Editorial

PIVOT and the challenges of localized prostate cancer care

Aviva E. Weinberg, James D. Brooks

Department of Urology, Stanford University, Stanford, CA 94305, USA

Correspondence to: James D. Brooks, M.D. Department of Urology, Room S287, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305-5118, USA. Email: jdbrooks@stanford.edu.

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Putting it mildly, prostate cancer screening and treatment has been a contentious issue over the past year. With the recent US Preventative Services Task Force grade D recommendation to abandon routine PSA screening, pressing questions regarding the utility of population-wide PSA screening and the harms of overdiagnosis and overtreatment have continued to make national headlines. Determining whether PSA screening and subsequent treatment provides a survival benefit, in particular for men with low risk disease, has become of paramount concern to patients and urologists.

While the issues surrounding PSA screening and overtreatment have been known to the urologic community for many years, the controversy came into public focus with the publication of the results of the Prostate, Lung, Colon and Ovarian (PLCO) Screening trial showing no benefit to PSA or digital rectal exam screening (1). This study has been justly criticized for heavy prescreening of the study population, significant contamination of the control group, and poor compliance in the screening arm. Besides, the European Randomized Study of Screening for Prostate Cancer (ERSPC), in many ways a superior trial, did show a 21% *relative* risk reduction in prostate-specific mortality in PSA screened men (2). This result was reassuring in many ways, although the number of men that needed to be screened and treated, and the lack of benefit on all-cause mortality has been held up as evidence of overtreatment and the lack of benefit of screening. In support of detection and treatment of localized disease is the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4), a randomized trial comparing radical prostatectomy to watchful waiting, which demonstrated significant reductions in all-cause mortality, prostate-specific mortality, and the risks of metastatic disease in men treated with radical prostatectomy versus watchful waiting (3). While many of the patients in this study had intermediate and high-risk disease, long-term follow-up showed significant benefit in men with low risk prostate cancer, who were similar to patients with low risk disease detected in the PSA-era.

Now adding to the controversy is the PIVOT study, published in a recent issue of the New England Journal of Medicine (4). PIVOT is a prospective randomized trial designed to address whether radical prostatectomy, as compared to observation, improved overall survival and prostate cancer-specific survival in men diagnosed with prostate cancer during the PSA era. Initially designed to randomize 2,000 men, the study recruited only 731 men, which was compensated for by lengthening follow-up. At a median follow-up of 10 years, there was no difference in either overall or prostate-cancer specific mortality among the two treatment arms. Multivariate analysis showed that the effect of treatment on mortality did not vary according to age, race, performance status, or comorbid conditions. Subgroup analysis found no benefit of surgery for men with low-risk disease; however, radical prostatectomy reduced all cause mortality in men with PSA values greater than 10 ng/mL, and approached significance in those with intermediate and high-risk tumors. Notably, there was a statistically significant reduction in bone metastases in patients treated by radical prostatectomy (4.7%) versus expectant management (10.6%), which became more robust in patients with PSA >10 ng/mL and in those with intermediate and high-risk disease.

Despite portrayals in the media, the PIVOT trial does not signal the end of PSA testing and treatment of localized disease. PIVOT must be viewed in the light of its limitations. When enrollment goals were not met, the power calculation for the study was redone such that the length of follow-up on their 731 men was increased and the study was then projected to have 91% power to detect

a 25% relative reduction in all cause mortality, a high bar indeed. Placing this endpoint in perspective, a meta-analysis by Yusuf *et al.* of 7 randomized trials of patients with stable coronary artery disease stratified to either early coronary artery bypass graft versus medical management, demonstrated only a 17% relative reduction in overall mortality (5). In a similar fashion, a systematic review of over 31 randomized trials examining the survival benefit of adjuvant chemotherapy in early breast cancer, showed only a 14% relative risk reduction in overall mortality (6). Additionally, as astutely pointed out by Thompson *et al.* in his accompanying editorial, the PIVOT study remained underpowered with their enrollment of only 731 patients, and would have required 1,200 patients to be adequately powered to detect a 25% relative reduction in overall mortality (7). Another shortcoming of the study is the large proportion of patients, nearly 20%, who were non-adherent to their assigned treatment group, thus even further diminishing the capacity to identify a treatment effect. Additionally, only 10% of the men in their study were under the age of 60, therefore leaving the question of surgical management in a younger, healthier cohort, unaddressed.

Despite assertions that the study population in PIVOT is representative of men in the general population who have received a diagnosis of prostate cancer, men in PIVOT appear to be sicker and therefore more likely to die of causes other than prostate cancer. More than 40% of their study population had Charlson comorbidity scores of 1 or more, with a high proportion of patients with congestive heart failure, chronic obstructive pulmonary disease and prior myocardial infarction and strokes. Given this high rate of comorbid illness, it is not surprising that the overall mortality rate was so high (47% and 49.9% in the surgery and observation arms). In stark contrast are the mortality estimates found in the SEER database, where men age >65 years undergoing prostatectomy for clinically localized prostate cancer were found to have only a 20.6% and 40.8% all-cause mortality rate at 10 and 15 years follow-up (8). Even more striking, are the more recent actuarial mortality rates after radical prostatectomy found in a recent study by Eifler *et al.* which found overall survival rates at 10 and 20-year of 92.6% and 69.2% (9). Perhaps the patients in the PIVOT trial simply didn't live long enough to document any survival benefit. Consequently, we have to be very cognizant of patient specific factors notable to the VA population, when attempting to make recommendations for population-wide prostate cancer care, especially when considering the most recent NCCN guidelines, which recommend directing care for patients with very low risk and low risk prostate cancer based on 20-year and 10-year life expectancies.

While the PIVOT trial adds to the current prostate cancer screening and treatment dilemma, it provides more questions than answers. The most pressing question is not whether we should diagnose and treat prostate cancer, but rather *who* should we be treating? Prostate cancer is a complex entity with a broad spectrum of disease, from those that are slow growing, asymptomatic, possibly non-fatal cancers to those that are high-grade, aggressive, and ultimately lethal if left untreated. Furthermore, prostate cancers diagnosed in the PSA era have been shown to be significantly different from those found in earlier eras; there has been a profound stage migration; the Gleason scores are lower, the volume of disease is smaller, and there is a lower proportion of metastatic disease at diagnosis. What we can learn from PIVOT, PLCO and ERSPC is that increasingly, patients with low risk prostate cancer should be managed initially with active surveillance. By uncoupling the diagnosis of prostate cancer from treatment, which active surveillance offers, the arguments against PSA screening and prostate cancer overtreatment become irrelevant. Results from several active surveillance studies show that active surveillance is safe in properly selected patients (10). Unfortunately, the portion of patients on active surveillance has not changed, even though an increasing number of men are diagnosed with low risk disease (11). Acceptance of active surveillance by patients and physicians will be facilitated by developing reliable biomarkers that will allow us to effectively identify clinically high risk disease so as to guide future appropriate and individualized care (12).

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Footnote

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