Asian Journal of Urology (2019) 6, 146–152

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Review

Contemporary approach to active surveillance for favorable risk prostate cancer

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Received 16 October 2018; accepted 5 November 2018
Available online 15 December 2018

KEYWORDS
Prostate cancer;
Active surveillance;
Watchful waiting;
Conservative management;
Low risk

Abstract The approach to favorable risk prostate cancer known as "active surveillance" was first described explicitly in 2002. This was a report of 250 patients managed with a strategy of expectant management, with serial prostate-specific antigen and periodic biopsy, and radical intervention advised for patients who were re-classified as higher risk. This was initiated as a prospective clinical trial, complete with informed consent, beginning in 2007. Thus, there are now 20 years of experience with this approach, which has become widely adopted around the world. In this chapter, we will summarize the biological basis for active surveillance, review the experience to date of the Toronto and Hopkins groups which have reported 15-year outcomes, describe the current approach to active surveillance in patients with Gleason score 3 + 3 or selected patients with Gleason score 3 + 4 with a low percentage of Gleason pattern 4 who may also be candidates, enhanced by the use of magnetic resonance imaging, and forecast future directions.

1. Introduction

Fifty percent of men diagnosed with prostate cancer by systematic biopsy are found to have low-risk disease, also called Gleason score 6 prostate cancer, or Grade Group 1. The 2011 United State Preventive Services Task Force (USPSTF) recommended against (prostate-specific antigen, PSA) screening, primarily reflecting the risks of overdiagnosis and overtreatment [1]. The main issue was a compelling concern about overtreatment of low risk disease. There is now an emerging consensus that most men with low-risk prostate cancer do not derive any meaningful benefit from radical treatment, and an initial conservative approach is warranted. The shift to expectant management has resulted in the USPSTF proposing to revise their recommendation regarding screening from "D" in 2011 to a "C" (neutral) in 2017 [2].

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Peer review under responsibility of Second Military Medical University.

https://doi.org/10.1016/j.ajur.2018.12.003

Prostate cancer develops in most men with age. In Caucasian men, the likelihood of harboring prostate cancer is approximately the age as a percentage, beginning in the 30s [3]. This trend has been confirmed in many autopsy studies of Caucasians, Asians, and other ethnic groups. These lesions are usually small (<1 mm^3) and low grade. In an autopsy study in Japanese and Russian men who died of other causes, about 35% of both groups harbored prostate cancer, and 50% of the Japanese men aged >70 years had Gleason score 7 or higher [4]. While the prevalence of histological prostate cancer was lower in Japanese men between the ages of 30 years and 60 years, there was essentially no difference in men older than 60 years.

2. Molecular hallmarks of prostate cancer

This disparity between the prevalence of histological prostate cancer and the lifetime risk of mortality from prostate cancer (3% in North America before the advent of screening, and approximately 2% more recently) emphasizes the risks of overdiagnosis and the value of conservative therapy for low-risk patients. Molecular and genetic analyses have shown that the hallmarks of cancer differ profoundly between the two commonest patterns of disease, Gleason score 3 and Gleason score 4. These hallmarks are a useful structure for determining the degree to which low grade prostate cancer (Gleason pattern 3) "looks" like a true malignancy [5]. In most cases, the molecular abnormalities associated with cancer are absent in Gleason pattern 3 and present in Gleason pattern 4 (Table 1). The differences are both qualitative and quantitative. It is remarkable how well the Gleason scoring system disaggregates prostate cancer between genetically normal and abnormal cells. According to those who knew him personally, Don Gleason himself thought that Gleason pattern 3 or less should not be called cancer.

The absence of genetic aberrations in Gleason pattern 3 is particularly true of genes regulating key oncogenic pathways [6]. Genes involved in proliferation, including *AKT* and *HER2neu*, are expressed normally in Gleason score 3 and abnormally expressed in Gleason score 4 (Table 1). Genes involved in cellular invasion and metastasis, and genes regulating the cell cycle transition are not overexpressed in Gleason score 3, but are in Gleason score 4. Genes associated with resistance to apoptosis, angiogenesis and the development of other pro-angiogenic factors, and genes involved in regulating cellular metabolism tend to be abnormally expressed in Gleason score 4 but not in Gleason score 3 [7–20].

Recent studies have indicated that the progression to higher grade cancer is characterized by both qualitative and quantitative genetic differences. For example, about 10% of Gleason pattern 3 cancers have a phosphatase and tensin homolog (PTEN) deletion. This is found much more commonly in Gleason score 3 pattern cells in men with co-existent Gleason pattern 4, *i.e.*, Gleason score 7 cancers [21]. This may indicate that a field defect is present, or that Gleason score 3 cells harbouring the PTEN deletion rapidly dedifferentiate to higher Gleason pattern. An alternative explanation is that the deleterious genetic alterations present in the higher grade cancers are transferred by exosomes into the lower grade cancers [22]. This phenomenon of inter- and intra-tumoral communication and influence through extracellular circulating exosomes may explain a number of otherwise hard to understand observations in the field, for example, the effect of treatment of the primary in patients with metastatic disease. Recent studies also suggest that PTEN deletion requires Myc activation to induce genomic instability and an aggressive phenotype [23].

2.1. Potential for metastasis

Gleason score 6 cancer has little or no metastatic potential. One study of 14 000 men with pathologically confirmed Gleason pattern 6, identified only 22 cases with lymph-node metastases [24]. All 22 men had higher grade cancer on re-examination of the tissue. Thus, the rate of lymph-node metastases in men whose surgical pathology contained no higher grade cancer was zero. Another study of 12 000 men treated with radical prostatectomy whose specimen had only Gleason score 6 cancer [25], found the prostate cancer mortality was 0.2% at 20 years. The few cases who had metastases had evidence of higher grade cancer on re-review. This low level of metastasis is remarkable given the imprecision and between observer variation in the assignment of Gleason score.

Co-existent higher grade cancer is common, but spontaneous grade progression (from Gleason score 3 to 4 or 5) is

Table 1 Gleason score 3 *vs.* 4 and hallmarks of cancer.

Pathway	Gleason score 3	Gleason score 4
EGF, EGFR [9]	No	Overexpressed
AKT, MAP2 kinase [8]	Expressed	Aberrant
HER2neu [9]	Expressed	Amplified
Insensitivity to growth inhibitory signals (cyclin D2, *etc.*) [10–12]	Expressed	Absent
Resisting apoptosis, BCL2 [13]	Negative	Strong expression
Absence of senescence, TMPRSS2-ERG [16–18]	ERG normal	Increased
VEGF, microvessel density, other pro-angiogenic factors [19,20]	Low expression	Increased
PTEN [21]	Present in 90%	Deleted in 70%–90%
Markers of tissue invasion and metastasis [14,15]	Normal	Overexpressed
Clinical evidence of metastasis/PCa mortality [23,24]	Virtually absent	Present

EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; MAP2, microtubule-associated protein 2; BCL2, B-cell lymphoma 2; TMPRSS2-ERG, transmembrane protease, serine 2-ERG; VEGF, vascular endothelial growth factor; PCa, prostate cancer; ERG, erythroblast transformation-specific-related gene; PTEN, phosphatase and tensin homolog.

uncommon. This has been modeled by several groups; the estimate is that 1%–2% of patients per year will undergo grade progression. In most cases, this occurs in the presence of high volume Gleason score 6 cancers [26].

2.2. Patient selection for active surveillance (AS)

Based on these concepts, AS should be offered to most men with Grade group 1 (Gleason score 6) prostate cancer. The limitation of this approach is misattribution of grade, that is, that 25%–30% of these men diagnosed on the basis of a systematic biopsy actually harbor higher grade cancer. While most of these misattributed cancers are Grade group 2 (Gleason score 3 + 4), and may still have a low metastatic potential, the presence of any Gleason pattern 4 cancer confers an increased risk of eventual metastasis. Thus the crux of managing men on AS is to evaluate the patient further for the presence of co-existent high grade cancer, and once higher grade cancer is excluded, monitoring them subsequently to ensure it does not develop.

The view that Gleason pattern 3 has little or no metastatic phenotype has had a significant impact on the management of patients with this cancer. Thus, there should be no lower age limit to entering a patient on AS. The quality of life benefits of maintaining normal erectile function and voiding function are greater in young men. Prostate cancers are not rare in young men; microfocal low-grade cancer is found at autopsy in around 40% of men in their 40s [3]. Finding small amounts of Gleason score 6 cancer on a transrectal ultrasound (TRUS)-guided biopsy cannot possibly mean that disease progression is inevitable. High-volume Gleason pattern 3 is important primarily as a marker for patients at higher risk for harbouring higher grade cancer. If highergrade cancer can be excluded in a patient with higher volume Gleason score 6 cancer (based on magnetic resonance imaging [MRI], targeted/template biopsies, and/or biomarkers), such patients are unlikely to require treatment. In rare instances, men under 55 years old present with extensive Gleason score 6 cancer. In these unusual cases, radical intervention, such as surgery, may be appropriate.

3. AS management

The clinical management of men on AS is as follows: Eligible patients are those with Gleason score 6 disease. Selected patients with Gleason score 3 + 4 cancers with a low percentage of pattern 4 may also be candidates. Patients are followed with serial PSA assessments and repeat biopsies. An initial confirmatory biopsy should be performed within the first 6–12 months, targeting those zones of the prostate that tend to be under-evaluated on the initial diagnostic biopsy. Since the lead time from diagnosis to clinical progression is usually long for low-risk disease, the concept is that delayed therapy at the first signs of risk reclassification will still be curative.

Following the initial assessment and confirmatory biopsy, patients should be followed with semi-annual PSA, annual digital rectal exam (DRE), and repeat biopsy and/or imaging at 3–5 year intervals. This interval depends on the patient's underlying risk factors and level of concern. Once the patient's life expectancy is less than 5–7 years (around age 80 years) in stable patients, follow-up should be limited to annual PSA.

An additional consideration is the patient in whom there may be a lower life-expectancy, either due to age or comorbidities. An example might be a patient with chronic obstructive pulmonary disease (COPD) or other serious comorbidity, with a higher-volume Gleason score 3 + 4 or 4 + 3 tumor. While there may be a greater risk of "disease progression" in such a patient, in most cases "progression" (rising PSA, for example) is not associated with any disease-related side effects. Consequential progression endpoints (pain, metastases, and death) are generally years away in such a patient.

Toxicity of treatment is also relevant. For example, consider the older patient with inflammatory bowel disease or another condition that could lead to severe side effects with radiation. If not a surgical candidate, the risk of disease progression and serious side effects of prostate cancer years later would need to be balanced against up-front serious consequences of radiotherapy; in such a situation, AS and delayed hormonal therapy (if necessary) may be a superior option.

MRI: While most guidelines consider the use of MRI in men on surveillance to be investigational, the National Institute for Clinical Excellence (NICE) guidelines from the UK mandate an MRI in all AS patients (Table 2).

Clearly, MRI effectively identifies large high grade cancers with high accuracy. These cancers are usually anterior, and may be missed by conventional TRUS guided biopsies. Thus an MRI with targeted biopsies of any area of restricted

Table 2 Summary of contemporary AS guidelines.

	Low-risk PCa	Intermediate risk	Tests	Other tests	5-ARI
Cancer Care Ontario CUAJ 2015 [56]	AS preferred management	Active treatment; AS for selected patients	PSA 3–6 months DRE 1 yr selected pts	MRI when clinical and path findings discordant	May have a role
ASCO JCO 2016 [57]	Same [1]	Same	Same	Other tests remain investigational	No clear role
NICE 2016 [58]	Same	Radical treatment for "disease progression" [2]	PSA 3–4 months, monitor kinetics	MRI at enrollment	
AUA 2017 [59]	Same	AS for selected patients	Same	Same	

PCa, prostate cancer; AS, active surveillance; DRE, digital rectal exam; MRI, magnetic resonance imaging; CUAJ, Canadian Urological Association Journal; ASCO, American Society of Clinical Oncology; JCO, Journal of Clinical Oncology; AUA, American Urological Association; 5-ARI, 5-alpha reductase inhibitors; NICE, National Institute for Clinical Excellence; PSA, prostate-specific antigen.

diffusion is likely to significantly enhance the early identification of higher grade cancer.

A Pirads 4—5 lesion has been reported to have a 90% positive predictive value for high-grade cancer in an AS cohort [27]. This abnormality in a patient on AS is very significant, and should result in a targeted biopsy. A recent large study comparing multiparametric MRI (mp-MRI) targeted biopsy to systematic biopsy reported 93% sensitivity for clinically significant cancer (compared to 48% with systematic biopsy) [28].

Can the biopsy be dispensed with if the MRI is normal? MRI is relatively ineffective at identifying small volume high grade cancers. The negative predictive value (NPV) of a normal MRI for Gleason score 7 or higher cancer is approximately 85%, although this figure varies between studies. This means that, in a patient at risk, 15% of those with a negative MRI will still be found to have significant cancer on systematic or template biopsies. In some patients with a positive MRI, systematic biopsies are positive despite negative targeted biopsies.

In our view, MRI should be viewed as a risk stratification parameter, much like PSA is today, but providing a much enhanced risk adjustment. Nomograms incorporating MRI to predict clinically significant cancer are in development [29]. Thus the patient on surveillance with a low PSA density, low cancer volume on initial diagnostic biopsy, and no other risk factors, whose MRI is negative, has less than a 5% chance of significant cancer. In contrast, those with positive risk factors, *i.e.* high PSA density, higher cancer volume, *etc*, should likely have systematic biopsies regardless of the MRI findings.

4. Biomarkers

Prospective AS cohorts now comprise >10 000 patients, thousands of whom have been followed for >10 years. Clinical parameters (PSA, PSA density, extent of disease on biopsy, race, and T-stage) allow for stratification for risk of co-existent highergrade disease. Monitoring low-risk patients on surveillance is associated with a risk of clinical progression of 0.2%—5% at 15 years. Therefore, the benefit to most patients of a biomarker to further stratify patients according to the risk of progression is modest.

However, selected patients, particularly those whose risk factors suggest they are at above average risk for higher-grade disease, may benefit from genomic testing. There are two potential benefits: Reassurance for those patients with a favorable genomic risk score that conservative management is likely to be safe, and earlier identification of those at risk for disease progression on AS who could benefit from treatment. Clinical studies have demonstrated a greater utilization of conservative management in those who have access to genomic testing.

As of the publication of this document, four genetic tissue assays have been approved by the Food and Drug Administration (FDA) to predict aggressive prostate cancer.

4.1. Genomic classifier (GC)

This is a 22-marker GC, based on RNA expression [30].

4.2. Genomic prostate score (GPS)

This assay incorporates 12 cancer genes that represent four biological pathways of prostate cancer oncogenesis: The androgen receptor pathway, cellular organization, stromal response, and proliferation. A 20-point increase in the GPS is associated with a statistically significantly increased risk of high-grade and/or non-organ-confined disease (odds ratio (OR) = 1.9, 95%CI: 1.3—2.9) [31—34].

4.3. Cell cycle progression (CCP)

This analyzes 31 cell cycle related genes and 15 housekeeping genes by quantitative RT-PCR [35,36]. The Transatlantic Prostate Group examined cell cycle progression (CCP) scores using needle biopsies of a conservatively managed prostate cancer cohort from the UK [37]. In this cohort, of 349 men managed without primary treatment, the cumulative incidence of death was increased among those with CCP scores >2 (19% of the population) compared with those with lower CCP scores. Patient outcomes could not be differentiated in those with lower CCP scores. The hazard ratio (HR) of prostate cancer death was 1.7 per unit increase in CCP score.

4.4. Confirm MDx

Confirm MDx tests for methylation of the *APC*, *GSTP1*, and *RASSF1* genes. Methylation alterations occur as a field defect, meaning that they may be seen in normal appearing cells in men with prostate cancer. There are two major limitations of tissue based genomic testing. The first is genetic heterogeneity. A recent study performed exome wide sequencing of individual prostate cancers microdissected from patients with multi-focality. The genes utilized in the GC, CCS, and CCP assays described above were then compared. Marked heterogeneity of the scores of all three tests between cancers from the same prostate was observed. The confounding problem of genetic heterogeneity of individual cancers in the same gland is considerable. A second important consideration in the Gleason score 6 population is the "Baysian" problem, related to low *a priori* risk. Thus if a patient with Gleason score 6 cancer has a 3% chance of metastases at 15 years, and a genetic biomarker has a positive predictive value (PPV) of 90% for significant cancer, the risk of overdiagnosis of significant cancer may be 3 times higher than the risk of metastases. Testing needs to be done in the "sweet spot" of the right patient with the right level of risk. Tenetic testing of the tissue should be restricted to AS candidates who are higher risk patients. This includes those with high cancer volume on biopsy, high PSA density, or patients with Gleason score 3 + 4 disease.

5. Expected outcomes

Death in men on AS occurs most commonly from cardiovascular disease, and death from prostate cancer is rare. In the most mature cohort [38], with a median follow-up of 9 years, the relative risk for non-prostate-cancer death was 10 times

that for prostate cancer mortality. There is no evidence that adverse psychological effects are significant in men on AS. Anxiety accompanies a diagnosis of prostate cancer, but seems to be influenced less by treatment. In the Scandinavian trial comparing radical prostatectomy to watchful waiting (without the option of definitive intervention), there was no difference in psychological functioning, anxiety, or depression between the two groups [39].

Nine prospective studies of AS have included about 10 000 men [38,40–48]. The largest most mature studies are summarized in Table 3. The limitation of these studies is the length of follow-up. One key study that generated a great deal of concern about conservative management in young patients in Sweden, reported that the HR for prostate cancer mortality in patients managed by watchful waiting was low for many years, but tripled after 15 years of follow-up [49]. These patients did not have the benefit of selective intervention. It will be 5–7 years before the most mature AS cohorts have a median of 15 years of follow-up. However, collectively, experience with AS includes 200 patients followed for more than 15 years. A few of these patients have had late disease progression, but there is no evidence of a sharp increase in mortality after 15 years.

AS inclusion criteria have varied between groups. Two groups, Toronto and Hopkins, represent the two extremes of an inclusive and restrictive approach, respectively. Both groups have reported 15-year outcomes and the comparison is instructive. The Toronto group took an inclusive approach, including all low risk and selected intermediate risk (Gleason score 7 or PSA >10 ng/mL) patients [43]. The actuarial 15-year prostate cancer mortality rate is 5%. Most of the metastatic cases were Gleason score 7 at diagnosis. The HR for metastasis at 15 years was 3.75 times greater for intermediate than low risk patients. The Gleason score 7 patients in particular were at risk; these patients had a 20% or greater metastasis rate at 15 years [50,51]. (Importantly, PSA >10 ng/mL had very little correlation with likelihood of metastasis). In contrast, the Hopkins group took a restrictive approach, offering surveillance only to patients who fulfilled the Epstein criteria (Gleason score 6 with no more than two positive cores, no core >50% involved, and PSA density <0.15 ng/mL/cc). The benefit was a prostate cancer mortality rate of 0.5% at 15 years. The cost was that only about 20% of newly diagnosed patients were eligible (*vs.* 50% in the Toronto cohort). Based on the data summarized in this chapter, there is an emerging consensus that the appropriate strategy lies between these two extremes. Most Gleason score 6 patients are appropriately managed with surveillance (*i.e.*, not just those fulfilling Epstein criteria), and surveillance should be offered only cautiously to Gleason score 7 patients. All of the mature surveillance cohorts reflect the pre-MRI/biomarker experience. While favorable, it is very likely that the incorporation of these augmented strategies will broaden the indications for surveillance while further reducing the already low rate of metastasis. The results of the Protect trial have recently been reported [52]. This was a randomized trial comparing active monitoring, radical prostatectomy, and external-beam radiotherapy [48]. The primary end point was prostate cancer mortality at 10 years. One thousand six hundred and forty-three men identified in a screening trial agreed to undergo randomization between the three arms. There were 17 prostate cancer-specific deaths overall, and there was no difference between the three groups in cause specific mortality (CSM) or overall survival (OS). The active monitoring group had more metastases (33 men; 6.3 events per 1000 person-years) *vs.* surgery (2.4 per 1000 person-years) or radiation (3.0 per 1000 person-years) [52]. The *p*-value was 0.004 for the overall comparison.

A key fact in understanding the significance of this important trial is that 77% of the patients had low grade cancer on biopsy at diagnosis. Patients with intermediate and high-risk cancer were included in the active monitoring arm. Given the low rate of metastasis, a higher rate of progression in the 23% of patients in the intermediate and high risk groups is more than sufficient to explain the increase in metastasis rate. Further, active monitoring in the protect trial did not mean AS as described above. Biopsies were not performed on an established schedule, and criteria for intervention were not clearly described. Quality of life on the active monitoring arm was the same or better in every domain measured [53].

6. PSA kinetics

The PRIAS multi-institutional AS registry recently reported that 20% of men having intervention did so based on a PSA doubling time <3 years [41]. The problem is that the correlation between PSA kinetics and adverse disease characteristics is not sufficiently reliable (due to lack of specificity) to be used as the basis for treatment decisions. An overview of this subject concluded that PSA kinetics did not add predictive value to absolute PSA concentration [54]. False-positive PSA triggers occurred in 50% of the patients with stable disease in the Toronto cohort at some point in time; this observation was noted a median of 3

Table 3 Results of mature active surveillance cohorts.

Study	*n*	Median follow-up (year)	Freedom from treatment	bNED after deferred treatment	PCa mortality %	OS
UCSF [41]	321	3.6	67% at 5 yr	1 recurrence at 3 yr	0	0
University of Toronto [38]	993	8.5	70% at 5 yr	5-yr bNED: 47%	5% at 15 yr	10-yr OS: 68%
Multicentre PRIAS [41]	2494	1.6	77% at 2 yr	No data	0	4-yr OS: 87%
University of Miami [42]	230	2.6	85.7% at 5 yr	No recurrences	0	No data
Johns Hopkins [43]	1298	5	59% at 5 yr	90.6% recurrence free at 2 yr	0.1% at 15 yr	15-yr OS: 69%
Royal Marsden [44]	471	5.7	70% at 5 yr	85% PSA-failure free at 5 yr	2% at 8 yr	9% at 8 yr

UCSF, University of California San Francisco; PRIAS, Prostate Cancer Research International Active Surveillance; bNED, biochemical no-evidence of disease; OS, overall survival; PCa, prostate cancer; PSA, prostate-specific antigen; yr, years.

times in these patients [55]. Thus, PSA kinetics are a useful guide for further evaluation, but not as the only trigger for intervention. Several groups have promoted guidelines for the use of AS. Recent guidelines from Cancer Care Ontario [56], ASCO [57], NICE [58], and AUA [59] are summarized in Table 2. It is reasonable to predict that, as data accumulates, both MRI and biomarkers will be increasingly utilized to enhance patient selection and outcome.

7. Conclusion

AS is an appealing approach for men diagnosed with low-risk prostate cancer, and is a compelling antidote to the overtreatment problem. MP-MRI and genetic biomarkers should reduce the need for serial systematic biopsies, and improve the early identification of occult higher risk disease and prediction of patients destined to have grade progression over time. All surveillance patients should have a confirmatory biopsy targeting the anterolateral horn and anterior prostate within 6—12 months. Subsequent biopsies should be done at 3—5-year intervals; these may be avoided if MP-MRI is negative in low-risk patients [60].

Approximately one quarter of men will eventually be upgraded, and treatment should be offered for most patients with upgraded disease. The outcome in patients managed in this way is very favorable. The risk of prostate cancer mortality is approximately 3% at 15 years, and this should drop further with the incorporation of the enhanced detection techniques described in this article.

Conflicts of interest

The author declares no conflict of interest.

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