Reviewer's report

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

Version: 0 Date: 27 Jun 2018

Reviewer: Dr. Oleksand N. Kryvenko

Reviewer's report:

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

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.).

3. 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.

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

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

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.

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.
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.

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.).

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

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If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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