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Seminar article

What is the best way *not* to treat prostate cancer?

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Abstract

Introduction: Selective treatment approaches for prostate cancer (PCa) are warranted given the highly varied nature of the disease and the consequences associated with definitive therapy.

Materials and Methods: We present a stepwise overview of strategies to not treat PCa, ranging from improved early detection practices that seek to improve the yield at initial diagnosis, as well as refinements to risk prediction and the performance of active surveillance.

Results: Adherence to screening guidelines is non-uniform. Preliminary measures to improve the quality of PCa screening would include greater including the integration of novel markers with higher specificity for clinically significant cancers that seek to stem the burden of over-diagnosis and consequential overtreatment of low-grade tumors. For men diagnosed with PCa we review the centrality of initial risk stratification to allow for greater certainty in management choices: consideration of active surveillance for those with low-risk status, and definitive therapy for men with intermediate and high-risk features. We review the efficacy and nature of active surveillance protocols, and offer a context for refinements that may be anticipated with future study.

Conclusions: The question of how best to not treat prostate cancer is often more complex than policies of universal treatment, yet stand to minimize morbidity and maximize health-related quality of life for patients with appropriately low-risk tumors. An array of refined risk stratification instruments, biomarkers, and genomic assays seek to improve the confidence both prior to, and following diagnosis.

Keywords: Active surveillance; Prostate cancer; PSA screening

Introduction: Why *not* treat?

The ability to offer curative treatment for localized malignancies is a mainstay of cancer care in the contemporary era of surgery and radiotherapy. The prospect of foregoing therapy for prostate cancer (PCa) emerges from insights into the limited biological capacity of histologically low-grade tumors, as well as a demonstrable detriment to health-related quality of life generated by definitive therapy [1–3]. Moreover, as the spectrum of disease contained within PCa is varied, ranging from low-grade tumors exhibiting distinct biologic features from high-grade tumors, characterized by genomic aberrations and the capacity for metastatic progression, there is also a supportive biological basis for tailoring management accordingly [4,5]. The complexity of these issues are magnified further when seen through the lens of the global burden of PCa where early detection practices—most notably serum prostate-specific antigen (PSA) testing of asymptomatic individuals—have resulted in the widespread early detection of PCa in over 1 million men each year [6]. As a result, identifying patients *not* to treat is often more challenging than policies of uniform intervention for all men diagnosed with PCa, an approach that would expose many to *over*-treatment.

Timely definitive treatment is of value for men with higher-grade tumors, where evidence is offered from randomized trials of treatment vs. expectant management, in addition to improvements in PCa-specific mortality associated with treatment of screening-detected disease [7,8]. The viability of *not* treating low-risk patients, incidentally detected PCas have also emerged in various forms. These include trials demonstrating limited benefit to overall or disease-specific survival associated with definitive therapy in low-risk patients [9,10]. In addition,

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prospectively after cohort studies of men managed with active surveillance (AS) offer insight into the long-term safety and viability of such an approach [11–15]. Indirect evidence is also available in the control arms of screening trials that offer insights into the outcomes in the absence of disease detection and treatment [16].

In the proceeding review, we aim to offer a stepwise overview for the rationale and practice for how to *not* treat PCa. We provide special emphasis on refined screening practices, which may minimize the detection of low-risk cancers, as well as the role of initial risk stratification, highlighting recent advances in staging and prognostication that may add certainty at the outset. Lastly, we overview the landscape of approaches to surveillance for favorable-risk men, including the role of thoughtful patient counseling, and the necessity of timely treatment for those demonstrating compelling disease features.

Step 1: Do not diagnose disease that should not be treated

Perhaps the most cost-effective and efficacious way to *not* treat PCa is to not diagnose it in the first place. In extended follow-up, screening of asymptomatic, younger, healthy males with PSA has been associated with improvements in PCa-specific mortality, and overall survival [17]. However, it is essential to emphasize that the benefits of screening have been demonstrated in selected populations—those in whom early detection may culminate in improved outcomes. Although virtually all consensus guidelines addressing the use of serum PSA screening advise cessation of screening among asymptomatic older men (generally >70 y) or limited life expectancy, this practice still occurs with regularity [18–20]. In an analysis of the screening practices of 1,963 primary care physicians in the United States, more than 40% of men age 75 and older received PSA screening including 28.8% ordered by primary care physicians [21]. In the wake of the 2012, U.S. Preventive Services Task Force recommendation against PSA-based screening reports indicate declines in screening within nearly all age demographics, though overall rates remained relatively high, including a large proportion of tests ordered among men more than 80 years of age [22,23]. Better detection practices may be accomplished through widespread adoption of more thoughtful screening with PSA and, at a minimum, adherence to readily accessible guideline recommendations, including obtaining a repeat PSA level before biopsy [24,25].

Research addressing the role of a baseline PSA levels earlier in life stand to foster more nuanced, risk-stratified approaches to screening [26]. Nested case-control studies of Swedish men in the Malmö Preventive Project, followed for a median of 27 years, indicated that midlife PSA concentration (assessed on archival serum specimens) was associated with the downstream risk of developing metastatic PCa [27]. In a recent analysis of the U.S. Physician's Health Study, a longitudinally followed cohort, baseline and midlife PSA levels were strongly associated with the risk of developing lethal PCa. For example, among men with PSA values below the median at baseline, the 30-year risk of developing lethal PCa was 0.19% for men age 40 to 44 years, 0.51% for men 45 to 49 years, 1.62% for men 50 to 54 years, and 0.59% for men 55 to 59 years. Conversely, for men in the top decile of PSA relative with men below the median, the odds of developing lethal PCa were dramatically higher: 8.7-fold higher among men 40 to 49 years, 12.6 for ages 50 to 54 years, and 6.9 for men 55 to 59 years [28]. Taken together these findings suggest that practices incorporating baseline risk levels may offer risk-stratified approaches including continued, vigilant screening for those at the higher-risk spectrum, whereas moderating the intensity of screening for those at very low-risk spectrum.

Efforts to refine candidacy for initial prostate biopsy would also serve to limit the detection of tumors unlikely to require treatment. Reliance on PSA alone to select men for biopsy is associated with reasonable sensitivity and only modest specificity for high-risk disease, leading to the inadvertent discovery of low-risk cancers [29,30]. The integration of novel serum PCa biomarkers with improved discrimination of biologically aggressive tumors may offer favorable discrimination before biopsy, including the PCa antigen 3 (PCA3) and 4-kallikrein and prostate health index (PHI) assays [31]. For example, the PHI score—incorporating free PSA, total PSA, and [-2]proPSA—has demonstrated use in the detection of high-grade (Gleason score $\geq 3+4$) disease [32–34]. When added to clinical predictors (age, digital rectal examination, and biopsy status) PHI improved the area under the curve for the detection of pathologically high-grade or high-stage disease or both [35,36]. Similarly, the 4K panel algorithm (consisting of total PSA, free PSA, intact PSA, and human kallikrein protein 2) has been evaluated in the setting of biopsy, where the diagnostic accuracies of an integrated 4K-clinical model surpassed a standard clinical model as well as individual components [37–39]. In addition, novel urine exosomal assays have been developed, which also appear to offer independent prediction of the likelihood of high-grade disease at biopsy [40]. Although promising validation studies now exist in abundance, empiric evidence has not yet been presented to suggest that potentially improved tools would culminate in better decisions when placed in the hands of practitioners.

The use of prebiopsy multiparametric (mp) prostate magnetic resonance imaging (MRI) has also been proposed as a means to avoid the incidental detection of low-grade cancers [41,42]. Although not yet routinely endorsed as a requirement before initial biopsy, the use of MRI coupled with ultrasound fusion guidance has been associated with increased rates of detection of clinically significant disease, as well as an associated lower detection of Gleason pattern $3+3$ and low-volume pattern $3+4$ cancers [43]. Whether men with highly favorable prostate magnetic resonance