Editorial

# Refining treatment for the men who need it: lessons from the PIVOT trial

**Michael R. Abern, Matvey Tsivian, Thomas J. Polascik**

Division of Urology, Department of Surgery, Duke Cancer Institute, Durham, NC, USA

*Correspondence to:* Dr. Thomas J. Polascik, MD. Associate Professor of Urologic Surgery, 2301 Erwin Road, DUMC Box 2804, Durham, NC 27710, USA. Email: polas001@mc.duke.edu.

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## Introduction

The diagnosis and management of asymptomatic prostate cancer (PC) are complex issues in the midst of several controversies and conflicting recommendations. Largely due to the results of two large PSA screening trials showing an unclear benefit of PSA screening on overall patient survival, the US PSTF has recommended against its routine use (1). If implemented, this policy would drastically reduce the number of organ-confined PC diagnosed. On the contrary, the NCCN recommends active surveillance for low-risk PC, and treatment for higher-risk disease (2). Therefore, we are faced with a dilemma: while decreased PSA testing may decrease detection of low-risk disease, one cannot risk-stratify and treat meaningful PC without screening-triggered biopsy and staging. Clearly, over-detection and over-treatment of PC are separate issues.

Drs. Wilt *et al.* helped to address the overtreatment question with the PIVOT trial, which sought to determine the overall and PC-specific survival in men randomized to watchful waiting versus radical prostatectomy (RP) (3). Importantly, the authors report a benefit in overall and PC -specific survival in men with intermediate-risk disease, but not low-risk (using the classification of d'Amico). The authors should be applauded for completing a randomized prospective trial as this has been historically difficult. However, due to an only 15% participation rate in eligible men, the sample sizes are modest for sub-group analysis leaving questions regarding the identification of groups of men that may derive the most benefit from treatment.

## Need for better risk stratification

As shown in PIVOT trial, higher risk men will benefit from expedient radical treatment of PC as compared to watchful waiting. Recent data from our group corroborates this finding—men with d'Amico intermediate-risk disease who had RP delayed by as little as 9 months had inferior outcomes to those treated in 3 months or less (4). Although the biopsy strategy employed in the PIVOT trial was not reported, it can be assumed that a standard 6-12 core TRUS guided random biopsy, along with serum PSA and DRE were used to classify risk. Several studies have shown the limitations to this approach—with Gleason upgrading rates as high as 47% in men thought to be low-risk (5). In addition, there has been a Gleason grade migration since the PIVOT trial patients were enrolled—it is likely that some men classified as low-risk would now be intermediate-risk (6). This prime example of a history-effect threat to validity is a potential pitfall of any trial with long term outcomes, and could attenuate some of the survival benefit from RP demonstrated in the trial for intermediate-risk men (7). Clearly, refinements in risk stratification of PC are of interest as several studies, including PIVOT, demonstrate its importance in predicting PC outcomes.

Advances in prostate imaging and biopsy techniques provide future directions to improve the accuracy of PC risk stratification. Multi-parametric MRI improves the visualization of anterior prostate tumors that may be difficult to detect using standard TRUS biopsy schemes. In addition, endorectal coil contrast enhanced MRI with 1 mm slice thickness shows excellent sensitivity and specificity for extracapsular extension which can help identify tumors that are locally advanced and require treatment (8). Other investigational imaging technologies under development, such as acoustic radiation force imaging, may provide a low cost yet more detailed differentiation of PC from

normal tissue compared to standard TRUS (9). More thorough and systematic prostate biopsy approaches will also provide a more detailed assessment of a man's burden of PC. Transperineal 3-D mapping biopsies can sample the entire prostate gland including the anterior zone, and provide not only extent but location of PC foci commonly missed with standard TRUS biopsy (10). This is important because tumor volume has been shown to correlate with PC outcomes, yet is not accounted for in most of the widely adopted risk stratification schemes. Finally, the fusion of prostate imaging and biopsy allows targeted sampling of worrisome lesions that may pose significant risk if left undetected.

## Treatment strategies

The PIVOT trial compared two treatment modalities that can be conceptualized as polar extremes: watchful waiting and palliation versus expedient radical treatment. Since the inception of the study, other management strategies have emerged between these extremes—specifically active surveillance (AS) and focal therapy (FT). Both of these aim to obviate or delay the need for potentially morbid radical treatment from men with localized disease. What lessons from the PIVOT trial can we apply to these approaches?

First, as shown by the authors, men with low-risk PC had no increase in overall or PC specific mortality when managed with watchful waiting. This is in line with a large body of literature that suggests that men with low-risk disease, especially those older than 65 years of age or with significant medical comorbidities, can be observed. However, in PIVOT, men under age 65 on watchful waiting had twice the number of PC deaths. FT may be an alternative for these men, as tumor foci may be identified and ablated providing oncological control of the disease while sparing the morbidity associated with radical treatment (11).

Second, higher risk men in the PIVOT trial did derive benefit from RP. There is little debate over the need for treatment of high-risk PC in most men. However, there is some debate regarding intermediate-risk disease. In the AS literature, one large center enrolling intermediate-risk men has shown more progression to radical treatment compared to low-risk men (12). Another report, however, has not shown this to be the case (13). Most would agree that intermediate-risk men would not be ideal candidates for AS. FT may be better suited to these men: intermediate-risk index lesions can be ablated without the urinary or erectile morbidity of radical therapy.

## Conclusions

The PIVOT trial is important in that it provides high-level evidence that low-risk PC generally does not require immediate radical treatment, while higher-risk disease does. This calls into focus the importance of risk-stratified approaches to PC management. Continued advances in prostate imaging and biopsy techniques, as well as better biomarkers, are still needed to determine which men need radical treatment. FT provides an attractive option other than observation and radical treatment for young, healthy men with low-risk disease or intermediate-risk disease. Future trials are needed that compare AS, FT, and watchful waiting with regard to not only mortality outcomes but quality of life.

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None.

## Footnote

*Conflict of Interest*: The authors have no conflicts of interest to declare.

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