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Role of Active Surveillance in the Management of Localized Prostate Cancer

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Active surveillance is an increasingly recognized treatment option for men with low-risk prostate cancer. Despite encouraging evidence for oncologic efficacy and reduction in morbidity, several barriers contribute to the underuse of this management strategy. Consistent selection criteria as well as identification and validation of triggers for subsequent intervention are essential. Incorporation of novel biomarkers as well as advanced imaging techniques may improve surveillance strategies by better defining eligibility as well as improving prompt detection of disease progression.

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In October 2011, the US Preventive Services Task Force (USPSTF) issued a draft recommendation against using prostate-specific antigen (PSA) testing for prostate cancer screening, proclaiming this practice provides "no benefit" and, in fact, "may be harmful." The panel failed to acknowledge severe methodological limitations in the trial purported to show no benefit from screening (1) and overestimated the harms of treatment in contemporary, experienced practice settings. More importantly, the recommendation demonstrated a poor recognition of the marked heterogeneity of prostate cancer in terms of biological behavior and prognosis. Despite a 40% decline in mortality rates since the start of the PSA screening era, high-risk prostate cancer still kills more men in the United States than any cancer except lung cancer (2). Nonetheless, the number of deaths attributable to prostate cancer is dwarfed by the number of men diagnosed and with downward risk migration driven by both screening and extended-pattern prostate biopsies, and many prostate cancers may never progress to a clinically relevant stage even in the absence of treatment. Growing concerns about overdiagnosis focus on resulting overtreatment of low-risk disease, because in the United States, like in many other developed countries, detection and treatment are tightly linked (3,4).

Active surveillance (AS) is an alternative initial management strategy that allows for definitive treatment for men with disease progression in addition to avoiding treatment-related morbidity in those without progressive disease. Though still infrequently applied in this country, AS is the subject of increasing interest in both the United States (5) and internationally and has been incorporated into National Comprehensive Cancer Network (NCCN) guidelines since 2010 (6). Eligibility criteria vary by institution (Table 1) but generally include low, stable serum PSA measurements (<10 ng/ml or PSA density <0.15); no Gleason pattern 4 or 5; clinical stage T1–2; and low volume of cancer on biopsy. Notably absent from most criteria is age at diagnosis. In general, younger men with prostate cancer undergo radical prostatectomy regardless of disease risk (19). However, younger men with low-risk and very low-risk disease may not exhibit progression for years or decades—if ever—and may enjoy at least a prolonged interval without the potential side effects of treatment. Indeed, proposals (20) to initiate PSA screening at age 40 years cannot gain traction if such men, found to have a microfocus of Gleason 3 disease, must undergo immediate treatment.

Contemporary AS protocols monitor potential progression by means of serial PSA testing, digital rectal exam (DRE), and prostate biopsies. Common "triggers" for intervention include tumor progression in subsequent biopsy reflected by higher grade and/or volume, short PSA doubling time (PSA-DT) or increasing PSA velocity, and changes on serial imaging or patient anxiety (Table 1) (21). Although frequently used as a biomarker for monitoring prostate cancer, the short-term use of PSA kinetics in AS has been questioned (22–24) and, therefore, is typically combined with information provided by biopsy and DRE. However, prostate biopsies are costly and invasive, pose potential for significant morbidity, and may underestimate true extent and grade of disease (25). Moreover, assessment of grade via biopsy, even among expert pathologists, is not always consistent, particularly in very low-volume tumors (26). These inadequacies reflect a need for novel biomarkers or other indicators of disease progression in order to improve AS and ultimately reduce the burden of overtreatment.

AS Efficacy and Limitations

Compelling evidence reported from multiple centers support the use of AS in patients with low-risk prostate cancer, at least in the short to intermediate term. Several academic centers are following cohorts of men undergoing AS using various protocols with intermediate follow-up (average 22–82 months) (7–18). For patients with low-risk disease, weighted mean values for overall survival, cancer-specific survival (CSS), and progression-free survival were 92%, 99%, and 67%, respectively (Table 1). Progression is

Table 1. Active surveillance series*

Institution	Cohort size	Median follow-up (mo)	Selection criteria	Intervention trigger	Progress by PSA/PSA kinetics, %	Progress by grade/volume, %	OS	CSS	PFS
Royal Marsden (7)	326	22	cT ≤2a; Gleason ≤3 + 4; PSA ≤15 ng/mL; ≤50% positive biopsy cores	PSA-V >1 ng/ml per year; repeat biopsy with primary Gleason ≥4 or >50% positive cores	18	13	98	100	73
University of Miami (8)	230	32	≤2 cores positive or ≥20% cancer in any core	Gleason upgrade, increase in tumor volume; >2 positive biopsy cores	n/a	10	100	100	86
Johns Hopkins (9,10)	769	32	T1c; Gleason ≤3 + 3 = 6; PSAd ≤0.15; max 2 positive cores	Surveillance biopsy no longer meets selection criteria; patient request	n/a	14	98	100	54
University of California San Francisco (11,12)	640	47	T1 or T2a, PSA ≤10; Gleason ≤3 + 3 = 6; <33% positive biopsy cores	Gleason upgrade; increase in PSA-V of 0.75 ng/mL per year	5 of 11†	35	97	100	54
University of Toronto (13,14)	453	82	T1c; PSA ≤10–15; Gleason ≤3 + 3 = 6	PSA-DT <3 y	14	9	68	97	70
Multicenter European study (15,16)	988	52	T1c or T2; PSA <10; Gleason ≤3 + 3 = 6; PSAd <0.2; max 2 positive biopsy cores	Gleason score ≥7 or >2 positive biopsy cores	13	n/a	91	99	68
Multicenter Japanese study (17)	118	36	T1c; PSA ≤20; Gleason ≤3 + 3 = 6; max 2 positive biopsy cores	PSA-DT ≤2 y; surveillance biopsy no longer meets selection criteria	19	19	n/a	n/a	n/a
Memorial-Sloan Kettering (10,18)	238	22	cT ≤2a; PSA ≤10 ng/mL; Gleason ≤3 + 3; ≤3 positive biopsy cores; ≤50% of any core positive	PSA ≥10 ng/mL, Gleason upgrade to ≥7; >3 positive cores; >50% of any core positive	14	13	n/a	n/a	n/a
Weighted averages							91.9	99.4	67.4

* CSS = cancer-specific survival; n/a = not available; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; PSAd = PSA density; PSA-V = PSA velocity; PSA-DT = PSA doubling time.

† Progression based on PSA doubling time <24 or <36 months.

suggested by changes in histology (increase in Gleason grade or cancer volume), PSA kinetics, stage, or active intervention. The longest AS follow-up has been reported by Klotz et al. on a cohort of 450 patients with a median follow-up of 6.8 years. CSS was less than 100% at 10 years, and half of the 30% of patients treated at 5 years experienced biochemical recurrence after intervention; however, this study included men who opted for AS despite not meeting standard AS criteria (23).

It is important to stress that AS often implies deferred rather than avoided treatment. The proportion of men who undergo subsequent intervention ranges from 14% to 51%, with higher rates during longer follow-up (15–26). Excellent PSA-free survival after delayed prostatectomy has been reported, with 96% and 91%–100% at 2 and 3 years, respectively (16–18,24). To date, death due to prostate cancer is uncommon in patients who choose initial AS. Krakowsky et al. reported results from a prospective 453-patient cohort on AS with 8 years of follow-up. Five men died of disease, only one of whom had favorable characteristics at presentation, and all had PSA-DT in less than 1.6 years (27).

In men who elect AS over immediate treatment, delayed treatment, as yet, does not appear to risk significantly poorer outcomes. Dall'era et al. compared pathological outcomes of men with low-risk prostate cancer who underwent prostatectomy after a period of AS with those undergoing surgery within 6 months of diagnosis (28). Thirty-three men underwent prostatectomy after a median of 18 months (range: 7–76 months) of AS.

Consistent with other reports (29,30), delayed intervention was not associated with pathological upgrade (odds ratio [OR] 0.35, 95% confidence interval [CI] 0.12 to 1.04), nonorgan confined disease (OR 1.67, 95% CI 0.32 to 8.65), or positive surgical margins (OR 0.95, 95% CI 0.16 to 5.76).

Despite promising outcomes, a major limitation of contemporary cohorts is the relatively short duration of follow-up; greater length of time (ie, 15–20 years) is necessary to support oncologic efficacy of this treatment strategy. Another limitation to the literature is the varying disease characteristics among studies, as optimal selection criteria have not been defined, complicating comparisons and generalizability. Furthermore, optimal monitoring strategies need to be better defined. Currently, serial PSA measurement every 3–6 months and annual prostate biopsy are associated with a small risk of cancer mortality (Table 1).

Risks

Risks associated with AS include patient anxiety over disease progression and inherent risks associated with serial prostate biopsy, including potential for erectile dysfunction and growing rates of sepsis due to antibiotic-resistant bacteria (31,32). Particularly worrisome for patients and practitioners is disease progression. It is estimated that at least 30% of patients who meet traditional AS criteria harbor adverse pathologic features at the time of prostatectomy, such as Gleason sum above 6 or pT3 disease (33). This problem of undersampling complicates treatment decisions, as the long-term impact of delayed identification in these cases is unknown. Most evidence to date, albeit with limited follow-up, has suggested that most men who receive active treatment after a period of observation have oncologic outcomes comparable to those with similar risk characteristics undergoing immediate treatment (18).

An increase in grade is currently considered to be the most reliable indicator of tumor progression, especially "late" upgrading because this more likely reflects true biologic progression rather than initial undersampling (34,35). However, as noted above, pathologists are not always consistent in distinguishing small Gleason 3 + 4 from Gleason 3 + 3 tumors (14), and in fact tumors with small foci of Gleason pattern 4 may be indistinguishable from pure pattern 3 tumors with respect to clinical behavior and prognosis (32). The argument against the utility of PSA kinetics on the basis that they do not predict Gleason grade change (34) may be based on a false assumption that grade change is the true "gold standard" in terms of true disease risk.

Overall, fewer than 10% of low-grade prostate cancers result in cancer-specific death after 20 years of follow-up, even in the absence of local therapy (37,38). When disease progression is suspected without histologic evidence on biopsy, PSA kinetics can be used to trigger use of other diagnostic tests, such as repeat 12-core biopsy or magnetic resonance imaging (MRI). In patients with known prostate cancer, MRI appears to have a high predictive value of identifying clinically significant disease (39). Furthermore, AS for low-risk patients is associated with the greatest quality-adjusted life expectancy when compared with open prostatectomy, radiation therapy, and brachytherapy (40), one of the major advantages to this treatment strategy.

Other Potential Barriers to Uptake

For a variety of reasons, relatively few men who are appropriate candidates are managed with AS. Large databases in the United States report that only 10% of eligible men elect AS protocols, whereas in Europe, approximately 30% of eligible men undergo AS (24,41,42). The literature on AS outcomes is complex, and long-term efficacy data are lacking. This results in inconsistencies in study interpretations as well as difficulty in defining optimal selection criteria and monitoring protocols during surveillance, creating barriers to AS adoption. Treatment conversations are expected to be comprehensive, offering "most options" to those with low-risk disease. Although some question whether AS is appropriate in men with long (>15 years) life expectancies, current screening practices will undoubtedly result in more men—including young men with minimal disease risk—who need decision support when considering AS. Patient and provider skepticism regarding oncologic safety are also thought to contribute to the limited use of AS (42). In fact, patient desire for "physical removal of cancer" contributes to treatment choice (43). Action-oriented management is traditional in our healthcare system. Patients often expect active intervention when diagnosed with cancer. Provider financial incentives and legal fears have also been implicated in such decisions (42).

Future: Use of Biomarkers and Imaging

For the past decade, researchers have investigated the use of potential serum and urine biomarkers in diagnosing and monitoring prostate cancer. In 2011, the National Institutes of Health granted $284 million to prostate cancer research (44), with significant funding dedicated to studying surveillance biomarkers (45). The Prostate Active Surveillance Study (PASS), a multicenter cohort study partly sponsored by the Canary Foundation and National Cancer Institute Early Detection Research Network, is currently enrolling AS candidates within five large academic centers. In addition to clinical data, biospecimens (blood, urine, prostate tissue) will be collected for purposes of such studies (46), because markers of disease progression could potentially identify AS patients who may harbor disease with higher risk features. RNA-based urine biomarkers (PCA3 test, the TMPRSS2-ERG fusion gene, transcript expression levels of GOLPH2, SPINK1) are the most well studied, and several of these have demonstrated potential for clinical utility (12).

PCA3 is a prostate-specific noncoding mRNA, significantly overexpressed in prostate cancer tissue and highly specific in predicting prostate cancer risk and aggressiveness (47). When used in AS cohorts, PCA3 was found to be superior to PSA in determining need for repeat biopsy (48). Tosoian et al. (47) used urine PCA3 to predict biopsy progression (though not an absolute endpoint) and found no association (P = .15). Another investigation found no predictive correlation between PCA3 and clinical stage, biopsy Gleason score, surgical pathology Gleason score, tumor volume, or pathological stage (49). PCA3 alone, like many potential markers, may lack predictive ability but may have value when used with nomograms or other biomarker combinations. Other markers that are currently being investigated in AS cohorts include measures of cellular proliferation, such as proliferating cell nuclear antigen

and Ki-67 (50,51); microRNAs, a class of small noncoding RNAs (52,53); and single nucleotide polymorphisms (54).

Diagnostic MRI, independent to other cancer-related characteristics, may help predict long-term cancer progression in men who choose AS and also helps to identify anteriorly found tumor (55–57). T2-weighted MRI sensitivity ranges from 60%–82%, and specificity is reportedly 55%–70% (58–60). Other MR techniques that serve as potential biomarkers of disease progression include MR spectroscopy (MRS), diffusion-weighted MRI (DW MRI), and dynamic contrast-enhanced MRI (DCE MRI). MRI combined with MRS has been shown to improve accuracy of prostate cancer detection and localization, but image acquisition can be cumbersome and time-consuming (61). DW MR measures diffusion of water molecules in tissue. Differing apparent diffusion coefficients between patients with low- vs higher-risk prostate cancer have been identified ($P = .005$). This technique may improve predictions of cancer aggressiveness and progression (61,62). DCE MRI is another potentially useful tool, providing evaluation of prostate tissue microvasculature. Cancers typically show early signal enhancement and washout of signal intensity. Lastly, standard positive emission tomography uses tracers that are ineffective in diagnosing localized prostate cancer. Targeted imaging by way of novel tracer agents with higher sensitivity and specificity, such as ^{11}C-choline and ^{11}C-acetate, are currently under investigation (63).

Clearly, much work is still required to validate both imaging tests and biomarkers for AS disease monitoring protocols, with challenges amplified by the fact that the PSA- and biopsy-based endpoints typically assessed are themselves somewhat problematic as described above. Moreover, it is not obvious exactly how new tests will be incorporated into decision-making algorithms, and which performance characteristics—discrimination, calibration, etc.—are most important to clinicians and patients deciding which if any novel tests to use. Eventually, though, as biomarkers and/or novel imaging tests are improved and validated, they should be able to stratify men not only to treatment vs AS but to AS vs "inactive" surveillance. Given the costs, anxiety, discomfort, and risks associated with serial prostate biopsy in particular, men with tumors biologically verified to be lowest risk—those that likely do not merit the moniker "cancer"—should be able to follow a less intense schedule of both PSA assessments and biopsies.

Conclusion

Widespread screening results in the diagnosis of many men with very low-risk prostate cancer. Such men are often treated immediately. However, to stop screening would risk the thousands of lives saved through early detection of high-risk disease. A far better solution to lessen overtreatment is preferential use of AS for low-risk disease. If this message is to gain traction in health policy circles, however, the burden lies with treating clinicians to address the fact that AS remains markedly underutilized in this setting.

This lag reflects multiple factors, including a lack of consensus on criteria both for patient selection and for early identification of disease progression, as well as multiple financial, legal, and social incentives that favor active treatment. Trials incorporating novel biomarkers and imaging tests and examining more- vs less-intense regimens of surveillance are needed. For men with low-volume, localized disease, AS appears safe to date, but further refinements in surveillance strategies, including both better decision support and detection and validation of novel biomarkers, will likely increase the appeal of AS to larger numbers of men facing a difficult management decision at time of prostate cancer diagnosis.

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