Active Surveillance for Favorable Risk Prostate Cancer: Background, Patient Selection, Triggers for Intervention, and Outcomes

7

Laurence Klotz

Contents

7.1 Introduction

Modern medicine, with its emphasis on early detection of disease, has enhanced the health of men and women throughout the world. However, early detection of disease carries with it a significant risk of overdetection of conditions that, although they fulfill pathological or clinical criteria for disease, pose little or no threat to the patient.

With the advent of increasingly sensitive and widely used diagnostic testing, cancer overdiagnosis in particular has emerged as a problem in multiple organ sites. Welch and Black (2010) recently estimated that the "overdiagnosis" rates for prostate, thyroid, and breast cancer, if the entire reservoir of disease were being detected, are 87–94%, 99.7–99.9%, and 43–90%, respectively. Those estimates reflect the high prevalence of microfocal disease in the healthy population (30–70% for prostate, 36–100% for thyroid, and 7–39% for breast cancer).

Because of the very high incidence of latent prostate cancer in aging men, the availability of the PSA test, and the long-term effects of definitive therapy, this has the greatest ramifications in the case of prostate cancer.

Screening for prostate cancer with prostate-specific antigen (PSA) is widely used in North America and Europe. Compared to clinical diagnosis, it results in the identification of potentially lethal prostate cancer at a much more curable stage. The widespread use of PSA has been associated with significant falls in prostate cancer mortality (Bray et al. 2010). The cost, however, is

L. Klotz, M.D.
Department of Surgery, Sunnybrook Health Sciences Centre, University of Toronto,
2075 Bayview Ave.#MG408, Toronto,
ON M4N 3M5, Canada
e-mail: laurence.klotz@sunnybrook.ca

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a very high rate of diagnosis—and treatment—of prostate cancer.

The recently published European Randomized Trial of Screening for Prostate Cancer (ERSPC) reported that, in 180,000 men randomized either to PSA screening every 4 years or to usual care, prostate cancer mortality was reduced by 20% (Schroder et al. 2009). A more recent randomized screening study from Goteborg (Hugosson et al. 2010) estimated the mortality reduction with screening at 50%. The number needed to treat for each prostate cancer death avoided in ERSPC was 48. It is widely anticipated that this NNT figure will fall with longer follow-up. Indeed, the NNT in the Goteborg study was 12. However, most patients dying of prostate cancer had intermediate- or high-grade disease (Van den Bergh et al. 2010a and 2010b). The number needed to treat with low-grade, small-volume prostate cancer for each death avoided is almost certainly higher.

Despite randomized controlled trials demonstrating survival benefits for prostate cancer screening among men with good life expectancy, the "harms of detection," primarily those related to overtreatment, underlie the negative assessments of screening promulgated by the U.S. Preventive Services Task Force (http://www.uspreventiveservicestaskforce.org/uspstf12/prostate/prostateart.htm) and others. Although the new recommendation by the American Urological Association to begin screening at age 40 for most men (Greene et al. 2009) might be expected to identify a higher proportion of lethal tumors at an earlier, curable stage, it will likely be associated with risks of further overdiagnosis of indolent tumors among men at even younger ages. The implication is that treatment must be applied selectively, and the timing and aggressiveness of treatment should reflect disease and patient characteristics.

Much recent evidence suggests that patients diagnosed with low-grade cancer who go on to die of disease have been undergraded at the original biopsy and in fact harbored higher grade cancer (Klotz et al. 2010). The likelihood of "true" microfocal low-grade disease actually progressing to metastatic disease appears to be extremely low (Eggener et al. 2011).

The condition of most men with favorable-risk prostate cancer is far removed from the consequences of a rampaging, aggressive disease. The majority of these men are not destined to die of their disease, even in the absence of treatment. Unfortunately, most of these patients are treated radically and are exposed to the risk of significant side effects. A selective approach to treatment is therefore appealing. The concept is to identify the subset that harbors more aggressive disease early enough that curative therapy is still a possibility, thereby allowing the others to enjoy improved quality of life, free from the side effects of treatment.

This review article summarizes the evidence supporting active surveillance and the current approach to this management strategy, including the roles of serial biopsy, PSA kinetics, and MR imaging.

7.2 Definitions

A key concept is the pathologic definition of clinically insignificant prostate cancer. For 30 years, this has been defined as Gleason 6 or less prostate cancer with a volume <0.5 cc, based on work by T. Stamey on cystoprostatectomy specimens (Kabalin et al. 1989). There is much evidence that this is an overly stringent definition. Recently, the ERSPC group performed a similar analysis based on the ERSPC patients (Wolters et al. 2011). Their conclusion was that the threshold for clinically insignificant disease was a cancer volume <1.3 cc. This has major implications for the use of MRI and other imaging modalities.

An emerging consensus therefore supports deferring treatment initially for a growing proportion of men diagnosed with low-risk (i.e., low volume, stage, and grade) prostate cancer. Under the management strategy of active surveillance, men are followed carefully with serial PSA assessments, repeat biopsies, and other tests intended to identify early signs of progression. The term "active surveillance" has supplanted "watchful waiting," but the two are not synonymous. The latter term generally applied to older men with significant comorbidity; they were advised to defer treatment unless symptoms developed, at which point palliative androgen deprivation could be offered. Active surveillance, on the other hand, rests on the presumptions that

Table 7.1 Summary of prospective active surveillance Cohorts

Author (Year)	*N*	Median F/U months	pT3 in RP pts	OS	CSS
Van As 2007	326	22	8/18 (44%)	98	100
Carter 2007	407	41	10/49 (20%)	98	100
Van den Bergh 2009	533–1,000	48	4/24 (17%)	90	99
Soloway 2008	99	45	0/2	100	100
Roemeling 2007	278	41		89	100
Khatami 2006	270	63		Not stated	100
Klotz 2010	452	73	14/24 (58%)	82	97@10 year
Total	2,130–3,000	43		90	99.7

the lead time from diagnosis to clinical progression is usually long for low-risk disease (Draisma et al. 2009) and that at the first signs of higher risk disease, the cancer can be treated, very likely well within the window of opportunity for cure. The distinction is particularly important in that neither oncologic nor quality of life outcomes from patients assigned to observation in older randomized trials (Bill-Axelson et al. 2011; Klotz and Thompson 2011), nor those identified in population-based registries as receiving conservative management (Johansson et al. 1997), can be considered representative of those expected with contemporary active surveillance.

Definition: Active surveillance in the context of localized prostate cancer is defined as initial expectant management, with close follow-up, and selective delayed intervention for the subset of patients reclassified over time as at higher risk for progression, based on clinical, pathological, or molecular parameters.

7.3 Experience with active surveillance

Table 7.1 summarizes the published experience with active surveillance, comprising more than 2,900 patients (Van As and Parker 2007; Carter et al. 2007; van den Bergh et al. 2009; Soloway et al. 2008; Roemeling et al. 2007; Khatami and Hugusson 2006; Klotz et al. 2010). Certain observations emerge from these data.

Over time, approximately one third of patients will be reclassified as higher risk for progression and will be treated. This proportion depends on how stringently patients are evaluated at baseline, how "liberal" the inclusion criteria for surveillance are, and how quick the clinician is to pull the trigger for treatment. A very stringent approach, restricting surveillance to men who have had extended biopsies with only one or two positive cores with minimal disease on those cores, will likely identify a cohort more likely to remain untreated. This will also mean that many men with indolent disease will not be offered surveillance.

In most cases that are reclassified as higher risk, the reclassification is due to upgrading at the time of repeat biopsy. This upgrading is not time dependent, suggesting strongly that it is due to more accurate sampling rather than true biologic progression. After an initial extended biopsy (10–14 cores), approximately 25% of patients will be found to have higher grade cancer on repeat biopsy. More than 90% of these are Gleason 3+4.

In the intermediate time frame (5–15 years), prostate cancer mortality is exceptionally low. To date, in the collected series, approximately 250 patients have been followed for between 10 and 15 years. The prostate cancer mortality in this group is also low. To date, none of the prostate cancer deaths in men on surveillance have occurred after the 10-year time point. The Toronto group has reported outcomes in the 30% of patients in that cohort treated radically. In that group, the PSA recurrence rate was 50%, representing 15% of the total cohort. Among the 453 patients in the cohort, the actuarial 10-year prostate cancer survival is 97%.

In most men on prostate cancer surveillance, mortality comes from other causes. In the most mature cohort (Toronto) (Klotz et al. 2010), with a median follow-up of 8 years, the relative risk for non-prostate-cancer death was 19 times that for

prostate-cancer mortality. Although prostate cancer mortality is likely to increase as the surveillance cohorts mature, so will non-prostate-cancer mortality. It is very plausible that the foregoing ratio will remain relatively constant.

The relative risk of prostate cancer in comparison with other-cause mortality is directly correlated with the age of the patients at diagnosis—insofar as the risk of other-cause mortality is a function of age. In men under 70 years of age, the cumulative hazard ratio for non-prostate to prostate cancer death was 9:1.

The limitation of these studies is the length of follow-up relative to the natural history of prostate cancer. It will require another 5–7 years before the most mature of these studies will have a median 15 years of follow-up. Nonetheless, the results to date are extremely encouraging.

Recently, the critically important Scandinavian trial of radical prostatectomy vs. watchful waiting reported their third update of overall and disease specific survival (Bill-Axelson et al. 2011). The magnitude of reduction in the rate of metastases and mortality in the "low-risk" group in this study is surprising, given the favorable outcomes reported above. These "low-risk" patients were clearly a heterogeneous group with many aggressive cancers. We have superimposed the data on prostate-cancer mortality in this study over those from the Toronto active surveillance cohort (Fig. 7.1) (Klotz and Thompson 2011). The differences are striking. The 10-year actuarial mortality from prostate cancer in the surveillance cohort is 3%, as compared with 8% in the watchful waiting group and 5% in the radical-prostatectomy group in the Scandinavian study. The favorable risk patients in the study by Bill-Axelson et al. differ from those in the Toronto surveillance cohort. Only 12% of the patients in the Scandinavian trial were diagnosed by means of PSA screening (stage T1c). Fine-needle aspiration or sextant biopsies, which can miss substantial cancers, were performed in the Scandinavian trial. Sampling with 10–12 cores, with confirmatory biopsies within 1 year, was performed in the Toronto cohort. Delayed curative therapy was available only in the surveillance cohort. The benefit of radical prostatectomy in low-risk patients should be extrapolated with caution to current low-risk screening-detected patients.

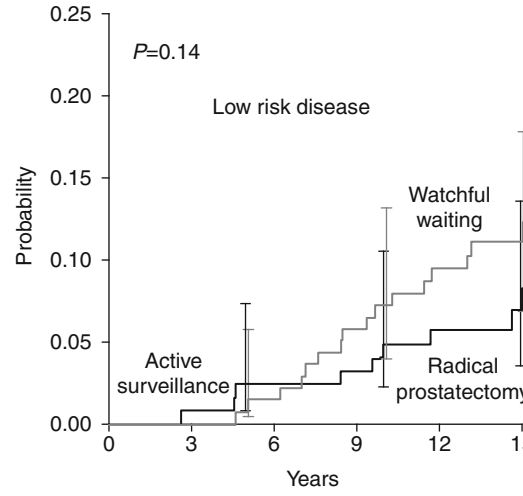

Fig. 7.1 Superimposition of Toronto active surveillance mortality over Scandinavian radical prostatectomy vs. watchful waiting mortality

7.4 Follow-up strategies

A number of recent publications have compared the pathologic findings at radical prostatectomy in men who fulfilled the D'Amico criteria for favorable risk prostate cancer (Oliveira et al. 2010; Kane et al. 2010; Raventós et al. 2010; Ploussard et al. 2010; Thaxton et al. 2010; Smaldone et al. 2010; Davis et al. 2010; Duffield et al. 2009; Mufarrij et al. 2010). Between 6% and 28% percent of men are upgraded to Gleason 3+4 or higher, and 15–20% have extracapsular extension. Several recent studies have indicated that, in most of the favorable risk patients with microfocal disease on biopsy harboring large-volume cancers, the occult cancers were anterior. This is logical given the posterior approach to biopsy taken with TRUS. This upgrading is thus primarily due to sampling error on the original biopsy rather than true grade progression over time. The implication is that the prostate must be characterized as carefully as possible after a diagnosis of favorable risk prostate cancer in order to identify the subset with adverse features early. How to do this most effectively is a matter of debate.

Biopsy: All patients contemplating surveillance must have a confirmatory biopsy within 12 months of the original biopsy. This biopsy should specifically target the anterior prostate

Table 7.2 Triggers for Intervention in surveillance series

	Klotz et al. (2010)	Van As et al. (2007)	Van den Bergh et al. (2009)	Soloway et al. (2008)	Carter et al. (2007)	Cooperberg et al. (2011)
PSA kinetics	DT < 3 years	PSA velocity <1 ng/ml/year	PSA DT < 3 years			<0.75 ng/ml/year
Grade progression		≥4 + 3 or >50% core	≥3 + 4 or >2 cores	≥3 + 4 or >2 cores	≥3 + 4 or >2 cores or >50% core	
Clinical progression	>50% increase in mass		>T2			

and anterolateral horn, as well as the traditional posterior peripheral zone.

If the confirmatory biopsy is negative or shows microfocal Gleason 6 disease, subsequent biopsies should be performed every 3–4 years, depending on PSA kinetics and/or clinical examination of the prostate. At age 80, biopsies may be discontinued (due to diminishing benefit of treatment of early prostate cancer) unless there are striking changes in PSA or prostate examination.

PSA should be performed every 3 months for 2 years and then every 6 months indefinitely. PSA doubling time or velocity should be calculated based, preferably, on 8–9 data points over a 2-year period. A PSA doubling time of >3 years is considered "stable," and such patients should be managed with ongoing surveillance unless there is a change in Gleason grade on biopsy.

In several of the published series, PSA doubling time or velocity has been used as a trigger for definitive intervention Table 7.2 (Klotz et al. 2010; Van As and Parker 2007; Carter et al. 2007; van den Bergh et al. 2009; Soloway et al. 2008; Cooperberg et al. 2011). A short doubling time and/or a PSA velocity >2.0 ng/ml/year is associated with a worse prognosis in many prostate cancer states. In men with an intact androgen axis, progression to metastatic disease is almost always accompanied by a substantial increase in PSA. In the Toronto cohort, 100% of patients who have progressed to metastatic disease have had a PSA doubling time <2 years (Loblaw et al. 2010). However, some recent studies have questioned the correlation between PSA kinetics and adverse disease characteristics (Ross et al. 2010). A recent overview of this subject concluded that PSA kinetics, although predictive, did not add predictive value to absolute PSA and should not be used for decision making in localized prostate cancer (Vickers 2008). Thus, our current approach is to use PSA kinetics as a guide for further evaluation rather than a trigger for intervention on its own.

Nonetheless, a common dilemma in managing surveillance patients occurs when the biopsy shows only minimal Gleason 6 disease, but the PSA is rising rapidly. MRI represents a way out of this dilemma.

Thus, the current recommendation is to use PSA kinetics as a trigger for further diagnostic tests, including MRI and/or repeat biopsy. The absence of a lesion has a negative predictive value of 94–97% for absence of high-grade cancer (Delongchamps et al. 2011), and these patients should remain on surveillance. The finding of a large lesion on MRI with definitive cancer characteristics in a patient with proven prostate cancer has had a very high predictive value for clinically significant prostate cancer (Villeirs et al. 2011; Fütterer et al. 2009). Thus, this finding in a patient on surveillance should trigger either a targeted biopsy or definitive intervention. An equivocal lesion should trigger a repeat biopsy of the lesion.

7.5 Summary and Conclusion

Active surveillance for localized prostate cancer entails initial expectant management rather than immediate therapy, with curative-intent treatment deferred until there is evidence that the patient is at increased risk for disease progression. This approach is a rational response to the clearly documented risks of overdiagnosis and overtreatment of favorable risk prostate cancer, which in most cases

poses little or no threat to the patient. It is based upon the prolonged natural history of prostate cancer and is an attempt to balance the risks and side effects of overtreatment against the possibility of disease progression and a lost opportunity for cure. Favorable risk prostate cancer is more accurately viewed as one of multiple risk factors for the presence of higher grade prostate cancer. Like PIN and ASAP, it should be managed with close follow-up but without radical intervention unless there is clear evidence of more aggressive disease.

For men who place a high premium on avoiding the side effects of definitive treatment and who accept the slight increased risk of late metastasis or death, active surveillance is recommended. The optimal criteria for patient selection have not been defined but include the clinical stage, serum PSA, and Gleason score from the diagnostic biopsy.

Eligibility criteria consist of clinical stage T1c or T2a prostate cancer, a Gleason score ≤ 6, and a serum PSA ≤ 10 ng/ml. For patients over age 70 years, less stringent criteria can be applied (Gleason score ≤ 7 [3 + 4] and/or PSA ≤ 15 ng/ml). An important corollary is that young patients who have microfocal disease only can be managed with an initial surveillance approach. The quality of life benefits of maintaining normal erectile and voiding function are enhanced in young men. The risk of progression of low-grade disease is low.

The optimal schedule for monitoring includes measurement of the serum PSA at 3-month intervals to calculate the PSA doubling time. We use a doubling time of 3 years or less as a flag for higher risk disease. In the past, these patients were offered radical intervention. Currently, a short PSA doubling time mandates multiparametric MRI, with further management depending on the imaging results. This approach requires further validation.

A repeat prostate biopsy is performed at 1 year to rule out higher grade disease that may have been missed on the original biopsy. Following this, biopsies are repeated every 3–4 years (until age 80) to look for evidence of biologic progression to Gleason 4 + 3 or higher.

This approach is associated with an extremely small risk of prostate cancer mortality, currently estimated at 3% at 10 years. Recognizing that not all prostate cancer deaths are preventable even with aggressive treatment of all patients, it is likely that the number of patients who will succumb "unnecessarily" is smaller, likely one in several hundred. Further, these "preventable" deaths occur many years after diagnosis, in many cases close to the end of the patient's natural life. Compared to the morbidity associated with treating all such patients radically, this is a small price to pay and makes active surveillance an easy choice for well-informed patients.

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