Asian Journal of Andrology (2012) 14, 803–804

www.nature.com/aja

RESEARCH HIGHLIGHT

Implications of the prostate intervention versus observation trial (PIVOT)

Oliver Sartor

Asian Journal of Andrology (2012) **14,** 803–804; doi:10.1038/aja.2012.93; Published online: 10 September 2012

PSA screening improves early detection of prostate cancer but can lead to overtreatment if all of these cancers are treated. The first randomized treatment study for men with PSA detected cancers has now been reported. The PIVOT (prostatectomy intervention versus observation trial) results are noteworthy. There were no overall or cancer-specific survival benefits from radical prostatectomy versus observation. This result was primarily driven by the largest subset, men with 'low risk' prostate cancer (organ-confined, Gleason 6, and PSA <10 ng ml^{-1}). Even though men enrolled in PIVOT were older and sicker as compared to most radical prostatectomy series, there was a strong tendency toward improved prostate cancer specific survival for participants with a PSA >10 ng ml^{-1} or Gleason scores of 7 or higher. This important study underscores the benefits of observation for those with 'low risk' prostate cancer and the potential benefits of surgery for those in higher risk categories.

The first randomized trial of radical prostatectomy versus observation trial (PIVOT) performed in PSA screened patients has now been reported.[1] The headline results indicate that neither overall survival nor prostate cancer-specific survival is prolonged by radical prostatectomy. This is an important study with many implications.

The PIVOT study was not perfect by any means. Both the age at treatment (mean age: 67 years) and the non-prostate cancer mortality rate were quite high relative to other studies utilizing radical prostatectomy.[2] Over 40% of patients died by 12 years after study enrollment and the vast majority of patients died from non-prostate cancer causes. There was an explicit entry criterion that excluded patients with a less than 10-year life expectancy; however, the non-cancerous death rate at 10 years was much higher than I would have expected.[2] Because the vast majority of the deaths in PIVOT within 10 years of treatment were not due to prostate cancer, it is clear that a very significant number of patients were too old or too sick at study entry to have benefited from radical prostatectomy. In truth, these patients should never have been enrolled on PIVOT and their inclusion biases results against intervention.

No cross-sectional imaging (CT or MRI scanning) was required in PIVOT, despite a number of these patients being in the 'high risk' D'Amico category.[3] Thus, it is conceivable that some patients already had detectable metastatic disease, but were operated on anyway. This would render surgery futile, again biasing results against intervention. A number of PIVOT patients did not actually have prostate-specific antigen (PSA)-detected prostate cancer; only 75% of the cancers were detected because of an elevated PSA.

Of the 364 patients randomized to radical prostatectomy, only 281 (76.6%) actually received surgery. Further, in the control arm, 74/367 (20.2%) had some form of local definitive therapy. Thus, both compliance and contamination issues were potentially significant. None of the reported PIVOT analysis took these contamination and compliance issues into account. Further, a number of subset analyses were performed and these subsets were almost all underpowered. It is well known that underpowered analyses have a significant potential to underestimate benefit.

All that being said, there is much to learn from PIVOT. Despite the many limitations in study design, patient selection and analyses of multiple underpowered subsets, there was a strong trend toward benefit for both 'intermediate' and 'high risk' prostate cancer patients. This underscores that patients with a PSA of more than 10, a Gleason score of 7 or higher and a clinical stage of T2b or higher are potentially good candidates for radical prostatectomy provided that they are healthy enough and young enough to live at least 10 years.

Estimating life expectancy is an issue that has attracted little attention but post-PIVOT, more thought and more analysis should be placed on this important concept to better define those likely to benefit from aggressive approaches. Failure to do so will not solve the overtreatment issues that are currently problematic.[4]

The PIVOT patient with a classification of 'low risk' prostate cancer (Gleason 6 on biopsy and clinical stage T1c or T2a and PSA <10 ng ml^{-1}) had a remarkably good prognosis when no treatment is given. Importantly, we learned more about outcomes for these low-risk patients in the PSA era. These patients are doing much better as compared to the much quoted observational studies in the pre-PSA era reported by Albertsen and colleagues.[5]

Today, there is much controversy of concerning what prostate cancer patients are eligible for surveillance instead of radical treatment. PIVOT basically makes clear that most men with 'low risk' prostate cancer should not be treated with radical treatment as the 'default' option. It is now clear that the risks and side effects of treatment outweigh the benefit of radical surgery for the vast majority of men with 'low risk' prostate cancer. Looking at men followed for 12 years after randomization, the 'low risk' prostate cancer subgroup had only a 2.7% risk of prostate cancer mortality in BOTH arms of the study. Demonstrating that any treatment provides further risk reduction, as compared to observation, is unlikely.

We also learned more about surveillance. How to best perform surveillance and when to remove someone from surveillance is a topic of much recent discussion.[6] At this

Departments of Medicine and Urology, Tulane University School of Medicine, New Orleans, LA 70112, USA
Correspondence: Dr O Sartor (osartor@tulane.edu)

point, it is fairly clear that much of this discussion is not warranted. Perhaps it is possible to detect 'low risk' men at high risk for prostate cancer death, but it will not be easy. Improving upon 97.3% prostate cancer-specific survival at 12 years is probably not going to be accomplished regardless of the intervention. This finding has implications for high intensity focused ultrasound, brachytherapy, external beam radiation, as well as surgery.

The PIVOT study demonstrates that a simple combination of biopsy Gleason score, clinical stage and PSA is quite good at predicting who will live and who will die from prostate cancer 12 years later. While parameters such as PSA density, multiparametric MRIs and repeated biopsies are incorporated into many current surveillance protocols, it is now clear that these factors are not critical for excellent outcomes in the 'low risk' patient population.

As we go forward, understanding the heterogeneity of localized prostate cancer is ever more critical. Those patients who entrust us with their care deserve careful consideration before radical prostatectomy is offered as standard of care given the side effects that are well documented from this treatment.[7]

1 Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ *et al*. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012; **367**: 203–13.
2 Stephenson AJ, Kattan MW, Eastham JA, Bianco FJ Jr, Yossepowitch O *et al*. Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. *J Clin Oncol* 2009; **27**: 4300–5.
3 D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K *et al*. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998; **280**: 969–74.
4 Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. *J Clin Oncol* 2010; **28**: 1117–23.
5 Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. *JAMA* 2005; **293**: 2095–101.
6 Cooperberg MR, Carroll PR, Klotz L. Active surveillance for prostate cancer: progress and promise. *J Clin Oncol* 2011; **29**: 3669–76.
7 Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L *et al*. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* 2008; **358**: 1250–61.