Active Surveillance Versus Radical Treatment for Favorable-risk Localized Prostate Cancer

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Opinion statement

Widespread prostate-specific antigen (PSA) screening in North America has resulted in a profound stage migration and a marked increase in incidence. One in six men is now diagnosed, many with small-volume, low-grade cancer. This incidence is dramatically higher than the 3% lifetime risk of prostate cancer death that characterized the pre-screening era. This article summarizes the case for active surveillance for "favorable-risk" prostate cancer with selective delayed intervention for rapid biochemical progression, assessed by increasing PSA levels, or grade progression. The results of a large phase II trial using this approach are reviewed. To date, this study has shown that virtually all men with favorable-risk prostate cancer managed in this fashion will die of unrelated causes. Based on the Swedish randomized trial of radical prostatectomy versus watchful waiting, the Connecticut observation series, and the Toronto active surveillance experience, a number needed to treat analysis of the benefit of radical treatment of all newly diagnosed favorable-risk prostate cancer patients, compared with a strategy of active surveillance with selective delayed intervention, is presented. This suggests that approximately 73 patients will require radical treatment for each prostate cancer death averted. This translates into a 3- to 4-week survival benefit, unadjusted for quality of life. This figure is confirmed based on an analysis of the 2004 D'Amico et al. PSA velocity data in favorable-risk disease. The approach of active surveillance with selective delayed intervention based on PSA doubling time and repeat biopsy represents a practical compromise between radical therapy for all patients (which results in overtreatment for patients with indolent disease) and watchful waiting with palliative therapy only (which results in undertreatment for those with aggressive disease).

Introduction

Prostate cancer screening based on prostate biopsy for men with increased levels of serum prostate-specific antigen (PSA) or abnormal digital rectal examination (DRE) results in diagnosing many men with prostate cancer that does not pose a threat to their life. The prevalence of histologic prostate cancer in men aged older than 50 years is 30% to 40% [1••]. A large proportion of this histologic or "latent" prostate cancer is never destined to progress or affect the lifespan of the patient. Since the introduction of PSA screening, the lifetime risk of being diagnosed with prostate cancer has doubled from 9% to 18% [2,3].

Aggressive screening results in a rate of prostate cancer diagnosis far out of proportion to the number of men at risk for prostate cancer mortality. Welch et al. [4] have calculated that there are 2.74 million men in the United States aged 50 to 70 years with a PSA of 2.5 or more. The Prostate Cancer Prevention Trial (PCPT)

demonstrated that the positive predictive value for a PSA between 2.1 and 4 is 24.7% [5••]. Thus, a strategy of performing biopsy in all men with a PSA more than 2.5 will result in the diagnosis of 775,000 cases of prostate cancer. This is 542,910 more than are currently diagnosed and approximately 25 times the number of men who die each year from prostate cancer.

This means that localized prostate cancer is overtreated, in that some patients not destined to experience prostate cancer death or morbidity are subject to radical therapy [6,7]. A fundamental research objective in this disease is to enhance prediction of the biological phenotype of the cancer. One method to do this is to use the window of curability that exists in patients with favorable-risk disease to estimate the biological aggressiveness of the tumor based on prostate-specific antigen doubling time (PSADT) and grade progression on repeat biopsy.

Although the disease remains indolent for life in most patients, even in those in whom it is destined to progress to clinical disease it has a 20- to 40-year natural history. Sakr et al. [1••] have shown that the disease is initiated in the fourth decade in a typical patient. Importantly, in their autopsy cohort, the prevalence of prostate cancer in men in their 30s (approximately 30%) was still about 10 times higher than the expected lifetime risk of prostate cancer. These data demonstrate conclusively that the presence of prostate cancer in a young man does not mean he will inevitably suffer the complications of the disease if he lives long enough. The Johns Hopkins University radical prostatectomy series [8••] showed that a median of 16 years elapses from surgery until death in patients who die of prostate cancer after disease recurrence. The watchful waiting studies, most of which accrued patients from the pre-PSA era, also demonstrate that disease-related mortality in populations of prostate cancer patients only becomes substantial after 10 years. Screening results in detection of disease earlier in the natural history of the disease. Modeling of the quantity of this lead time, calculated by several different groups using various techniques, suggests it is approximately 10 years in 65-year-old men and increases with younger age [9]. The lead time afforded by PSA screening is likely to increase the interval from diagnosis to death (in patients destined to die of the disease) to 20 years or more in screened populations. In addition, it is particularly clear that low-grade prostate cancer is associated with low progression rates and high disease-specific survival rates at 20 years [10••].

Many authors have attempted to identify "clinically insignificant" prostate cancer based on biopsy and clinical criteria. The gold standard for this entity, used by virtually all authors, is a radical prostatectomy specimen containing less than 0.5 cm^3 of Gleason 6 or less prostate cancer. The origin of this gold standard is relevant. Stamey et al. [11] examined prostate glands obtained from 139 consecutively sampled radical cystoprostatectomy specimens, of which 55 (40%) had incidental prostate cancer. Because the clinical prevalence of prostate cancer was 8%, the authors concluded that only tumor volumes above the 92nd percentile (0.5–6.1 mL) were clinically significant, based on the assumption that the clinically significant cancer rate was 8%. The arbitrariness of this is of concern. If the clinically significant cancer rate were set at 4%, then the clinically significant cancer volume would be closer to 1 mL; conversely, if it were set at 12%, the clinically significant cancer volume would be 0.2 mL. Nonetheless, this pathologic definition of clinically insignificant disease is widely used.

Using this definition, many groups have reported on the incidence of insignificant disease [12–22]. The incidence varies widely, from up to 30% in T1c patients, as reported by the Johns Hopkins group [12], to values as low as 9% to 12%. Common clinical parameters predicting for minimal disease include Gleason 6 or less, less than 3 mm of cancer in toto, and less than or equal to one in three cores involved. Importantly, the Epstein criteria permit any one core to have up to 50% involvement, representing much more substantial disease than a few microfoci. As mentioned, this definition is based on a pathologic endpoint. The definition of insignificant cancer as less than 0.5 cm^3 of low-grade disease has never been validated in a trial with a clinical endpoint. Based on substantial data, including the PCPT, and the incontrovertible ratio of 7:1 between the current lifetime likelihood of diagnosis (approximately one in six) and death (one in 40), it understates the proportion of patients who harbor prostate cancer that is not destined to pose a threat to their life (approximately six of seven).

Studies of watchful waiting consistently report a large proportion of patients enjoying long-term survival, particularly with low-grade disease. These studies all incorporated an "either-or" approach (radical treatment or surveillance; surveillance offered no opportunity for delayed radical local therapy). They also all consist of pre-stage migration cohorts. Thus, many patients with favorable prognostic factors, diagnosed considerably earlier in disease development than the average patient in these unscreened populations, will have prostate cancer with an even longer natural history free of progression than suggested in these studies. But even this understates the case. Because many men will be diagnosed by PSA screening who would never have been diagnosed during their lifetime in the absence of screening, the natural history of low-grade, screen-detected prostate cancer is likely to be dramatically more benign than suggested by the watchful waiting reports.

Nonetheless, some patients with low-grade, small-volume, screen-detected prostate cancer are destined to progress; in rare cases, these patients harbor very aggressive disease. This may be because of pathologic miss of higher-grade or large-volume disease, or phenotypic outliers

(a few low-grade cancers are truly aggressive). Given the long natural history of prostate cancer, it seems logical and reasonable to use a period of observation in good-risk patients to identify those at higher risk for progression, and treat them accordingly, while observing the rest.

A major challenge with this approach is to develop a strategy that identifies high-risk patients accurately and early enough so that curative treatment is still possible. As of 2006, this strategy is based on an analysis of PSA kinetics and repeat biopsy.

Treatment

PSA kinetics in patients on active surveillance

- Several authors have reported that the median PSADT in a good-risk cohort is 7 years. The range is dramatic, from less than 3 months to more than 100 years. The distribution amongst Asians and North Americans is remarkably consistent [23,24].
- There are now robust data that a short PSADT is correlated with disease aggressivity and the likelihood of prostate cancer mortality.
- Egawa et al. [25] examined PSADT before radical prostatectomy and found that a doubling time of 3 years or less was more common with pT3 disease at radical prostatectomy. McLaren et al. [26] reported PSADT in a watchful-waiting cohort and found that a PSADT of less than 3 years was associated with clinical progression (defined as palpable enlargement in the tumor nodule or increase in T stage) in more than 80% of patients by 18 months from diagnosis. D'Amico et al. [27•] reported that an increase in PSA of more than 2 ng/mL/year before surgery identified a group of patients who had a 15% prostate cancer mortality rate at 7 years. No patients with a PSA increase of less than 2 ng/mL/year before surgery died of the disease. Therefore, clearly an increase in PSA of more than 2 ng/mL/year, which corresponds to a PSADT of approximately 3 years or less in a patient with a PSA of 6 ng/mL, identifies a group at risk.
- The primary concern with using PSADT as a trigger for curative intervention is that it may act as a marker of aggressive disease that has already progressed and is no longer localized. However, although a PSA velocity more than 2 identified 100% of patients dying of prostate cancer within 10 years of surgery in the study by D'Amico et al. [27•], cause-specific survival at 10 years in this high-risk group was still 85%. In addition, most of the cancers were higher grade. In fact, the mortality rate amongst the Gleason 6 or less group was only 7% in the quartile with a rapid PSA velocity, and 1.4% of the total Gleason 6 or less group. Therefore, aggressive therapy is still warranted in favorable-risk patients with a rapid PSADT or velocity.
- There are several prospective and retrospective phase II series in the literature evaluating the outcome of active surveillance with selective delayed intervention. The largest prospective study is the Toronto experience [23,28•,29,30].
- This study consisted of 299 patients followed with active surveillance with selective delayed intervention. Patients aged younger than 70 years were restricted to PSA 10 or less and Gleason 6 or less. Patients aged older than 70 years were eligible if PSA was less than 15 and Gleason was 7 (3 + 4) or less. This intermediate-risk group represented 20% of the cohort.
- Initially, the criteria for selective delayed intervention included patients with a PSADT less than 2 years, or grade progression to Gleason 8 or higher on rebiopsy. In 2001, these criteria were relaxed somewhat to include patients with a PSADT less than 3 years, or progression to Gleason 7 (4 + 3) or higher. In addition, patients were free to choose radical intervention at any time.

Table 1. Active surveillance: suggested algorithm for eligibility and follow-up*

Eligibility
PSA ≤ 10
Gleason ≤ 6
T1c–T2a
Depending on age and comorbidity: < three cores involved, < 50% of any one core
Follow-up schedule
PSA, DRE every 3 months for 2 years, then every 6 months assuming PSA is stable
10–12 core biopsy at 1 year, and then every 3–5 years until age 80
Optional: TRUS on alternate visits.
In patients who appear borderline at 2 years (PSA doubling time 3–5 years, or increase in disease volume, or small amount of Gleason 4 pattern on repeat biopsy), continue PSA every 3 months and consider more frequent biopsies
Intervention: for PSA doubling time < 3 years (in most cases, based on at least eight determinations; approximately 20% of patients)
For grade progression to Gleason 7 (4 + 3) or higher (approximately 5% of patients)

*These are guidelines and should be modified according to patient age and comorbidity.
DRE—digital rectal examination; PSA—prostate-specific antigen; TRUS—transrectal ultrasound of the prostate.

- With a median follow-up of 76 months, 101 patients (34%) came off watchful observation, whereas 198 have remained on surveillance. Fifteen percent of patients came off surveillance because of rapid biochemical progression, 3% for clinical progression, 4% for histologic progression, and 12% because of patient preference. At 8 years, overall survival is 85%; disease-specific survival is 98%. Only four of 299 patients have died of prostate cancer. All patients who died had a PSADT less than 2 years, were treated radically within 6 months of diagnosis, and developed metastatic disease within 1 to 2 years. This fraction is not dissimilar to the experience by D'Amico et al. [27•], in which disease-specific survival in Gleason score 6 or less patients was 98.25% at 7 years.
- Twenty four of the patients in this cohort have had a radical prostatectomy for a PSADT less than 2 years. All had Gleason score 5 to 6, PSA less than 10, and pT1-2 at study entry. Final pathology was as follows: 10 (42%) were pT2, 14 (58%) were pT3a-c, and two (8%) were N1. For a group of patients with favorable clinical characteristics, this is a high rate of locally advanced disease.
- There is no risk-free strategy in prostate cancer. Active surveillance carries the risk that, in some patients, the disease will progress to incurability during the period of observation, resulting in an avoidable prostate cancer death. Should this risk drive definitive therapy in all patients? To put it more quantitatively, what is the best estimate of the number of screen-diagnosed, favorable-risk patients needed to be treated with definitive therapy for each prostate cancer death avoided during the lifetime of the average patient?
- This number can be estimated by combining the results of the Scandinavian randomized trial of watchful waiting versus radical prostatectomy [31••], the Connecticut watchful waiting series [10••], the Toronto active surveillance experience [28•], and the D'Amico et al. [27•] PSA velocity data (Tables 1 and 2). The Scandinavian study [31••] demonstrated a 44% reduction in prostate cancer mortality with surgery, with an absolute survival benefit of 5% at 10 years and a cancer-specific survival benefit of 5.3%. There are three caveats: 1) only 5% of the patients were screen detected; 2) the following period is too short (10 years); and 3) the cohort was a higher-risk group, based on a median PSA of 13, and 40% of patients having Gleason 7 or higher disease.

Table 2. Estimate of the number needed to treat for each prostate cancer death averted, favorable-risk screen-detected disease, radical prostatectomy vs active surveillance, at 20 years

	Bill-Axelson et al. [31••]	Correct for PSA lead time	Adjust for low grade/grade shift	Adjust for salvage in "high-risk" patients
Factor	—	Add 10 years	1.5–2.5	Assume 50% curable
10 years	20	—	30–50	60–100
20 years	9	18	27–45	56–90

PSA—prostate-specific antigen.

- Therefore, the number needed to treat in the Scandinavian trial [31••] for each death averted is 20:1 at 10 years. Assuming that lead time in a screened population is approximately 10 years, this figure is likely to apply at 20 years in a screened population. The data of Albertsen et al. [10••] indicate that the mortality for intermediate-risk disease was about 2.5 times greater at 20 years than for favorable-risk disease. Thus, a reasonable extrapolation is that, in contrast with the intermediate-risk cohort in the Scandinavian trial [31••], approximately 27 to 45 screen-diagnosed favorable-risk patients need to be treated for each death prevented by surgery at 20 years, compared with no treatment. But clearly, a proportion of patients can be salvaged by delayed intervention. Based on the very favorable results reported by the Toronto group [28•], it is likely that at least 50% of the patients whose PSA kinetics or repeat biopsy results suggest they are at higher risk can be salvaged. The conclusion is that approximately 73 (range 56–90) radical prostatectomies would be required for each prostate cancer death averted in favorable-risk disease.
- This can also be estimated using the D'Amico et al. [27•] PSA velocity cohort. The mortality rate amongst the Gleason 6 cases at 10 years was 1.4% with prostatectomy. If the hazard ratio of 0.56 from the Scandinavian trial [31••] for the benefit of surgery compared with watchful waiting is applied, this means that approximately 2.5% would have died with watchful waiting. The benefit is 1.1% survival improvement, for a number needed to treat of 91.
- The data of Pound et al. [8••] suggest that each prostate cancer death averted would have occurred on average 16 years after diagnosis, meaning that the number of life years saved in each of these one in 73 averted deaths is modest. For the average 60 year old, life would be prolonged an average of 5 years by having prostate cancer death averted. If each prostate cancer death averted adds 5 years to that individual's life, each radical prostatectomy would add 0.9 months of life (60 months per 73 operations). This is uncorrected for quality of life. This benefit would be of dubious merit compared with the frequently life-altering effects of radical intervention for prostate cancer. It is not a stretch to suggest that treating all favorable-risk patients radically in this context evokes the story of the emperor with no clothes.
- It should be emphasized that this number-needed-to-treat calculation applies to the favorable-risk population. For higher-risk groups, with more aggressive disease and a higher risk of cancer death, the number needed to treat is likely to be much lower, the benefit greater, and the trade off of quality of life for survival very worthwhile for most patients.
- The psychological effects of living for many years with untreated cancer are uncertain. However, evidence suggests that a cancer diagnosis has a psychological impact relatively independent of whether the patient is treated curatively or not. A companion study to the Scandinavian randomized trial [31••] of

surgery versus watchful waiting in Sweden found no significant psychological difference at 5 years (in worry, anxiety, or depression) between the two arms [32•]. Surveillance is clearly stressful for some men. However, patients with prostate cancer, whether treated or not, are often concerned about the risk of progression. All practitioners are familiar with the all too frequent patient, 5 or more years free of disease after local therapy, who is obsessed with his PSA, detectable or not. Concern about PSA recurrence is common amongst treated and untreated patients. Patients who are educated to appreciate the very indolent natural history of most good-risk prostate cancers may avoid much of this anxiety.

Practical aspects of active surveillance

- Candidates for active surveillance should, in most cases, have favorable-risk prostate cancer characterized by the absence of Gleason 4 or 5 pattern, PSA less than 10, and T1c or T2a disease. Patients who have less than a 10-year life expectancy based on age and comorbidity may qualify with higher grade or PSA. Based on the compelling data referred to earlier on the prevalence of histologic cancer in young men, young age in no way should preclude surveillance. Within the favorable-risk category, clinical judgment with respect to disease volume and other risk factors is called for. For example, a 50-year-old man with a PSA of 3 and one or two microfoci of Gleason 6 disease is a perfect candidate; the same patient with multiple positive cores containing extensive disease with a strong family history would not be.
- Patients on surveillance should have a PSA and DRE every 3 months for at least 2 years, and a confirmatory biopsy within 1 year of the first biopsy. After 2 years, stable patients should be monitored with PSA and DRE every 6 months for life, and repeat biopsy every 3 to 5 years, depending on age, comorbidity, and risk. Approximately 20% of patients can be expected to have a PSADT of less than 3 years, and 5% to 10% will demonstrate a significant increase in Gleason score on repeat biopsy. These patients should be regarded as high risk and treated appropriately. The remainder (70%) are low risk and should be managed with ongoing surveillance.
- A doubling time of 3 years is not an absolute cutoff. For patients in the grey zone, patient age and comorbidity, extent of disease on repeat biopsy, and patient expectations must also be taken into account. Most patients do not demonstrate grade or volume progression or significant PSA progression in spite of prolonged follow-up. Borderline patients (with PSADT of 3–5 years, or an increase in cancer volume or small amounts of Gleason 4 pattern on repeat biopsy) should continue on more intensive surveillance until they declare themselves one way or the other. Clinical judgment is a critical part of the equation.
- In most patients, a determination that the patient has an aggressive phenotype should be made at approximately 2 years after surveillance has been initiated, based on 8 to 9 PSA data points and two sets of 8 to 12 core biopsies.
- The risk assessment approach could be enhanced by incorporating a molecular profiling–based evaluation of progression risk. Using SNP chips, gene array, and proteomics, markers will likely be identified that, individually or aggregately, characterize more aggressive phenotypes amongst favorable-risk patients. This would readily translate from bench to bedside in patients who are surveillance candidates. One can easily envisage a scenario in which patients with favorable-risk disease based on Gleason score, PSA, and cancer volume are assigned further risk groupings based on clinical and genetic factors (including family history, race, total prostate volume,

body mass index, and a panel of genetic polymorphisms). Risk grouping assignment, based on high-quality data, would permit accurate estimates of the risk of progression and death. This would enhance the appeal of the surveillance approach. For example, a patient told that he had a 1% to 2% chance of prostate cancer death and a 5% to 10% chance of progressing in 20 years would likely choose surveillance in most cases.

- The active surveillance–selective delayed intervention approach is currently the subject of evaluation by a prospective randomized trial, called Surveillance Therapy Against Radical Treatment (START). In this trial, patients with favorable-risk disease are randomized between the approach described earlier and the patient's choice of standard therapy (surgery, brachytherapy, or external beam). The endpoint is prostate cancer–specific mortality. The trial will be implemented through the intergroup mechanism by the Clinical Trials Support Unit of National Cancer Institute.
- There is also a major opportunity for intervention studies during the period of surveillance. The PCPT experience suggests that 5-alpha reductase inhibitors may inhibit the progression of microfocal prostate cancer, and studies of this intervention during surveillance are warranted. Micronutrients may also play a protective role, and studies are ongoing to determine whether dietary modification or vitamins may further stabilize the prostate cancer cells in these patients.

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