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# Managing localized prostate cancer in the post-PSA era

**James D. Brooks, M.D.**
Department of Urology, Stanford University, Stanford, CA 94305, USA

## Abstract

Because prostate cancer is diagnosed by blind biopsy, there is underlying uncertainty as to its extent and aggressiveness, evidenced by 40% of cases being upgraded after surgery compared to the diagnostic biopsy. This uncertainty contributes to the overtreatment of low risk localized prostate cancer that fuels the current debate surrounding prostate cancer screening and treatment. This issue presents presents a validated tool that uses clinical variables to predict upgrading of Gleason score 6 prostate cancer. Ideally, this and other tools should increase the acceptance, safety and use of active surveillance in men with localized prostate cancer detected by screening and help to address the problem of overtreatment.

### Keywords

Prostate cancer; Gleason grade; upgrading; biopsy; prognosis

Despite its status as the most common cancer diagnosed in U. S. men, with 238,590 estimated cases in 2013, prostate cancer is largely diagnosed by random blind biopsies in response to an elevated serum Prostate Specific Antigen (PSA) level[1]. Since most prostate cancers cannot be seen on transrectal ultrasound, the clinically and biologically most important cancers (which are usually the largest and highest grade lesions) can be missed by chance, while non-representative portions of the incident cancer or secondary cancers are sampled. The uncertainty that arises from not being able to visualize cancers within the prostate has fueled two decades of research to improve the clinical prediction of the presence and aggressiveness of prostate cancer. In this issue on page___, Truong and colleagues present a validated tool to predict upgrading between the diagnostic biopsy and final pathology on radical prostatectomy specimens. This and other prognostic tools mark a new phase in managing localized prostate cancer and are a direct response to the current controversies in prostate cancer screening and treatment.

For most of the PSA-screening era, the primary concern has been that PSA lacks sensitivity and specificity, meaning that many men receive unnecessary biopsies for false elevations, while a large number of cancers are missed because of false negative PSA levels or false negative biopsies due to under sampling of the prostate. The fear of missing important cancers led to several strategies to improve detection including lowering of PSA thresholds from 4 to 2.5 ng/ml, using adjuncts such PSA velocity, and increasing in the number of biopsies taken from 6 to 12 or more cores. The concerns about under detection were amplified in when an analysis of the control arm of the Prostate Cancer Prevention Trial (PCPT) showed that 15% of men had prostate cancer despite having a “normal” serum PSA level<4 ng/ml[2]. In the context of this drive to detect every single prostate cancer, the

Address correspondence to: James D. Brooks, M.D., Department of Urology, Room S287, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305-5118, Telephone: (650) 725-5544; Fax: (650) 723-4200, jdbrooks@stanford.edu.

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phenomenon of upgrading was regarded more as a curiosity. Since all prostate cancer had to be found and treated, the "true" grade was intellectually interesting but of little clinical importance.

Everything changed with the reporting of the 10 year results of the Prostate, Lung, Colon and Ovarian (PLCO) and the European Randomized study of Screening for Prostate Cancer (ERSPC) trials of PSA screening[3, 4]. While PLCO demonstrated no survival benefit to PSA screening, ERSPC showed a small but significant prostate cancer specific survival benefit at the cost of a proportionately large number of men being over treated. These studies formed the basis for the recent US Preventive Task Force (USPTF) recommendation against PSA screening for the detection of prostate cancer. One can debate the relative merits of these recommendations and these studies; however, they underscore what we have long known about prostate cancer: it occurs late in life and many men die with it rather than from it.

While it is too early to tell what will be the upshot of the USPTF recommendations for the use of PSA screening or for prostate cancer mortality in the U.S. and elsewhere, it is highly unlikely that PSA screening will stop altogether. Practice patterns are slow to change generally, and patients are unlikely to forgo a screening test for a common malignancy as we have already observed with screening mammography. Furthermore, critics of the recommendations justly point out that annual death rates from prostate cancer have dropped significantly since their peak in 1992-1994 and modeling attributes much of that drop to the introduction of PSA screening and subsequent increases in treatment[5]. Therefore, the next phase in management of localized prostate cancer will entail careful selection of men for treatment and expanded use of active surveillance to avoid the significant and life altering consequences of therapy.

Active surveillance is hardly a new concept. Autopsy studies have long shown that small low grade cancers are found commonly in men dying of other causes with prevalence rates almost matching men's age at their time of death[6]. In light of that knowledge, active surveillance had long been used in T1a cancers in the era prior to PSA screening, and, as T1a cancers became increasingly uncommon after the introduction of PSA screening, has been employed in patients with small amounts of low grade cancer (Gleason score 6 or below) on biopsy, particularly in men too old or ill to undergo therapy. Reports of very high prostate cancer specific survival rates in relatively large cohorts of patients on active surveillance showed the safety of this approach and has added impetus to recommending this approach in low risk patients[7]. In addition, the Göteberg site in the ERSPC trial used active surveillance frequently in low risk patients and posted significant survival benefits in the PSA screened arm, while avoiding treatment in 28% of men[8]. In fact, they reported needing to treat only 12 men in order to save 1 man's life, a highly acceptable ratio for any therapy.

Because of heavy PSA screening in the U.S., the number of men who are candidates for active surveillance is expanding. Since PSA screening started, the number of men with low stage prostate cancer has increased dramatically, while the number with high stage disease has fallen[7, 9-11]. Average tumor volumes at radical prostatectomy have likewise fallen[11], and tumor volume has been associated with risk of recurrence after surgery and death from prostate cancer[12]. Screening also has led to a shift of Gleason scores to lower grades. In both PLCO and ERSPC cancers discovered in the second round of screening had significantly lower Gleason scores compared to those discovered in the first round[3, 13]. Interestingly, in ERSPC, much of the survival benefit was derived from first round screening[4]. Indeed, it is likely that the shift in prostate cancer risk induced by PSA screening accounts for the lack of benefit observed in PLCO as well as the Prostate Cancer Observation Versus Observation Trial (PIVOT) that showed no overall or prostate cancer specific survival benefit to surgery

compared to observation[14]. On the other hand, the ERSPC trial and Scandinavian Prostatic Cancer Group Study Number 4 (SPCG4) randomized trial of prostatectomy vs. observation, both initiated in Scandinavia before PSA screening was widely practiced, showed benefits to active screening and treatment[15].

In light of this shift to lower risk prostate cancer, more men should be enrolled in active surveillance. However, since 1990, the percentage of men initially managed with observation has remained stubbornly flat at approximately 9%[16]. Furthermore, in recent years a greater proportion of men with low risk disease are undergoing treatment with advanced technologies including Intensity Modulated Radiation Therapy (IMRT) and robotic prostatectomy, adding to the cost of treating disease that could otherwise be managed expectantly[10]. The presumed reason for high treatment rates of low risk prostate cancer: the uncertainty of the future risk and behavior of these cancers.

If anything, the uncertainty surrounding low risk prostate cancer is decreasing, particularly after recent modifications in Gleason grading[17]. A recent analysis of over 14,000 radical prostatectomy cases with Gleason scores of 3+3=6 revealed an extraordinarily low rate of concurrent lymph node metastases of 0.16% (22 cases). When the cases with lymph node metastases were re-graded using contemporary criteria, all lymph node positive cases were upgraded, meaning that no case of Gleason score 6 prostate cancer had coincident lymph node metastases[18]. This finding concurs with the absence of mortality at Stanford University in Gleason 6 cases where contemporary Gleason scoring has been practiced for many years, and is also likely true at Johns Hopkins, if one discounts Gleason score 6 cases with concurrent positive lymph nodes since they were likely misgraded[12, 19]. Furthermore, the lack of association of tumor volume with recurrence or death in Gleason grade 6 cancer at the time of prostatectomy shows the indolence of these cancers[12]. Since Gleason grade 6 cancers represent nearly half of patients diagnosed currently in the U. S., a large number of men could be safely managed with surveillance, were it not for the uncertainty.

As a step toward addressing this uncertainty, Truong and colleagues have developed a predictive tool for identifying patients at risk for upgrading at the time of surgery. They investigated more than 30 variables and found 4 that predicted upgrading in a multivariable model. Factors that reflect tumor volume, including number of cores involved and maximum extent of involvement on a single core, as well as PSA density have been reported previously to predict low risk disease[20]. Somewhat surprising was the finding that obesity predicted adverse outcome. While obesity has been linked to more aggressive cancer in some studies, others have found no association[21]. To their credit, the authors have validated this predictive tool in 2 independent datasets, with AUC values above other predictive tools based on ROC analysis. Hopefully this tool and others will increase physician and patient confidence that their cancer is truly low risk and thereby increase the acceptance of active surveillance.

This predictive tool is not alone in addressing the issue of upgrading and adverse prognosis. Identification of molecular prognostic biomarkers, particularly transcripts and proteins in the tumor, has been an active area of research for years. Two tests, the Prolaris test from Myriad and the Oncotype Dx prostate cancer test from Genomic Health, recently have been released for use in prostate biopsies to predict disease aggressiveness with the intent of helping to select men for active surveillance[22, 23]. Both tests were developed and tested in surgical cohorts and found to predict recurrence and prostate cancer mortality. The Prolaris test also has been shown to predict mortality in a watchful waiting cohort that included patients from the pre-PSA screening era and patients with a broad range of PSA values and disease states[23]. The Oncotype DX test has recently been shown to predict upgrading between the pre-operative biopsy and radical prostatectomy[22]. Unfortunately neither tool has been tested

in a contemporary active surveillance cohort to see whether they predict disease progression or mortality. While predicting mortality is a high bar, identifying patients at high risk for progression while on surveillance is an important endpoint, since earlier intervention in these men could improve their outcome. Regardless, the hope is that these tests will help men choose surveillance with greater confidence and add unique prognostic information beyond clinical predictive algorithms such as that of Truong et al.

Whether these or other tools will actually increase the number of men on active surveillance will depend upon how they are applied. If the tools are used to identify with high confidence men who are at low risk for up grading, the tests could actually limit the number of men placed on active surveillance. In other words, if the output of these prognostic tools is ambiguous for most men, the added uncertainty could drive them to treatment, while only those whose tests consistently show low risk will opt for active surveillance. In addition, it is not entirely clear whether the prediction of up grading from Gleason score 6 to 7 represents a valid endpoint for deciding against active surveillance, even though upgrading to Gleason 7 has been used as a progression endpoint in many active surveillance trials[7]. In the PLCO, ERSPC, PIVOT and SPCG-4 trials, the magnitude of overtreatment of prostate cancer was so high that it had to extend into patients with Gleason scores of 7 or above. Furthermore, half of patients in the Canadian Active Surveillance trial had Gleason scores of 7, yet 8 year mortality rates were extremely low for the entire cohort (3%)[24]. This raises the question whether more attention should be spent on predicting aggressiveness of Gleason score 7 cancers, in addition to accurately predicting the presence of Gleason score 6. Finally, it will be critical to investigate how these predictive tools influence the use of active surveillance, and affect patient anxiety, cost of care, quality of life and survival.

Soon additional approaches will be deployed to help in treatment selection in men with localized prostate cancer[25]. Imaging approaches, such as multimodal MRI and molecular imaging, as well as new serum and urine biomarkers will better define which patients need to be biopsied and help refine treatment selection by improving prognostication. As each promising approach is introduced, however, constraints in health care spending will dictate that the new technology not only improve outcomes but also lower costs. Undoubtedly, these technologies that allow us to improve on PSA screening will find use in the detection of other malignancies at early stages in other organ sites. Broadly speaking, new cancer diagnostic biomarkers will be discovered for many malignancies through large consortia such as The Cancer Genome Atlas and the Early Detection Research Network and will allow us to identify malignancies early when they can be eradicated by local therapy such as surgery. However, one of the most important lessons from the past 2 decades of PSA screening and treatment is that the ability to diagnose early needs to be directly coupled with meaningful prognostication so that we do not unnecessarily over treat lesions that are not destined to cause harm[25].

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