Active surveillance for prostate cancer: patient selection and management

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ABSTRACT

Screening for prostate cancer using prostate-specific antigen (PSA) has been appealing. However, the significant associated decline in prostate cancer mortality comes at the cost of a very high rate of diagnosis, and many patients with indolent, non-life-threatening cancer are exposed to the risk of significant side effects from radical treatment. Most men with favourable-risk prostate cancer are not destined to die of their disease, even in the absence of treatment. The challenge is to identify the subset that harbour 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 article reviews current research into active surveillance in favourable-risk disease and some of the issues that arise when prostate cancer is monitored rather than being treated immediately.

KEY WORDS

Cancer screening, PSA, overdiagnosis, active surveillance

1. INTRODUCTION

Screening for prostate-specific antigen (PSA) is appealing because, compared with historical approaches, it results in the diagnosis 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 [1]. The cost, however, is a very high rate of diagnosis—and treatment—of prostate cancer. Many patients with indolent cancers who are not destined to die or have other clinical problems from their disease are treated radically and exposed to the risk of significant side effects.

2. DISCUSSION

The phenomenon of cancer overdiagnosis is a general one in oncology. Welch and Black [2] 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).

According to recent data from the U.S. Surveillance, Epidemiology and End Results program, new cases of cancers of the prostate, breast, thyroid, kidney, and skin (melanoma) have increased substantially in number between 1975 and 2005. A true increase in cancers should be accompanied by an increase in death rates. In fact, mortality rates for all the foregoing cancers have remained stable or declined while, at the same time, the imaging studies performed in North America have sharply increased in number. The stable or falling mortality rates for those cancers suggest that overdiagnosis is accounting for a significant proportion of the additional cases.

The biology underlying the nonprogression of these "latent" cancers is likely complex. Some may lack telomerase or other "immortalizing" pathways, resulting in cell senescence. Others may lack vascular endothelial growth factor and fail to induce angiogenesis, limiting their proliferation potential. Micronutrient ingestion or hormonal influences may induce differentiation or apoptosis. A slow-growing cancer may simply not proliferate fast enough to become clinically apparent before the patient dies of other causes. Regardless, the phenomenon of histologic cancer having a benign, nonprogressive, non-proliferating phenotype is well recognized in many cancer sites.

Because of wide utilization of the PSA test, acceptance of falling thresholds for biopsy, high prevalence of microfocal disease in the aging population, and older age at diagnosis compared with other cancers (breast cancer, for instance), the problem of overdiagnosis is greater for prostate cancer than for other cancers.

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% [3]. A subsequent

analysis that corrected for contamination calculated the "true" benefit as a 31% reduction [4].

The number needed to treat for each prostate cancer death avoided in ERSPC was 48. Furthermore, most patients dying of prostate cancer had intermediate- or high-grade disease. The number needed to treat for each death avoided in low-grade, small-volume prostate cancer is almost certainly higher.

A diagnosis of cancer often results, at least initially, in "cancer hysteria"—that is, a perfectly understandable reflexive fear of an aggressive life-threatening condition. Historically, a diagnosis of cancer was a death sentence. In Western society at large, the cancer "zeitgeist" is that this disease is dreadful and must be caught early and treated aggressively to avoid what would otherwise be a painful and premature death. This widely shared preconception often leads the patient to make a quick and early decision for treatment, regardless of the risks and benefits.

For some cancers this fear is warranted, but for most men with favourable-risk prostate cancer, their condition is far removed from that of a rampaging, aggressive disease. Most men with favourable-risk prostate cancer are not destined to die of their disease, even in the absence of treatment. The challenge is to identify the subset that harbour 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.

2.1 Scope of the Problem and Rationale for Active Surveillance

Autopsy studies in men dying of other causes have documented a high prevalence of histologic prostate cancer—about 50% in men over the age of 50 years [5]. Those studies also demonstrated that prostate cancer typically begins in the third or fourth decade of life. In their autopsy series, Sakr and colleagues demonstrated that 30% of men in their 30s had foci of prostate cancer. That observation is startling in the context of the typical age of death from prostate cancer: about 80 years. It implies a 50-year time course from inception to mortality! It means that, in most patients with lethal prostate cancer, a period of slow subclinical tumour progression that lasts at least 20 years is followed by a period of clinical progression (potentially to metastatic disease and death) lasting about 15 years. The implication is that most patients have a long window of curability, which is particularly true for patients with favourable-risk, low-volume disease. It also implies that young age at diagnosis should not preclude a surveillance approach.

Of course, patients are occasionally diagnosed with advanced disease at a young age and die rapidly of aggressive prostate cancer. These outliers are likely not helped by screening because of time bias (screening tests preferentially identify slower growing cancers); they generally have high-grade disease at the outset and represent a very small proportion of prostate cancer patients.

2.2 How Does Active Surveillance Work?

Active surveillance has four key components:

- Identification of appropriate patients
- Patient education and reassurance
- Close monitoring over time, with serial PSA measurements, periodic biopsy, and (possibly) imaging studies
- Appropriate therapy for patients whose disease is reclassified as higher risk

2.3 Review of Earlier Studies

Table I summarizes the published experience with active surveillance, comprising more than 2000

TABLE I Summary of surveillance studies

Reference	*Pts (*n*)*	*Median age*	*Median follow-up (months)*	*OS*	*CSS*	*Pts on surveillance (%)*
van As and Parker, 2007 [6]	326	67	22	98	100	73
Carter *et al.,* 2007 [7]	407	66	41	98	100	59
Khatami *et al.,* 2007 [8]	270	64	63	Not stated	100	61
Roemeling *et al.,* 2007 [9]	278	70	41	89	100	71
Soloway *et al.,* 2008 [10]	99	66	45	100	100	92
van den Bergh *et al.,* 2009 [11]	533	70	48	90	99	50
Klotz *et al.,* 2010 [12]	452	70	73	82	97 (10-year actuarial)	53
TOTAL	2130	68	43	90	99.7	64

Pts = patients; OS = overall survival; CSS = cancer-specific survival.

patients [6–14]. 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. In the intermediate timeframe (5–15 years), prostate cancer mortality is exceptionally low. Collectively, approximately 200 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.

Only the Toronto group reported outcomes in the subset of patients treated radically. In that group, representing 15% of the total cohort, the PSA recurrence rate was 50%. 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 [2–15]. In the most mature cohort (Toronto), 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 patient 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.

A population-based study recently reported the results of delaying treatment in 343 men initially placed on surveillance as compared with treatment at the time of diagnosis in 3000 men [15]. Of the surveillance patients, 50% were eventually treated. At a median follow up of about 8 years, absolutely no difference was observed in the mortality or the metastasis rate.

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

2.4 Are the Clinical Tools Available to Make Active Surveillance Safe?

The challenge in managing patients on surveillance is to avoid excessive delay in patients who appear to be at higher risk for progression over time and to avoid overtreating patients based on a transient change in PSA or other biomarkers. All groups with prospective surveillance cohorts have used a combination of PSA kinetics and serial biopsy. The specific approach varies. The Toronto group uses a doubling time of 3 years or less, based on multiple determinations at 3-month intervals, calculated using a general linear mixed model that corrects for baseline PSA, grade, and age [16]. That model is freely available to all (visit Asure.ca). Others use a calculated or actual PSA velocity exceeding 2.0 ng/mL annually.

Most groups advise serial biopsies at intervals varying from 1 to 4 years. Our group recommends a confirmatory biopsy at 1 year to identify higher grade disease that may have been missed on the original biopsy; after that, biopsies are performed every 4 years to identify biologic progression, a much more uncommon event. The Johns Hopkins group performs biopsies annually or when a rise in PSA occurs [17].

In the Toronto series, patients with a PSA doubling time of 3 years or less constituted 22% of the cohort. This cut-off point for intervention remains empirical and speculative. However, the 20%–25% of patients with a 3-year doubling time represents a rough approximation of the proportion of good-risk patients "at risk" for disease progression. For patients with a PSA in the 6–10 ng/mL range, it also approximates an annual rise of 2 ng/mL, an adverse predictor of outcome as described by D'Amico [18].

Biopsy sampling error is a significant limitation of surveillance. It has been addressed in part by serial biopsies, with particular attention to the anterolateral horn, a common site for disease missed on routine biopsies. Some authors have advocated saturation biopsies (50 or more cores obtained under general anesthesia) for patients contemplating surveillance [19]. That approach, which may identify some patients with higher risk disease, has not been embraced by most advocates of active surveillance and does not appear necessary in most patients. Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) is emerging as a means to further assess extent of disease in patients with, for example, borderline PSA kinetics and minimal disease on biopsy [20].

The accurate characterization of disease extent is a critical component of surveillance and the area in which the greatest progress is likely to be made. Some patients (perhaps 20%) diagnosed as favourable risk in fact harbour large, often higher grade, cancers. These tumours tend to be located anteriorly, where they are more likely to be missed by the biopsy needle. The term "prostatic evasive anterior tumours" (PEAT) has been used to describe this phenomenon [21]. These patients tend to have a shorter PSA doubling time and are often diagnosed on the confirmatory biopsy directed at the anterior prostate.

With more accurate early identification of the PEAT subset, the outcome of the "true" favourable-risk patient—that is, one who has not had a pathology miss of a more serious cancer—is likely to be even better than previously described. If it can be said that a given patient truly harbours only microfocal low-grade prostate cancer, then it can also be confidently said that the likelihood of clinical progression during that man's lifetime will be exceedingly small. Furthermore, the radical intervention rate in these "true" favourable-risk patients will be much lower than has been described in surveillance series to date.

If the DCE MRI data are validated by further studies, it would be plausible that this test would be indicated at baseline to identify, among all patients that are candidates for surveillance, those with extensive anterior tumours. Such testing would substantially improve the expected outcome in the remaining patients.

The psychological effects of living for many years with untreated cancer are a potential concern. Cumulatively, does this knowledge lead to depression or other adverse effects? The best comparative data on this question come from a companion study to the Holmberg *et al.* [22] randomized trial of surgery compared with watchful waiting in Sweden. It found absolutely no significant psychological differences between the two groups of patients after 5 years. Worry, anxiety, and depression were all equal between the two arms [23]. The absence of any adverse psychological effect in patients on surveillance as compared with patients treated radically has been reported by others [24]. A more recent longitudinal study gave questionnaires to 150 patients at baseline and at 9 months. Anxiety and distress remained low during that period [25].

Surveillance may be stressful for some men, but the reality is that most patients with prostate cancer, whether treated or not, are concerned about the risk of progression. Anxiety about PSA recurrence is common among treated and untreated patients alike. Patients who are educated to appreciate the indolent natural history of most good-risk prostate cancers may avoid much of this anxiety.

2.5 Who Is a Candidate?

Identifying patients for surveillance requires a knowledge of the natural history of prostate cancer and of the impacts of age and comorbidity on life expectancy. While there are no absolute rules, some general considerations are these:

- ***Age:*** The longer the patient's life expectancy, the more stringent should be the criteria, but youth alone is not a contraindication for surveillance. Men under 60 years of age, for example, are better candidates if they fulfil the Epstein criteria for insignificant prostate cancer (no more than one third of all cores positive, no more than half of any one core involved, and a PSA density below 0.15). Men over 70, particularly with comorbidity, who have a PSA greater than 10 ng/mL or minor elements of a Gleason 4 pattern may still be appropriate candidates. Conversely, men under 70 with substantial Gleason 4 pattern (or any Gleason 4 pattern, some would argue [26]) are not good candidates for surveillance. The evidence suggests that their likelihood of disease progression is about 3 times that of patients without a Gleason 4 pattern. Shared patient decision-making and "buy-in" is critical.
- ***Follow-Up:*** Table II contains a suggested calendar for follow-up. It is the responsibility of the physician and the patient to maintain regular follow-up on surveillance, to monitor PSA kinetics, and to have periodic repeat biopsies (although these can be relatively infrequent). A key task of the physician is to regularly reassure the patient as to the indolent course of the disease.
- ***Clinical Trials:*** The National Cancer Institute of Canada (NCIC), in conjunction with four U.S.-based cooperative oncology trials groups, have opened a trial called START (Surveillance Therapy Against Radical Treatment). This trial, which opened to accrual in September 2007, will randomize 2100 patients either to the active surveillance approach described earlier or to the patient's choice of radical treatment (surgery or radiation). The primary endpoint is prostate cancer survival. The trial has a major correlative science component. Successful accrual to this trial will demonstrate conclusively whether active surveillance is equivalent to radical treatment in the favourable-risk patient. The trial opened widely on the NCIC Cancer Trials Support Unit Web menu in May 2010.

The surveillance approach is driven, in part, by the morbidity and cost of currently available therapy. Any effective treatment producing minimal or no side effects and being reasonably inexpensive would likely replace surveillance. Advocates of focal therapy make this claim [27]. The limitations of focal therapy are similar to those of surveillance—namely, some patients with favourable clinical parameters will harbour higher risk disease and be inadequately treated. Focal therapy risks being a treatment that is effective only in patients who don't require treatment and ineffective in those who do. It may well have a role

TABLE II Active surveillance: suggested calendar for follow-up

Follow up schedule[a]
PSA, digital rectal exam every 3 months for 2 years, then every 6 months (assuming PSA is stable)
Confirmatory 10- to 12-core biopsy within 1st year, including anterolateral horn
Repeat biopsy every 3–5 years until age 80
(Optional) MR imaging at baseline, or for borderline PSA kinetics or pathology, or both
Intervention
When PSA doubling time is less than 3 years (in most cases, based on at least 8 determinations; about 20% of patients)
When grade progresses to Gleason 7, with a substantial proportion of 4 pattern (about 5% of patients)

[a] These are guidelines; they should be modified according to patient age and comorbidity.

PSA = prostate-specific antigen; MR = magnetic resonance.

in selected patients. However, the appeal of active surveillance is the ability to use the observed natural history of the patient's disease over time to identify patients who in fact have more aggressive disease. Focal therapy may contaminate those observations. Given the low mortality rate for favourable-risk prostate cancer managed with active surveillance, advocates for focal therapy face a major challenge in demonstrating that the natural history is improved with their approach. Focal therapy may have a role in treating some of the 30% of patients on surveillance who are reclassified as higher risk based on an increase in cancer volume on biopsy. It is likely that with better imaging, active surveillance and focal therapy will have complementary roles.

2.6 Future Advances

Two major modifications to the surveillance approach as described earlier will likely enhance its performance in the near future. A clear unmet need is better prediction of an individual patient's likely risk of disease progression. Advances in this field have already occurred in MRI for prostate cancer, and imaging of this kind will have an increasing role. Indeed, several groups have already adopted routine MRI imaging for all patients on surveillance. Major progress is also being made in the molecular characterization of higher risk disease based on multiplex analysis of biopsy specimens or somatic single-nucleotide polymorphisms, or both [28]. All hold the promise of more accurate characterization of disease aggressiveness in the near future. This research area continues to be active.

It is plausible that MRI may reduce the requirement for serial biopsies. The recently reported increased urosepsis rate post biopsy [29] reinforces the need for an effective noninvasive means of monitoring disease progression.

The second major development may be the emergence of data supporting the use of 5α-reductase inhibitors (5ARIS) in this setting. Two large trials, PCPT (Prostate Cancer Prevention Trial) [30] and REDUCE (Reduction by Dutasteride of Prostate Cancer Events) [31] have reported that the rate of prostate cancer diagnosis declines by 25%–30% with 5ARIS. Many men in these studies harboured undiagnosed prostate cancer at entry. Thus, it is a reasonable inference that these drugs act to stabilize or to reduce the volume of existing prostate cancer; indeed, that may be their main mode of action as prevention agents. One study testing that hypothesis in surveillance patients, the REDEEM (Reduction with Dutasteride of Clinical Progression Events in Expectant Management of Prostate Cancer) trial, has been completed but not yet reported. It is possible that, for many men with favourable-risk prostate cancer, a 5ARI represents a low-cost minimal intervention that is sufficient to further reduce, to exceedingly low levels, their risk of progression. At this point, however, there is no direct evidence to support that hypothesis. Giving men on surveillance 5ARIS is appealing, particularly if they have other indications for the drug (that is, symptoms of benign prostatic hyperplasia), but it should not be considered a definitive therapy. Such patients still require close monitoring and periodic biopsies. The PSA kinetics in men on 5ARIS are simply recalibrated from the new baseline once nadir is reached.

3. SUMMARY

The advent of widespread PSA screening has had the positive effect of identifying patients with life-threatening prostate cancer at a time when they are more curable, and the negative effect of identifying many patients with non-life-threatening cancer who are susceptible to overtreatment. In a serially screened population, the latter group is far more prevalent. However, conservative management has been resisted in many constituencies because of concern about the inaccuracies of clinical staging and grading.

A rational approach is to offer definitive treatment to the intermediate- and high-risk groups and little or no treatment to the low-risk group. However, some patients apparently at favourable risk harbour more aggressive disease. In those patients, curative treatment has benefits. A policy of close monitoring over time, with selective intervention for those men whose cancers exhibit characteristics of higher risk disease, is an appealing way forward. Intervention is offered for a PSA doubling time of less than 3 years (depending on patient age, comorbidities, and so on) or grade progression to a pattern predominantly Gleason 4. This approach is currently the focus of several prospective trials. Results of the phase II observational studies reported to date have demonstrated that this active surveillance is feasible and safe in the intermediate timeframe. Most patients who understand the basis for the approach will remain on long-term surveillance. If patients are selected properly (that is, they have good-risk, low-volume disease) and are followed carefully to enable early intervention upon evidence of progression, most men with indolent disease will not suffer from clinical disease progression or prostate cancer death, and the few with aggressive disease will still be amenable to cure. Thus, the proportion of patients dying from their disease is not likely to be significantly different from the proportion dying in spite of aggressive treatment in all good-risk patients at the time of diagnosis. This approach is currently being evaluated in a large-scale phase III study which has been opened in Canada, the United States, and Great Britain. Support for this trial and for others evaluating the outcome of surveillance is a clear priority. Ongoing studies of multiplex biomarkers to better predict natural history, of MRI to more accurately identify patients with larger volume of disease unappreciated at baseline, and of

the benefits of 5ARIS and other secondary prevention strategies in surveillance patients are ongoing and likely to have a favourable impact on the surveillance approach.

In my view, small-volume favourable-risk prostate cancer should be viewed much as atypical small acinar proliferation is viewed now—in other words, merely as a risk factor or marker for more significant disease that may have been missed on the original biopsy. It should be managed, in most cases, by close monitoring, with no treatment for most and delayed intervention for the subset who are reclassified as higher risk. The untreated patients can be assured of having an exceedingly low risk of cancer progression.

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