Point: Active Surveillance for Favorable Risk Prostate Cancer

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Abstract
Active surveillance for favorable risk prostate cancer has become increasingly popular in populations where prostate cancer screening is widespread, because of evidence that prostate cancer screening results in the detection of disease that is not clinically significant in many patients (i.e., untreated, would not pose a threat to health). This approach is supported by data showing that patients who fall into the category of clinically insignificant disease can be identified with reasonable accuracy, and that patients who are initially classified as low-risk who reclassify over time as higher-risk and are treated radically are still cured in most cases. Active surveillance means 1) identifying patients who have a low likelihood of disease progression during their lifetime, based on clinical and pathologic features of the disease, patient age and comorbidity; 2) close monitoring over time; 3) developing reasonable criteria for intervention, which will identify more aggressive disease in a timely fashion and not result in excessive treatment; and 4) meeting the communication challenge to reduce the psychological burden of living with untreated cancer. This article reviews the results of active surveillance, the criteria for patient selection, and the appropriate triggers for intervention. (JNCCN 2007;5:693–698)

Why would any healthy person, newly diagnosed with cancer, elect not to undergo curative treatment? Newly diagnosed prostate cancer patients presented with the option of active surveillance often ask this reasonable question. Communicating the answer to this question clearly is a critical component of an active surveillance strategy. This article reviews the basis for this approach and the principles of patient selection and indications for intervention while on surveillance. Active surveillance for screen-detected, low-volume cancer is based on the following 5 postulates: 1) prostate cancer screening results in the detection of prostate cancer that is not clinically significant in many patients (i.e., if left untreated, prostate cancer would not threaten health); 2) patients who fall into this category can be identified with reasonable accuracy; 3) no treatment is minimal in terms of side effects and cost; 4) patients who are initially classified as low risk who reclassify over time as higher risk and are treated radically are still cured in most cases; and 5) the psychological burden of living with untreated cancer has less impact on quality of life than unnecessary curative therapy.

Rational selection of patients for a surveillance strategy should be guided by these postulates. This means 1) identifying patients who have a low likelihood of disease progression during their lifetime, based on clinical and pathologic features of the disease, and patient age and comorbidity; 2) close monitoring over time; 3) developing reasonable criteria for intervention, which will identify more aggressive disease in a timely fashion and not result in excessive treatment; and 4) meeting the communication challenge to reduce the psychological burden of living with untreated cancer.

For men with elevated levels of serum prostate-specific antigen (PSA) or abnormal digital rectal examination (DRE), prostate cancer screening based on prostate biopsy causes many men to be diagnosed with prostate cancer for whom the disease is not life-threatening. In the United States, 2.74 million men aged 50 to 70 years have a PSA level more than 2.5 ng/mL. If all American men in this age group underwent PSA testing, and a PSA level more than 2.5 ng/mL is used as an indication for biopsy, then 775,000 cases of prostate cancer would be...
Many Gleason score 6 prostate cancer and showed that grade interpretation as a result of stage migration caused by PSA. Although patients with Gleason score 6 or less prostate cancer, approximately 65% died of prostate cancer within 20 years. For Gleason score 7 prostate cancer, approximately 65% died of prostate cancer within 20 years. In addition, the same authors recently reanalyzed the original slides using contemporary Gleason scoring, and showed that grade interpretation has changed over the past 20 years, largely because of the reclassification of cribriform pattern as Gleason grade 4 instead of 3. Many Gleason score 6 prostate cancers diagnosed 20 years ago would be called Gleason score 7 today. Thus, the Connecticut results are unrepresentative of contemporary PSA-diagnosed patients, who would be expected to have much lower mortality rates from untreated Gleason score 6 prostate cancer. Therefore, the prostate cancer mortality of untreated non-screen-detected contemporary Gleason score 6 prostate cancer may be as low as 10% at 20 years.

Identification of Clinically Insignificant Disease

The gold standard for clinically insignificant prostate cancer, used by virtually all authors who attempt to predict minimal disease based on clinical parameters, is a radical prostatectomy specimen containing less than 0.5 cm³ of Gleason score 6 or less prostate cancer. This gold standard was established in a paper by Stamey et al., who examined prostate glands obtained from 139 consecutively sampled radical cystoprostatectomy specimens and found that 55 (40%) had incidental prostate cancer. Because the clinical prevalence of prostate cancer was 8%, the authors concluded that tumor volumes above the 92nd percentile (0.5–6.1 mL) were clinically significant. The arbitrariness of this is concerning. If the clinically significant prostate cancer rate was set at 4%, the clinically significant prostate cancer volume would be closer to 1 mL; conversely, if it were set at 12%, the clinically significant prostate 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 clinically insignificant disease. The incidence varies widely, from up to 30% in T1c patients, as reported by the Johns Hopkins group, to values as low as 9%. Common clinical parameters predicting for minimal disease include Gleason score 6 or less, less than 3 mm of prostate cancer in toto, and less than one third of cores involved (Table 1). Importantly, the Epstein criteria permit any 1 core to have up to 50% involvement, representing much more substantial disease than a few microfoci. This definition is based on a pathologic end point. The definition of clinically insignificant prostate cancer as less than 0.5 cm³ of low-grade disease has never been validated in a study with a clinical end point. Based on substantial data, including the Prostate Cancer Prevention Trial, and the incontrovertible ratio of 7:1 between the current lifetime likelihood of diagnosis (about 1 in 6) and death (1 in 40), this definition of clinically-insignificant prostate cancer understates the proportion of patients who harbor prostate cancer that is not destined to pose a threat to their life (about 6 of 7). In any case, patients fulfilling the Epstein criteria for insignificant disease represent optimal candidates for active...
surveillance. An option is to relax the volume criteria for patients older than age 65 years and include patients older than 75 years with a Gleason score 7 (3+4).

**PSA Kinetics in Patients on Active Surveillance**

Several authors have reported that the median PSA doubling time (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 among Asians and North Americans is remarkably consistent.\(^\text{18,19}\) Robust data suggest that a short PSADT correlates with disease aggressivity and a higher likelihood of prostate cancer mortality. Egawa et al.\(^\text{20}\) 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. In a watchful-waiting cohort, McLaren et al.\(^\text{21}\) 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.\(^\text{22}\) reported that a rise in PSA of more than 2 ng/mL/y before surgery identified 100% of those patients at risk for prostate cancer mortality at 7 years. No patients whose PSA increased less than 2.0 ng/mL/y before surgery died of the disease. Therefore, a rise in PSA of more than 2.0 ng/mL/y, which corresponds to a PSADT of 3 years or less in a patient with PSA 6 ng/mL, clearly identifies a group at risk for prostate cancer.

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 greater than 2.0 identified 100% of patients dying of prostate cancer within 10 years of surgery in the D’Amico group, cause-specific survival at 10 years in this high-risk group was still 85%.\(^\text{22}\) In addition, most prostate cancer deaths occurred in men with high-grade prostate cancer. The 10-year cancer mortality rate among the Gleason score 6 or less group was only 7% in the quartile with a PSA velocity greater than 2.0 per year. Aggressive therapy is therefore still warranted in favorable-risk patients with a rapid PSADT or high velocity.

**Results of this Approach**

Choo et al.\(^\text{18,23}\) and Klotz et al.\(^\text{24}\) were the first to report on a prospective active surveillance protocol incorporating selective delayed intervention for the subset with rapid PSA progression or Gleason grade progression on repeat biopsy. The eligibility criteria for this group included patients with T1c or T2a prostate cancer, Gleason score 6 or less, and PSA 10 or less. For patients older than 70 years, these criteria were relaxed to include a Gleason score 7 (3+4) or less and/or PSA 15 or less. The current cohort comprises 331 patients. The median age was 70 years, with age ranging from 49 to 84 years; 80% of patients had Gleason score 6 or less, and PSA 10 or less. For patients older than 70 years, these criteria were relaxed to include a Gleason score 7 (3+4) or less and/or PSA 15 or less. The current cohort comprises 331 patients. The median age was 70 years, with age ranging from 49 to 84 years; 80% of patients had Gleason score 6 or less, and the same proportion had PSA less than 10 ng/mL (median, 6.5 ng/mL). With a median follow-up of 6 years, 101 patients (34%) came off active surveillance and 198 remained on surveillance. Of patients discontinuing surveillance, the reason was biochemical progression in 15%, clinical progression in 3%, histologic progression in 4%, and

<table>
<thead>
<tr>
<th>Study</th>
<th>PSA Density</th>
<th>N Cores Positive</th>
<th>Maximum % of Cores Positive</th>
<th>Grade</th>
<th>% Tissue Positive</th>
<th>Extent (mm)</th>
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<td>Epstein et al.(^\text{8})</td>
<td>&lt; 0.10</td>
<td>&lt; 3</td>
<td>&lt; 50</td>
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Abbreviation: PSA, prostate-specific antigen.
patient preference only in 12%. With median follow-up 7 years (range, 2–11 years), overall survival was 85% and disease-specific survival was 99% (Figures 1 and 2).

Only 3 of 331 patients had died of prostate cancer at the writing of this article, all of whom had PSADTs of less than 2 years, and death occurred 3.0, 5.1, and 5.2 years after diagnosis. All 3 exhibited the same pattern of clinical progression: initial favorable prognostic factors; rapid rise in PSA which led to treatment 6, 9, and 11 months after the initial diagnosis; and progressive rise in PSA and clinically apparent bone metastases within a year after treatment, which resulted in androgen deprivation therapy. All 3 patients died within 3 years of the initiation of androgen deprivation therapy. The rapid progression after diagnosis suggested that these patients had occult metastases at initial disease presentation, and that their outcome would not have been altered by earlier treatment. This assumption is supported by the randomized Swedish trial comparing radical prostatectomy to watchful waiting. In that study, there was a 44% reduction in prostate cancer mortality at 10 years, with an absolute survival benefit of 5%. The median PSA in the study was 13, and 40% of patients had Gleason 7 or higher. Only 5% were screen-detected. Thus, this group was considerably higher risk than the typical screen-detected man with a mild elevation of PSA and small-volume Gleason 6 disease. Importantly, however, survival was similar in both groups until 5 years had elapsed. Local therapy for localized prostate cancer is very unlikely to alter survival before 5 years.

The median PSADT, calculated using logarithmic regression, was 7 years. In this study, 22% of patients had PSADT less than 3 years, whereas 42% had PSADT more than 10 years, suggesting an indolent course of disease. The Gleason score remained stable in 92% of patients; only 8% showed a significant rise in Gleason score, classified as an increase of 2 or more. From this group, 29 patients (10% of the cohort) underwent a radical prostatectomy as a result of a short PSADT or grade progression. Of these patients, all had initial Gleason score 5 to 6, PSA less than 10 ng/mL, and tumor stage pT1–2 at study entry. The final pathology was stage pT2 in 18 patients (64%), pT3a in 11, pT3b in 1, and N+ in 1. Among the 18 patients with PSADT less than 3 years, 7 had positive margins. Even among the worst subset of the cohort (those reclassified over time as higher risk), most remained curable with delayed therapy.

**PSADT or Velocity as a Trigger for Intervention?**

The authors’ group used PSADT less than 3 years as the trigger for intervention. This is calculated by modeling the natural log PSA (ln(PSA)) using a general linear mixed model (GLMM) based on a multivariate analysis of the authors’ active surveillance cohort. In this model, baseline PSA, Gleason score, and age predicted subsequent PSADT. Thus the model allows for correction of these variables. The GLMM method of calculating PSADT is available at [http://psakinetics.sunnybrook.ca/](http://psakinetics.sunnybrook.ca/) (Accessed June 28, 2007).
site is freely available and allows clinicians to store their own patients’ PSA data on the site. The GLMM method will be used for patients entered in the Surveillance Therapy Against Radical Treatment (START) trial comparing active surveillance with standard radical treatment.

Using this approach, the author calculated the proportion and frequency of stable, untreated patients who would have been offered treatment based on the following PSADT triggers for radical intervention: 1) PSA threshold (PSAt) 10 ng/mL for patients with initial PSA less than 10; 2) PSAt 20; 3) a linear regression of ln(PSA) versus time less than 2 years for all PSA values; 4) ln(PSA) versus time less than 2 years using the first and last PSA on record; 5) actual PSA velocity more than 2 years over past year; 6) calculated PSA velocity more than 2 years; and 7) a GLMM of ln(PSA).

In this study, 134 patients remain on surveillance with a minimum of 2 years follow-up. As of January 2007, the median follow-up was 5.8 years (range, 2.0–10.5 years). No patient has died of prostate cancer or had metastatic disease; 14 (10.4%) have died of other causes. The proportion of patients who would have received treatment using various triggers is listed in Table 2.

The authors’ group conclude that patients followed up with surveillance may be overtreated if the PSADT is calculated using PSAt more than 10, PSAt more than 20, linear regression of PSADT, PSADT based on first and last values, or actual or calculated PSA velocity more than 2 years. The follow-up strategy for managing patients with active surveillance and selective delayed intervention is described in Table 3.

**Conclusions**

A rational approach to active surveillance involves patient selection for initial surveillance based on Gleason score 6 or less, PSA 10 or less, and T1c–T2a. For younger patients (age < 60 years), the Epstein criteria of one third or fewer of cores positive, and no more than 50% involvement of any one core, are warranted. For older patients (age > 75 years) or those with a life expectancy less than 10 years because of comorbidity, PSA may be as high as 15 and Gleason score 7 (3+4), based on the Connecticut watchful waiting data of Albertsen et al.

The second component of the rational approach involves patient selection for radical intervention during surveillance. The authors’ approach has been to use PSADT less than 3 years (20% of patients) or grade progression to Gleason 4+3 or higher (5%). The authors used the GLMM method based on ln(PSA) to calculate PSADT. Using a trigger of PSA velocity greater than 2.0 ng/mL/y may result in overtreatment of stable patients. In the authors’ cohort, 50% of the stable patients (100% of whom remain untreated and free of disease progression) would have undergone

### Table 2 Results of Various PSA Triggers for Radical Intervention in the Sunnybrook “Stable” Cohort

<table>
<thead>
<tr>
<th>PSA Trigger</th>
<th>% Who Would Have Been Treated Using This Trigger</th>
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<tbody>
<tr>
<td>GLMM</td>
<td>0</td>
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<tr>
<td>PSA &gt; 10</td>
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<tr>
<td>PSA &gt; 20</td>
<td>10</td>
</tr>
<tr>
<td>PSADT &lt; 2 years by linear regression</td>
<td>39</td>
</tr>
<tr>
<td>PSADT &lt; 2 years by first and last value</td>
<td>39</td>
</tr>
<tr>
<td>Actual PSA velocity &gt; 2 ng/mL/y</td>
<td>49</td>
</tr>
<tr>
<td>Calculated PSA velocity &gt; ng/mL/y</td>
<td>49</td>
</tr>
</tbody>
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**Abbreviations:** GLMM, general linear mixed model; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time.

### Table 3 Active Surveillance: Suggested Algorithm for Eligibility and Follow-Up

**Eligibility:**

| PSA ≤ 10, Gleason score ≤ 6, T1c–T2a (for men aged < 75 years and with > 10-year life expectancy) |
| For men aged 50–60 years: < 3 cores involved, < 50% of any one core |

**Follow-Up Schedule:**

| PSA, DRE every 3 months over 2 years, then every 6 months assuming PSA is stable |
| 10–12 core biopsy at 1 year, and then every 3 to 5 years until age 80 years |
| Optional: TRUS on alternate visits |
| Intervention: for PSA doubling time < 3 years (in most cases, based on at least 8 determinations; about 20% of patients) |
| For grade progression to Gleason score 7 (4+3) or higher (about 5% of patients) |

These are guidelines, and should be modified according to patient age and comorbidity

**Abbreviations:** DRE, digital rectal examination; PSA, prostate-specific antigen; TRUS, transrectal ultrasound.
radical intervention while on surveillance using this criterion.

References