al. [33] developed AS protocols for Japanese patients: T1c, PSA≤20 ng/mL, ≤2 positive cores, GS≤6, and ≤50% cancer involvement

in any of the positive cores. Goto et al. [43] reported that the JHMI and PRIAS criteria were most helpful for use in Japanese Pca patients. In addition, Jin et al. [46] reported the strong correlation between PSAD and GS upgrading after RP, emphasizing the use of PSAD for choosing ideal AS candidates. According to their analysis, the optimal PSAD cutoff value was 0.13 ng/mL².

AS PROTOCOL: USE OF MAGNETIC RESONANCE IMAGING

In an effort to enhance accuracy during selection of AS candidates, there have been several reports on the use of magnetic resonance imaging (MRI) for prediction of insignificant PCa. Some authors [47,48] have reported that the use of apparent diffusion coefficient from diffusion-weighted magnetic resonance imaging (DW-MRI) might be helpful for choosing AS candidates. Early experience supports the use of multiparametric MRI in biopsy protocols for better risk-stratification of patients on AS [49,50]. Recently, Park et al. [51] reported associations between adverse pathological features in PCa patients eligible for AS and clear tumor identification on 3.0-T multiparametric MRI (combination of T2WI, DCEI, and DWI). Lee et al. [52] reported preliminary results that a simple measurement of the diameter of a suspicious tumor lesion on DW-MRI improves the prediction of insignificant PCa. According to their study, the possibility of insignificant Pca increased when tumor diameter was smaller than 1 cm.

CONCLUSIONS

Determination of AS candidates should be based on

careful individualized weighing of numerous factors: life expectancy, general health condition, disease characteristics, potential side effects of treatment, and patient preference. The timing of intervention should be based on change in PSA or pathology or clinical disease progression. Patients with clinically localized PCa who are candidates for definitive treatment but choose AS should undergo regular follow-up. In addition, follow-up should be more rigorous in younger men than in older men due to the higher life expectancy in the former group.

Currently, NCCN panels emphasize the urgent need for further clinical studies regarding the criteria for recommending AS, the criteria for reclassification on AS, and the schedule for AS, especially as it is associated with prostate biopsy, which unfortunately come within an increasing burden. Literatures report that up to 7% of men undergoing prostate biopsy will experience side effects [7], those with urinary tract infection are often quinolone-resistant [53], and surgery may become difficult after multiple prostate biopsies [54].

Considering the racial differences in behavior of PCa between Western and Asian populations, more stringent AS protocols for Asian patients should be established from additional, well-designed, large clinical studies.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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