

Active surveillance for low-risk prostate cancer

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F1000 Medicine Reports 2012, 4:16 (doi:10.3410/M4-16)

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Abstract

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 is a response to the clearly documented risks of over diagnosis and overtreatment of low-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. Low-risk prostate cancer is more accurately viewed as one of multiple risk factors for the presence of higher grade prostate cancer. Like atypical small acinar proliferation, (ASAP), it may be managed with close follow up but without radical intervention, unless there is clear evidence of more aggressive disease.

Introduction and background

Prostate cancer is the commonest internal malignancy in males, and the second commonest cause of cancer death in men [1]. In North America, one in six men (17%) are now diagnosed with the disease at some point during their life. The life-time risk of dying of the disease is approximately 3%. Thus, approximately 6 times as many men will be diagnosed with the disease as will die from it.

The advent of sensitive diagnostic testing has resulted in the problem of cancer overdiagnosis in multiple organ sites. 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).

Because of the high incidence of latent prostate cancer in aging men, the widespread availability of the prostate-specific antigen (PSA) test, and the long term effects of

definitive therapy, this has the greatest ramifications in the case of prostate cancer.

Screening and overdiagnosis

Screening for prostate cancer with PSA is widely used in North America and Europe. Compared with clinical diagnosis, it results in the identification of potentially lethal prostate cancer at a much more curable stage. The widespread use of PSA screening has been associated with significant falls in prostate cancer mortality [2]. There is some controversy, however, as to the degree to which PSA-based early detection has been responsible for this reduction. A credible estimate is that 50% of the mortality reduction is related to PSA screening [3]. On the other hand, the cost is 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% [4]. The “number needed to treat” for each prostate cancer death avoided in ERSPC was 48

(i.e. each cancer death avoided required treating an extra 48 patients). It is widely anticipated that this number needed to treat figure will fall with longer follow up. A more recent randomized screening study from Goteborg [5], which had considerably longer median follow up (14 years) than the other screening studies, estimated the mortality reduction with screening at 50%, and, indeed, the number needed to treat was 12. Further, a sub-analysis of the negative PLCO study showed that in men with little or no co-morbidity, the number needed to treat was 5 at 10 years [6]. However, most patients dying of prostate cancer had intermediate- or high-grade disease. The number needed to treat with low-grade, small-volume prostate cancer for each death avoided is likely to be considerably higher.

Recently, the US Preventive Services Task Force published new recommendations on the use of PSA for screening, assigning it to level 'D', i.e. the risks outweigh the benefit [7]. The primary reason for this was due to concerns about overdiagnosis and overtreatment. The problem with accepting the Task Force recommendation, and discarding PSA testing altogether, is that this will result in a return to the pre-PSA era of men with prostate cancer presenting with advanced, incurable disease. We believe, based on one large randomized trial, as well as inferences from many other studies, that treatment of some prostate cancers saves lives and reduces mortality from the disease [8].

An alternative strategy, which potentially offers the best of both worlds, is based on the idea that treatment must be applied selectively, and the timing and aggressiveness of treatment should reflect disease and patient characteristics.

The likelihood of 'true' microfocal low-grade disease progressing to metastatic disease appears to be extremely low. Historically, of course, a few patients with apparent low-risk prostate cancer develop metastatic disease and die of prostate cancer. Recent evidence indicates that these patients were almost certainly under-graded at the original biopsy, and in fact, harbored higher-grade cancer from the start [9]. Thus, the challenge of selective therapy is the early identification of the patients with higher-grade cancer than seen diagnosed on the basis of the original biopsy.

Definition of clinically insignificant prostate cancer

Low-risk prostate cancer has been defined by D'Amico as Gleason score of 6 or less, PSA less than 10 mg/ml, and a tumor that is either non-palpable or only palpable in less than half of one lobe of the prostate (clinical stage T1c or T2a) [10]. Very low-risk disease has been defined by

Epstein as low-risk patients who have only one or two positive cores, no more than 50% involvement of any one core, and a PSA density of < 0.15 [11]. This definition is based on data demonstrating that these patients have a very high likelihood of "clinically insignificant" prostate cancer. A key concept is the pathologic definition of clinically insignificant prostate cancer. For 30 years, this has been defined as Gleason score of 6 or less, prostate cancer with a prostate tumor volume < 0.5 cc, based on work by T. Stamey on cystoprostatectomy specimens [12]. There is much evidence that this is an overly stringent definition. Recently, the ERSPC group performed a similar analysis based on the ERSPC patients [13]. Their conclusion was that the threshold for clinically insignificant disease was a cancer volume < 1.3 cc. This has major implications. It means that a better test for prostate cancer would ignore small volume disease, and identify cancers of 1.3 cc or greater.

Active surveillance results

Active surveillance means deferring treatment initially for a growing proportion of men diagnosed with low-risk (i.e. low volume, stage and grade) prostate cancer. Men are followed carefully with serial PSA assessments, repeat biopsies, and in some cases other tests intended to identify early signs of progression (such as MRI and biomarkers). The term "active surveillance" has supplanted "watchful waiting," but the two are not synonymous. The latter term is generally applied to older men with significant comorbidity, who were advised to defer treatment unless symptoms of advanced disease developed, at which point palliative androgen deprivation could be offered. Active surveillance, on the other hand, rests on the presumptions that the lead time from diagnosis to clinical progression is usually long for low-risk disease [9], and that at the first signs of higher-risk disease the cancer can be treated, 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, [8,14], nor those identified in population-based registries as receiving conservative management, can be considered representative of those expected with contemporary active surveillance.

Table 1 summarizes the published prospective experience with active surveillance, comprising more than 2900 patients [15-23]. These studies differ in terms of their eligibility and triggers for intervention. However, certain consistent themes emerge from these data.

Over time, approximately one third of patients will be reclassified as higher risk for progression and will be offered treatment. This proportion depends on how

Table 1. Outcomes of active surveillance in large prospective series

Author, location	Year published	Patients	Median follow-up (month)	% treated; treatment free %	Overall/Disease specific survival (%)	% BCR post deferred treatment
Klotz <i>et al.</i> [15] University of Toronto, Canada	2009	450	80	30; 72 at 5yr	79/ 97 at 10yr	50% (13% overall)
Van den Bergh <i>et al.</i> [16], Multicentre, Europe	2009	616	47	32; 43 at 10yr	77/100 at 10yr	20%^
Dall'Era <i>et al.</i> [17] University of California San Francisco (UCSF), USA	2008	328	43	24; 67 at 5yr	100/100 at 5yr	NR
Takechi <i>et al.</i> [18], Multicentre, Japan	2008	118	36	51; 49 at 3yr	NR	NR
Carter <i>et al.</i> [19], Johns Hopkins, USA	2007	407	NR	36; NR	NR	NR [50% "incurable" based on pathology post surgery]
Roemeling <i>et al.</i> [20], Rotterdam Netherlands	2007	273	41	29; 71 at 5yr	89/100 at 5yr	NR [31% of 13 RP positive margins]
Soloway <i>et al.</i> [21], Miami, USA	2007	99	35	8; 85 at 5yr	NR	NR
Hardie <i>et al.</i> [22], Royal Marsden, UK	2005	80	42	14; 79 at 5yr	NR	0%
Patel <i>et al.</i> [23], Memorial Sloan Kettering, USA	2004	88	35	35; 58 at 5yr	NR	NR

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 [9]. 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 have Gleason scores of 3 + 4. This emphasizes the critical importance of a confirmatory biopsy performed within a reasonable time period (i.e. within one year) of the initial diagnosis.

In the intermediate time-frame (5-15 years), prostate cancer mortality is exceptionally low. In the collected series, approximately 300 patients have been followed for between 10 and 15 years. To date, none of the prostate cancer deaths in men on surveillance have occurred after the 10-year time point. Among the 453 patients in the Toronto cohort, the actuarial 10-year prostate cancer survival is 97% [15].

In most men on prostate cancer surveillance, mortality comes from other causes. 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.

In the Toronto cohort, only PSA doubling time was a predictor for prostate cancer mortality. The doubling time amongst the five patients who died of disease was 1.6 years or less, falling within the lowest 10th percentile of PSA doubling times for the cohort. All patients who died were found to have a Gleason score of 7 or greater disease on repeat biopsy [24].

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.

The limitation of these studies is the length of follow-up, as 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.

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 and antero-lateral horn, as well as the traditional posterior peripheral zone.

If the confirmatory biopsy is negative or shows microfocal Gleason score of 6, 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 testing

PSA testing should be performed every three months for two years, and then every six months indefinitely. PSA doubling time or velocity should be calculated based, preferably, on 8-9 data points over a two 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.

Triggers for intervention

In several of the published series, PSA doubling time or velocity has been used as a trigger for definitive intervention. 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. However, some recent studies have questioned the correlation between PSA kinetics and adverse disease characteristics [25]. 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 [26]. Our own experience was that, in the stable, untreated patients in our cohort a "false PSA trigger" for intervention occurred in up to 50% [27]. Thus, our current approach is to use PSA kinetics as a guide for further evaluation, rather than a trigger for intervention on its own.

A common dilemma in managing surveillance patients occurs when the biopsy shows only a minimal Gleason score of 6, but the PSA is rising rapidly. Multiparametric MRI represents a way out of this dilemma. A "normal" MRI has been reported to have a negative predictive value of 94-97% for high-grade cancer, based on a single centre experience [28]. This figure must be validated. Nonetheless, this makes multiparametric MRI extremely useful in this setting [29]. The finding of a "significant" lesion on MRI in a patient on active surveillance should trigger either a targeted biopsy or definitive intervention. An equivocal lesion should trigger a repeat biopsy of the lesion.

Role of 5-alpha reductase inhibitors

In the Prostate Cancer Prevention Trial (PCPT), the likelihood of low-grade prostate cancer being found on

a biopsy was reduced by 25% by finasteride [4,30]. A similar finding was observed in the REDUCE trial [31]. An obvious inference is that 5-alpha reductase inhibitors may be beneficial in men on surveillance. This was evaluated in a prospective randomized trial [32]; men on surveillance were randomized between dutasteride and placebo for 3 years, and had a mandated biopsy at 18 months and 3 years. At 3 years, 54 (38%) of 144 men in the dutasteride group and 70 (48%) of 145 controls had prostate cancer progression (pathological or therapeutic; hazard ratio 0.62, $p = 0.009$): 35 (24%) men in the dutasteride group and 23 (15%) controls had sexual adverse events or breast enlargement or tenderness. There was no increase in high-grade cancer (although the study was not powered to find a 0.5%–1% increase, seen in the PCPT and REDUCE trials). The study suggests that there may be a benefit of 5-alpha reductase inhibitors in reducing the rate of progression in men on surveillance.

Quality of life

Several studies have addressed quality of life issues in men managed conservatively. Compelling data come from the comparison of men in the Scandinavian randomized trial comparing radical prostatectomy to watchful waiting [33]. This showed no difference in any psychological domain between the surgery and watchful waiting group, but distress was more common in the former. A recent Finnish quality of life study in 126 men on surveillance found that this approach did not provoke short-term quality-of-life disturbances, as assessed by standardized RAND-36, IIEF-5 and IPSS questionnaires [34]. None of the patients changed treatment due to anxiety. Unexpectedly, prostate cancer patients on active surveillance had significantly better general mental and physical health-related quality of life than did a sample of the general age-stratified Finnish male population. Another US study reported improved quality of life in 125 men on surveillance compared to men treated shortly after diagnosis [35]. The published literature supports improved quality of life in men managed conservatively, with no apparent adverse psychological effect of living with untreated cancer.

Future studies

The PROTECT trial, a trial of newly diagnosed prostate cancer patients carried out in the UK, has randomized 900 men between surgery, radiation, and 'watchful waiting'. The patients on the latter arm were offered intervention if re-classified as higher risk over time, although this was not formally built into the protocol. This trial should provide invaluable information about the relative mortality associated with these treatment approaches.

The next five years will also see the publication of more mature prospective surveillance trials, including the outcome of patients followed conservatively for 15 years or more. Other areas of very active research include the role of multiparametric MRI and new biomarkers in patient selection and decision making. Further data on long term quality of life effects are also anticipated.

Summary and conclusion

For men with low-grade prostate cancer 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 an appealing strategy. The optimal criteria include clinical stage T1c or T2a, serum PSA < 10mg/ml, and a Gleason score of 6 or less. This represents about 45% of newly diagnosed patients in the US and Canada, approximately 150,000 men per year.

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.

A repeat prostate biopsy should be performed at one year, to rule out higher-grade disease that may have been missed on the original biopsy. Following this, biopsies should be repeated every three to four years (until age 80) to look for evidence of biologic progression to a Gleason score of 4 + 3 or higher.

Active surveillance is becoming widely accepted. A recent National Institutes of Health "State of the Science" report concluded that "an independent panel" convened by the NIH has concluded that many men with localized, low-risk prostate cancer should be closely monitored, permitting treatment to be delayed until warranted by disease progression [36].

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.

Abbreviations

PSA, prostate-specific antigen; ERSPC, European Randomized Trial of Screening for Prostate Cancer; PCPT, Prostate Cancer Prevention Trial; MRI, magnetic resonance imaging.

Competing interest

The author declares that he has no competing interests.

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