Platinum Opinion

Optimizing Active Surveillance

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Active surveillance (AS) evolved to address the overtreatment associated with prostate cancer screening. While AS is one approach to reducing overtreatment, questions remain regarding AS safety in specific subgroups and the optimal follow-up strategies. There are areas of consensus that inform clinical decisions, uncertainty arising from evidence gaps, and research needs to improve individualization of care. This Platinum Opinion addresses AS only, and not watchful waiting (see definition below).

1. **Areas of consensus**

1.1. **Definitions related to AS**

AS is an alternative to immediate treatment for men fit for curative intervention, with the option for delayed treatment. Men who are not fit for curative intervention should be offered watchful waiting/observation and palliative therapy for disease progression [1]. Reclassification refers to the finding of a greater extent of low-grade cancer (Gleason score 6) or of higher-grade cancer (Gleason score >6) on prostate biopsy that should trigger consideration of treatment [1].

1.2. **Selection of candidates for AS**

A large body of evidence suggests that older men with favorable-risk prostate cancer (Table 1) are those least likely to benefit from treatment [2]. There is agreement that men with Gleason score of 4 + 3 or greater should not be offered surveillance because of the association between primary pattern 4 and cancer-specific death [1].

1.3. **Follow-up during AS**

A rational approach is digital rectal examination annually, prostate-specific antigen (PSA) at 3–6-mo intervals, a transrectal ultrasound–directed confirmatory biopsy within 12 mo of diagnosis, and serial prostate biopsies at 2–5-yr intervals thereafter. There is general consensus that PSA kinetics are not specific for disease progression, but should trigger further evaluation rather than intervention [1].

2. **Areas lacking consensus**

2.1. **Disease classification**

There is no consensus on drawing a distinction between very low-risk and low-risk disease (Table 1), although the rationale seems strong. First, cancer extent on biopsy and PSA density are directly associated with grade reclassification during AS in most studies [2]. Second, there is a twofold higher risk of non–organ-confined cancer and Gleason pattern 4 in low-risk compared to very low-risk disease [3]. Third, at median follow-up of 8 yr on AS, there is a twofold higher risk of metastatic progression, prostate cancer death, and treatment failure for those treated on AS when comparing low-risk and very low-risk disease [4]. Thus, for men who do not meet strict criteria for very low-risk prostate cancer and whose personal preference is to avoid treatment, novel markers and image-guided biopsy may be helpful in informing decisions [2]. For example, magnetic resonance imaging (MRI)–guided fusion biopsy when combined with systematic biopsy may help in safely expanding the pool of candidates beyond the very low-risk stratum by excluding the presence of high-grade cancer. Furthermore, expression profiling of low-grade cancers may allow identification of those with a higher risk of disease progression in the future, despite the microscopic appearance of indolent disease. These tests may be most appropriate when there is discordance between pathologic and clinical findings [1], such as high PSA density despite...
small-volume, low-grade cancer, or higher-volume, low-grade cancer but otherwise very low-risk disease.

2.2. Safety of AS for specific subgroups

There is a lack of consensus on the safety of AS for specific subgroups: younger men, African-American (AA) men, and those with Gleason score 3 + 4 cancer. The median age of men in randomized trials of surgery versus observation and in AS cohorts is 65–68 yr. Thus, the safety of AS among younger men with lower competing risks has not been proven [4].

Compared to Caucasians, AA men have double the risk of death from prostate cancer, have higher rates of grade reclassification during AS, and are more likely to have higher-grade and higher-volume cancers [2], with some evidence of a propensity for anterior cancer location easily missed on a systematic biopsy. The disparity in outcomes between AA and Caucasian men may well be due to more aggressive disease biology [5]. Given this apparent difference in aggressiveness and the fact that fewer than 1 in 10 men in AS programs are AA, the safety is uncertain for this subgroup of men.

Although AS is being considered for men with small-volume secondary pattern 4 prostate cancer (Gleason score 3 + 4) that is otherwise of low risk, there are many reasons to be overly cautious in recommending a noncurative approach for this subgroup. First, upgrading to Gleason ≥ 4 + 3 on surgical pathology from biopsy is 5% for Gleason score 6 and 20% for Gleason score 3 + 4 [6]. Thus, misclassification rates are substantially higher for men with Gleason 3 + 4 compared to Gleason score 6. This misclassification rate (5%) is consistent with the 15-yr reclassification rate to Gleason ≥ 4 + 3 (5%) for men with very low-risk to low-risk disease on AS [7]. Second, after 32 yr of follow-up without curative intervention in the prePSA era, cancer-specific survival was 88% for Gleason score 6 compared to 75% for Gleason score 3 + 4 [8]. Third, in an AS program that allowed enrollment of Gleason score 3 + 4 prostate cancer, progression to metastatic disease was three to four times higher for Gleason 3 + 4 compared to Gleason 3 + 3 [9].

3. Research needs and solutions

Outcomes for AS suggest that 24–40% of men undergo treatment after 5 yr on surveillance; the three most common triggers for intervention are volume and/or grade reclassification on biopsy, PSA kinetics, and patient preference. Some 0.1–2.8% of patients develop metastases, and 0–2.0% die of prostate cancer at a median follow-up of 5–8 yr [2] (Table 2).

Two programs (Johns Hopkins and Sunnybrook) prospectively enrolled patients using criteria for enrollment and follow-up protocols that differed but were determined a priori [2] (Table 2). Comparison of outcomes suggests that enrollment criteria and follow-up, including triggers for intervention, may influence disease-specific outcomes. However, an unmet need is how best to balance selection (restrictive vs less so) and follow-up (intense vs less so) with the risk of harm without treatment. It seems rational to use the strictest criteria for selection (ie, very low risk), more intense follow-up, and lower thresholds for intervention for the youngest men in the best health and with the most years of life remaining [4], including those who are AA and potentially at greater risk of harm without treatment.

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**Table 1** – Schemes most commonly used for active surveillance risk stratification [2]

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Stage</th>
<th>Grade</th>
<th>PSA (ng/ml)</th>
<th>PSAD (ng/ml/cm²)</th>
<th>Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>T1, T2a</td>
<td>Gleason 6</td>
<td>&lt;10</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Very low risk</td>
<td>T1c</td>
<td>Gleason 6</td>
<td>&lt;10</td>
<td>&lt;0.15</td>
<td>&lt;3 biopsy cores with cancer ≤50% cancer involvement of any core</td>
</tr>
</tbody>
</table>

PSA = prostate-specific antigen; PSAD = PSA density; NA = not applicable.

**Table 2** – Five active surveillance programs with 5–8-yr median follow-up for more than 4000 patients in total and results published between 2010 and 2016[^1^]

<table>
<thead>
<tr>
<th>Cohort</th>
<th>GS ≥7 (%)</th>
<th>Median FU (yr)</th>
<th>5-yr treatment (%)</th>
<th>Metastases (%)</th>
<th>Prostate cancer (%)</th>
<th>Overall mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johns Hopkins</td>
<td>0</td>
<td>5</td>
<td>37</td>
<td>0.4</td>
<td>0.15</td>
<td>4</td>
</tr>
<tr>
<td>Sunnybrook</td>
<td>13</td>
<td>6</td>
<td>24</td>
<td>2.8</td>
<td>1.9</td>
<td>15</td>
</tr>
<tr>
<td>Göteborg</td>
<td>NR</td>
<td>8</td>
<td>39</td>
<td>0.02</td>
<td>1.2</td>
<td>22.7</td>
</tr>
<tr>
<td>UCSF</td>
<td>8</td>
<td>5</td>
<td>40</td>
<td>0.1</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Royal Marsden</td>
<td>7</td>
<td>6</td>
<td>30</td>
<td>NR</td>
<td>0.4</td>
<td>6</td>
</tr>
</tbody>
</table>

GS = Gleason score; FU = follow-up; NR = not reported; UCSF = University of California at San Francisco.

[^1^] Adapted from Tososan et al. [2].
By contrast, a more relaxed approach to selection and follow-up may be reasonable for older men with associated comorbidities and fewer years of life remaining.

AS involves selection, monitoring, and determining when or not to treat, a process that requires accurate risk assessment and communication of that risk to patients. To individualize the process and safely expand the pool of candidates for AS will require (1) further definition of the host and tumor factors that influence outcomes; (2) identification of markers of adverse outcomes and disease progression; (3) development of tools for assessing a patient’s personal preferences for living with cancer and the side effects of treatment; and (4) development of strategies for increasing adherence to AS. The use of prognostic grade groups is a start towards improving the communication of risk to men with favorable-risk disease. It is believed by some, but as yet unproven, that men will view their disease differently when told that the aggressiveness of their cancer on a scale from 1 to 5 is 1, rather than 6 on a scale from 2 to 10 (Supplementary Table 1).

Novel biomarkers, genomic testing, and image-guided biopsy (MRI-targeted biopsy or fusion biopsy) may further refine disease classification, moving the process of surveillance towards a more individualized approach (Supplementary Fig. 1). These newer tests will be increasingly used with current predictors in models for assessing risk [10]. However, which patients will benefit from these tests is not clear and will require further evaluation.

AS has been increasingly adopted worldwide (Supplementary Table 2) and may overtake curative intervention for management of favorable-risk prostate cancer. This change in practice may shift the balance between benefit and harm for PSA-based screening towards greater benefit, and change public policy regarding prostate cancer screening. Conversely, if AS for favorable-risk prostate cancer is replaced by focal therapy without evidence of improved outcomes, urologists may once again find themselves defending the wholesale adoption of an expensive technology without supporting evidence.

Conflicts of interest: The author has nothing to disclose.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2016.07.017.

References


