Author’s response to reviews

Title: Impact of Bilateral Biopsy-Detected Prostate Cancer on an Active Surveillance Population

Authors:

Jonathan Wang (wang@UWhealth.org)
Pablo Sierra (sierra@urology.wisc.edu)
Kyle Richards (richards@urology.wisc.edu)
E. Jason Abel (abel@urology.wisc.edu)
Glenn Allen (allen@urology.wisc.edu)
Trach Downs (downs@urology.wisc.edu)
David Jarrard (jarrard@urology.wisc.edu)

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BURO-D-18-00085 re: Impact of Bilateral Biopsy Detected Prostate Cancer on an Active Surveillance Population

Dear Sir:

Thank you for the opportunity to respond to the comments. We have revised our paper to include further statistical analyses and respond to the comments in a point by point fashion.

Reviewer reports:

Trevor Flood (Reviewer 1):

1. Which version of the Gleason scoring system did you use? The study interval was 2007-2014. In 2014, the International Society of Urologic Pathology (ISUP) held a consensus meeting and adopted several major modifications to the existing grading system. The modifications
which are likely most pertinent to this study are: a) the inclusion of all cribriform architecture as a Pattern 4 morphology compared to the previous grading system that included some cribriform structures as Pattern 3, and b) classifying all glomeruloid morphology as Pattern 4 whereas previously there was no consensus with regard to grading. These changes could create possible grade migration within your cohort. Ideally, all biopsy and prostatectomy samples should be graded according to the current guidelines. Please comment.

Thanks for the comment and agree. The pathology has been rereviewed and the updated grading system utilized throughout the manuscript including the utilization of the grade group system. All biopsy pathology was GG 1 or 2 (Table 3).

2. Who analyzed the biopsies? Do you have Genitourinary trained pathologists at your institution? Did they read all of the biopsies and RPs?

Yes. Dr Wei Huang an experienced and fellowship trained pathologist read all of the biopsy and specimen pathologies. This has been added (Section 2.1, paragraph 4)

3. There is a typo in the first sentence of the "2.1 Cohort definition" section. The word "our" should be inserted before "institution". There is another typo in second last paragraph of the Discussion. The words "Saturation biopsies, including have been reported" should be erased.

Changes made. Thanks.

Dr. Oleksandr N. Kryvenko (Reviewer 2):

1. The authors' low risk criteria are different from AUA low risk and are more like very-low risk prostate cancer but short of inclusion of PSA density <0.15.

Changes made to acknowledge very low risk criteria in section 2.1, paragraph 1. Analysis indicates 86% of patients were very low risk and this is added.
2. The authors did not cite a recent paper which dealt with the exact same matter of unilateral and bilateral cancer at biopsy and active surveillance and actually studied 550 patients compared to 130 in this series (Urology. 2014 Apr;83(4):869-74.).

This paper compares the original Epstein criteria and the modified Epstein criteria, in which the presence of bilateral prostate cancer replaces >50 Maximal Core involvement as an exclusion criterion for active surveillance. They demonstrate that the modified criteria performed as well as the original criteria, and remain valid with updated Gleason scoring system. This paper has been acknowledged and referenced in discussion paragraph 2.

1. The authors provide in table 1 PSA density threshold as 0.2, but should rather change it to 0.15 as this is a commonly used cut-off.

Changes made to table 1

4. In table 1 the authors use '*' sign to refer to different comments. Needs to be fixed.

Changes made to table 1

5. The authors need to be providing expanded abbreviations below the tables even if the abbreviation was introduced in the text.

All abbreviations added

6. From the statistical point, if the authors lump the patients who had original unilateral positive biopsy and then became bilateral, it may be incorrect. At the time when the biopsy revealed the bilateral disease, the patient may already be failing these authors' criteria of AS particularly by number of the involved cores. The right analysis may be only if the groups of originally unilateral vs. bilateral cancer are compared but these may not have sufficient statistical power as only 7 patients with bilateral disease were present vs. 123 with unilateral. Another option is to
take those men who had unilateral disease but had bilateral on the repeat biopsy but still qualified for active surveillance and see if this group of men is any different from those who had unilateral disease.

A Kaplan Meier analysis was performed looking at the risk of men developing failure after finding bilateral cancer on biopsy (Figure 2). This was performed and double checked by our statistician Glen Allen. This analysis takes into account time of risk after developing a bilateral biopsy for failure. This is addressed and clarified in section 3.3, paragraph 1 and in Discussion, paragraph 2.

7. From the authors' radical prostatectomy cohort it appears that there is no difference in outcome of bilateral vs. unilateral positive biopsy cohorts. This is in line with the above comment that potentially some of the men who were unilateral and became bilateral were already failing active surveillance at the time of bilateral disease discovery.

Multiple studies have shown that the AS criteria used in this study are predictive of cancer outcomes. Our study looked at whether unilateral or bilateral biopsy presence predicted AS failure.

The point of comparing a synchronous group of patients who met AS criteria but elected surgery to our AS group is to ask the question ‘how frequently is unilateral biopsy cancer found bilaterally”? (Table 3) The answer is very commonly suggesting that cancer is missed by biopsy. With regard to pathologic outcomes, there was a trend toward increased tumor volume in bilateral biopsy cancer (p=0.1).

8. The presence of bilateral disease at radical prostatectomy is also not a significant point. With the latest AJCC classification, substaging of pT2 (organ confined) carcinoma is no longer used. Volume of Gleason score 3+3=6 prostate cancer is an important factor in considering insignificant prostate cancer amenable to active surveillance (J Urol. 2016 Dec;196(6):1664-1669.). Rather than substaging pT2 cancer, the major clinical question is extraprostatic extension (both pT3a and b) and positive surgical margin.
We used the presence of bilateral prostate cancer on final pathology in unilateral biopsy disease in our radical prostatectomy cohort not to discuss insignificant prostate cancer, but instead to demonstrate that bilateral prostate cancer seen on biopsy leads to an increased risk of failure of AS. There was a trend toward increased volume in the bilateral group (p=0.1; Table 3).

9. When the authors speak about PSA density in the discussion, the study indicated in comment 2 had tested the utility of PSA vs PSA density and demonstrated a significant superiority of PSA density. This is particularly true for men with large glands whose PSA may be elevated because of benign prostatic hyperplasia. PSA density superiority was also documented in earlier studies addressing active surveillance (JAMA. 1994 Feb 2;271(5):368-74.).

Excellent points. We acknowledge that there is evidence that PSA density is predictive in many cohorts in Discussion paragraph 3. In our AS group, PSA density did not perform as well. This is likely due to the fact that the majority of our patients (86%) had PSA densities <0.15, which makes its utility in predicting AS failure limited.