PROSTATE CANCER

CHAPTER 6

Watchful Waiting
Active Surveillance

Abbreviations and Acronyms

%	= Percentage
5-ARIs	= 5-Alpha Reductase Inhibitors
AS	= Active Surveillance
BOO	= Bladder Outlet Obstruction
DRE	= Digital Rectal Examination
DT	= Doubling Time
ED	= Erectile Dysfunction
FDA	= Food And Drug Administration
GS	= Gleason Score
HT	=Hormonal Therapy
ng/Ml	= Nanogram per milliliter
No	=Number
PCa	= Prostate Cancer
Pts	= Patients
REDEEM	= The Reduction By Dutasteride Of Clinical Progression Events In Expectant Management Of Prostate Cancer
RT	= Radiotherapy
TURP	= Transurethral Resection Of Prostate
WW	= Watchful Waiting

Prostate cancer (PCa) is one of the leading causes of morbidity and mortality around the world[1,2,3].Fortunately because of widespread use of PSA, prostate cancer is increasingly diagnosed at earlier stages, often when it is still localized [1,2].

Watchful waiting (WW), active surveillance (AS), brachytherapy, external beam radiotherapy, and radical prostatectomy and some other modalities, which will be discussed later, are different options for the patients. Final choice is determined by disease characteristics and patients decision.

Men with Gleason score (GS) 2-4 disease are at little risk of death from prostate cancer within 15 years of diagnosis[4]. On the other hand, men with Gleason score 7-10 are at high risk of death from prostate cancer if treated conservatively, even if they are 74 years old[4]. Patients with Gleason score 5-6 are at modest risk of death from this disease[4].

Watchful waiting is an active decision not to treat the patient. The term was first used in 1990s and characterizes the conservative management of prostate cancer until the development of local or systemic progression. At that point the patient would be treated palliatively[5]. Watchful waiting is a reasonable option for patients with a life expectancy of less than 10 years and clinically localized, well- moderately differentiated prostate cancer[6].

Active Surveillance is a different scenario and should not be confused with watchful waiting (figure 1). Active surveillance which was first described in 2002 is now an accepted management strategy for men with low-risk prostate cancer[5]. It is a modality which can be offered to some patients with clinically localized prostate cancer who are candidate for definitive treatment[7]. In other words, we have to offer the option of active surveillance together with other options like radical prostatectomy, brachytherapy and external beam radiotherapy to appropriate, low risk patients.

Section 1
Watchful Waiting

Watchful waiting is considered in older men with localized prostate cancer who have limited life expectancies and cancer with Gleason score of ≤7 who are not candidates for definitive therapies or active surveillance especially if clinical stage and PSA values are favorable[6, 8]. Candidate patients are older than 70 and have a life expectancy of less than 10 years[6, 8]. Appropriate patients are asymptomatic and have a PSA value of < 50 ng/Ml and PSA DT > 12 months [6, 8, 9.] PSA monitoring is less important here than other programs like active surveillance and therapeutic modalities. There is no need for repeat prostate biopsy[6, 8].

Palliative measures will be done at time of symptomatic disease progression. These measures include hormonal therapy, palliative radiotherapy especially to address metastatic lesions and TURP or similar procedures to address urinary tract obstruction [5, 6, 8].

Candidate patients' characteristics, monitoring and treatment policies of this program have been summarized in the tables 1-3.

Table1- Criteria for patients for whom watchful waiting may be suitable

Parameter	Remarks
Age	>70
Life expectancy	<10
Clinical findings	Asymptomatic
PSA	PSA < 50 ng/mL PSA DT > 12 months
Gleason score	≤7
Stage	Any T

Table 2-Patients monitoring policies during watchful waiting program

Parameter	Remarks
PSA	less important
Repeat biopsy	No

Table3- Treatment policies in watchful waiting program

Parameter	Remarks
Indication	Symptomatic disease progression
Timing	Delayed
Intent	Palliative
Modality	TURP or other procedures for BOO HT RT for the palliation of metastatic lesions

Section 2
Active Surveillance

Active surveillance is an accepted management policy for men with low-risk localized prostate cancer[5].The goal of this strategy is to avoid over treatment in majority of candidates and to provide active treatment just in selected patients with progressive disease[10]. The most appreciable benefit of this method is the reduction of morbidity associated with treatment options by delaying or avoiding them[5].The most important risk associated with active surveillance is disease advancement and need for adjuvant treatment[5].

Results of large prospective series show that only 14-32% of patients need active treatment at 5-10 years[5, 11-19].Studies have also reported a disease-specific survival of 97-100% at 10 years[5].

Appropriate patient selection criteria and triggers for active treatment are important basis of active surveillance protocol[5]. Patients should also follow the scheduled surveillance policy which includes PSA tests, DRE examinations and repeat biopsies closely. In other words, patients' compliance with scheduled surveillance protocol is also an important factor. PSADT, PSA velocity and result of repeat prostate biopsy are the most commonly used items for initiation of active treatment[5].

Definitive therapy is advised to men who show signs of cancer progression[6]. These therapies appear to be effective in the majority of patients[6]. Active treatment should be offered to patients as soon as disease progression is identified.

Risks and benefits, outcomes, candidate patients' characteristics, active surveillance protocol, indications for initiation of treatment and treatment policies have been summarized in the figures 2 and 3 and tables 4-7 [5, 6,9,10].

Figure 2 –Risks and benefits of active surveillance

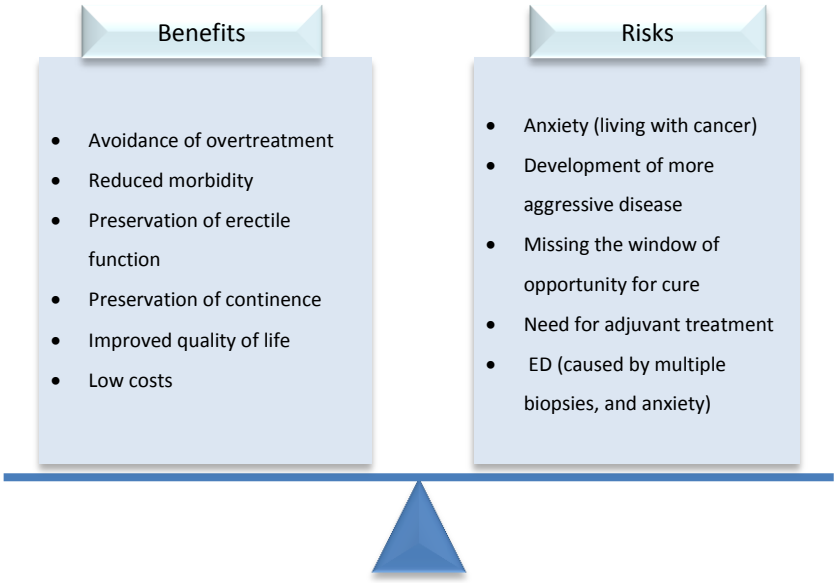


Figure 3- Outcomes of active surveillance

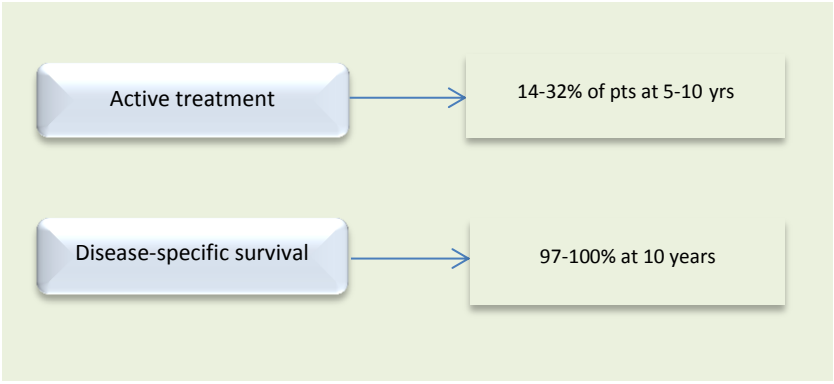


Table4- Appropriate patients for active surveillance

Parameter	Remarks
Age	50-80 year
PSA	≤10–15
T stage	T1c*
GS	≤3 + 3 = 6**
No and % of positive cores	≤2 (of 8–12 cores) < 50% cancer per biopsy

*T2a is considered by some groups.

**Gleason score 7 in men over 70 years old is considered by some groups.

Table5- Active surveillance protocol (University of Toronto)

Parameter	Remarks
PSA	3 monthly PSA for 2 years 6 monthly PSA thereafter
DRE	6 monthly DRE for 2 Annual DRE thereafter
Prostate biopsy	6–12 months in the first year Every 2–3 years thereafter

Table6- Indications for initiation of active treatment

Parameter	Remarks
PSA	PSADT <3 years PSA velocity> 0.75 ng/ml per year
Repeat biopsy	Surveillance biopsy breaching selection criteria
Others	Patient request

Table 7- Treatment policies in active surveillance

Parameter	Remarks
Timing	Early (as soon as progression is established)
Modalities	Definitive treatment including radical prostatectomy

Magnetic Resonance Imaging

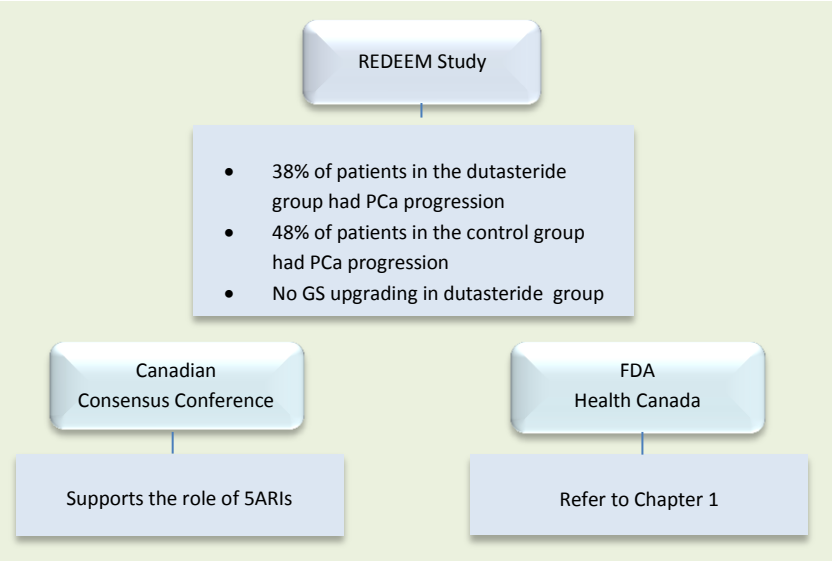
MRI is the best imaging modality for localization and local staging of prostate cancer[9, 20]. This ability can be used to direct prostate biopsy. In a study which was performed in university of Toronto, MRI revealed unrecognized significant lesions in 22% of patients and biopsy of these areas showed that 17.85% of cases were no longer fulfilling criteria for Active surveillance[21]. This study shows that MR imaging of prostate has a high yield for predicting reclassification among men who elect active surveillance[21].In other words, MRI may help to better localize prostate cancer in some patients who are on active surveillance and may have a role to avoid misclassification on repeat prostate biopsy[22].

5α-Reductase Inhibitors

5-ARIs role in chemoprevention of prostate cancer has been discussed in details in chapter 1. The role of these agents for men on active surveillance is a new avenue for research[5]. Current data show that the 5-ARIs are associated with a significantly lower rate of pathologic progression and abandonment of active surveillance[23]. REDEEM study showed that dutasteride could provide a beneficial adjunct to active surveillance for men with low-risk prostate cancer[24]. By 3 years, 54 (38%) of 144 men in the

dutasteride group and 70 (48%) of 145 controls had prostate cancer progression[24]. There was no evidence of Gleason score upgrading over time among men on dutasteride therapy[24]. During Canadian consensus conference about the role of 5ARIs, consensus was attained about the role of these agents in active surveillance[25]. The conference concludes there are data to support the role of 5ARIs in maintenance of active surveillance patients with prostate cancer although this issue is still investigational[25]. REDEEM study results, Canadian consensus conference remarks and some other related subjects have been summarized in figure-4.

Figure 4- 5-ARIs role in active surveillance



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