Author's response to reviews

Title: Level of invasion into fibromuscular band is an independent factor for positive surgical margin and biochemical recurrence in men with organ confined prostate cancer

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Version: 2 Date: 01 Dec 2017

Author's response to reviews:
BURO-D-17-00286R1

Level of prostatic capsular invasion is an independent factor for positive surgical margin and biochemical recurrence in men with organ confined prostate cancer

BMC Urology

Editor Comments:
As both reviewers have indicated, the use of the word "capsule" should either be eliminated from the manuscript or its use minimized to match contemporary usage. Extra-prostatic extension (EPE) is the preferred term. Attention must also be paid to the designated EPE level when different ones were present in the same specimen, and a distinction made to indicate the presence of anterior versus non-anterior EPE which have different prognostic significances. Thus, major revisions are needed.
Thank you for reviewing our manuscript. We have changed the term “prostatic capsule” to “extra-prostatic extension (EPE)” according to the editor’s recommendation.

We have added and corrected the following sentences in the introduction (page 3):
The level of prostatic capsular invasion, which focuses on the extra-prostatic extension (EPE), was reported to affect the incidence of BCR. However, recent articles have avoided the term “prostatic capsule” [6-8], as the prostate does not have a true capsule at the apex, anterior side, and base. Therefore, we instead revisited the level of EPE as an independent factor for a PSM or BCR in patients with organ-confined prostate cancer.

Many researchers are interested in the effect of the location of EPE on prognosis; however, in the present study we focused on the level of EPE in patients with pT2 prostate cancer. We also conducted a sub-group analysis to compare anterior vs. non-anterior EPE, as suggested by the editor. Unfortunately, we could not identify any significant differences between these subgroups. Our study cohort included only 50 cases of PSM and 13 cases of anterior PSM, and was therefore not sufficiently large to yield significant results. However, the editor’s comment was very important and valuable. Thank you so much.

Reviewer reports:

Kenneth Iczkowski (Reviewer 1):
1. A major flaw with this paper is the use of the term capsule, for the prostate. The notion of a prostatic "capsule" is not relevant to staging for two reasons.

First, the prostate does not have a true capsule but a pseudocapsule that is discontinuous at the apex, the anterior surface (where it interdigitates with skeletal muscle), and bladder base. In order for the authors to validly use the term, PCI, only patients whose cancers were posterolateral would have to be included, while excluding those with dominant anterior or apex nodules. Are the authors willing to exclude such cases?

Thank you so much for this review, Dr. Iczkowski. Your opinion regarding the concept of the prostatic capsule is correct. Uropathologists in this study performed a thorough slide review. Tumors in the apex, bladder base, and anterior were also categorized according to the level of
EPE. Therefore, we might not experience logical problems if we change the term “prostatic capsule” to EPE. We added and corrected the following sentences in the Introduction (page 3):

The level of prostatic capsular invasion, which focuses on the extra-prostatic extension (EPE), was reported to affect the incidence of BCR. However, recent articles have avoided the term “prostatic capsule” [6-8], as the prostate does not have a true capsule at the apex, anterior side, and base. Therefore, we instead revisited the level of EPE as an independent factor for a PSM or BCR in patients with organ-confined prostate cancer.

Second, the notion of whether cancer is "into the capsule" or "through the capsule" has poor interobserver reproducibility. However, cancer in contact with fat has excellent reproducibility. It is for these reasons that the International Society for Urologic Pathology recommends the term Extraprostatic Extension (EPE) and is against the "into the capsule versus through the capsule" which has become outdated since Dr. Tom Wheeler's 1998 paper.

Again, we thank you. We will change the term “prostatic capsular invasion (PCI)” to “extraprostatic extension (EPE)” according to your recommendation.

2. Anterior cancer is not recognized as having a worse outcome than posterior. For that reason, the distance of tumor from the posterior margin was found not to predict recurrence, while tumor that was <1 mm from the anterior margin did predict recurrence. It was recommended to report tumor that is <1 mm from the anterior margin. 1 Also, both margin positivity and tumor volume correlate with presence of anterior tumor. 2 Kryvenko et al. have shown that patients with significant prostate cancer more commonly had anterior-dominant cancer (58%) versus patients with insignificant cancer (21%). 3 Are the authors willing to include anterior versus posterior location of “PCI” and anterior versus posterior location of “PSM” in their multivariate analysis?

References


Thank you for your kind comments. Koppie et al. reported the characteristics of anterior dominant prostate cancer according to data from the MSKCC 2006. These cancers had lower Gleason scores and levels of EPE, but higher tumor volumes and rates of PSM; however, posterior prostate cancers had higher levels of EPE. Therefore, the prognoses of these two groups of cancer patients remain to be compared. Recently, Shun et al. reported different results using Japanese data. Specifically, the authors demonstrated that although anterior prostate cancer was less aggressive than posterior cancer, the former group included significant numbers of clinically important cancers. This interesting issue remains controversial. We also wanted to include a sub-group analysis, but our cohort included only a small number of cases of anterior dominant prostate cancer. Moreover, the 50 cases of PSM included only 13 cases of anterior dominant disease (we included only pT2 prostate cancer cases, which did not include a sufficient number of PSM cases). This low number of cases was not enough to determine statistical significance. However, we understand the importance of your comment, and have added a sentence regarding this issue in the discussion of limitations (page 7):

Furthermore, the effect of the level of EPE according to the tumor location remains controversial, and additional studies are needed.

3. On top of page 5, it is stated that PTV and level of PCI were independent predictors on multivariate analysis. What went into the MVA? Patient age? Gleason grade group? Serum PSA? Margin status? Focal versus extensively positive margin? This critical information is missing from the Materials and Methods as well as from Table 2. It needs to be, at least, in Materials and Methods and/or Table 2 legend.

Thank you for your kind comments. We have corrected Table 2, which was lacking PSA data, according to your recommendation. A 1998 paper by Dr. Tom Wheeler, which analyzed T3 prostate cancer, included variables such as focal vs. extensively positive margins. In the present study, however, we focused on pT2 prostate cancer, and therefore included only 50 cases with positive surgical margins. Moreover, only a few (3–4) of these cases had extensively positive
margins, and therefore we were unable to include the suggested variables. However, your
comments were very valuable. Thank you so much.

4. Toward the end of the Results, it is stated that among groups with Gleason score greater than
4+3, certain rates of 4 groups were given. That would be men with Gleason 8-10 prostate cancer,
or Grade Groups 4-5 (p=0.012). Was this same analysis done for Grade Group 1, Grade Group 2,
and grade Group 3 and found to be insignificant? That is, it was significant only for merged
Gleason Grade Groups 4 and 5? This is incomplete information, and so the effect of PSM and
EPE as a function of all of the possible Grade Groups should be shown along with respective p-
values.

Thank you for your thoughtful comments. The present study did not include any cases with
Gleason scores of 3+5 and 5+3, and included only 33 cases with Gleason grades 8–10.
Subdivision of these cases yielded specific groups with very small numbers of cases.
Accordingly, we included only pT2 prostate cancer.

5. English language usage is faulty and makes the paper hard to read. An expert or native English
speaker needs to go over the language to eliminate (just one example) "despite of pT2 disease
status" in the Conclusions. Top of page 4: "perpendicular to the major" should be "perpendicular
to the major axis."

We apologize for this issue. Although an expert from the USA had previously reviewed our
manuscript, the quality of grammar remained poor. We have selected another expert to review
our manuscript and correct the English language. We hope that this will address your concerns.

Gladell P. Paner (Reviewer 2):
1. Since the paper by Wheeler et al. was published way back in 1998, the authors should provide
a more explicit definition of the "Wheeler's method", rather than citing the original paper and
showing a figure labeling the levels of PCI. This is for the benefit of the readers as most are not
familiar with this method and some may have no access to the original article.

Thank you so much for your kind suggestions. This recommendation was very good. We have
added a description of the level of EPE to the Materials and Methods (page 4):
In level 0, the cancer cells are located in the prostatic stroma with a normal gland. Level 1 involves cancer cells within the prostatic stroma but beyond the boundary of normal gland. Level 2 involves cancer cells confined to the prostate, within a layer more fibrous than muscular.

2. It is now well recognized that the prostate does not have a true capsule. The authors must acknowledged this in the introduction by citing the original paper by Ayala et al. (PMID 2909195), and describing the prostatic capsule as an outer condensation of fibromuscular tissue that is an inseparable component from the prostatic stroma and the use of "capsule" to describe this fibromuscular band in the paper is only for convenience. Further, at least in the title, the authors should double apostrophe the word "capsular".

Thank you for your thoughtful and accurate review. We fully agree with your opinion. Accordingly, we have included the suggested paper as Reference 7. Moreover, we included a description of the levels in the Materials and Methods (page 4):

In level 0, the cancer cells are located in the prostatic stroma with a normal gland. Level 1 involves cancer cells within the prostatic stroma but beyond the boundary of normal gland. Level 2 involves cancer cells confined to the prostate, within a layer more fibrous than muscular.

We have changed the term “prostatic capsule” to “extraprostatic extension (EPE)” according to the editor’s recommendation. We have added and corrected the following sentences in the Introduction (page 3):

The level of prostatic capsular invasion, which focuses on the extra-prostatic extension (EPE), was reported to affect the incidence of BCR. However, recent articles have avoided the term “prostatic capsule” [6-8], as the prostate does not have a true capsule at the apex, anterior side, and base. Therefore, we instead revisited the level of EPE as an independent factor for a PSM or BCR in patients with organ-confined prostate cancer.

3. The laterality and/or site of the levels of PCI and PSM were not provided in the paper. The authors must provide this data if available. For example, level 2 PCI could be present on the right and level 0 PCI is present on the left, but the PSM is at the left side. The authors must mention that the side/site of highest PCI does not always correspond to the side/site of PSM, if that’s the case.
This is a very important point. Thank you for your comments. We used the highest level of EPE for cases involving several tumors in the prostate; however, no case involved a PSM location that did not have a level 2 EPE. However, we considered your comment about this issue to be critical. Therefore, we have added sentence regarding this issue to the discussion of study limitations (page 7):

and a critical reproducibility of our results regarding the level of EPE. Pathologists must re-evaluate the level of EPE, as well as the levels of all tumors. The highest level of EPE should be used for cases involving multiple tumors in the prostate.

4. How did the authors interpret when there were different levels of PCI present at different sites in a RP? While most likely based on the highest level of PCI, the authors however must specify this in the methodology.

Thank you again. We used the highest level of EPE for cases involving several tumors in the prostate. We fully agree with your opinion, and have added a sentence addressing this issue at the end of Materials and Methods (page 4):

We used the highest level of EPE if there were several tumors in prostate.

5. How many pathologists assessed the levels of PCI? What were the interobserver agreement? The authors should comment about the need to further assess the interobserver reproducibility of this method as among the limitations of this study in the discussion.

Again, we thank you. The levels of EPE in this present study were evaluated by two pathologists, who confirmed the results. As we consider this comment to be very important, we have added sentences addressing the issue to the Materials and Methods and the discussion of limitation:

(page 4) the levels of EPE were evaluated and confirmed by 2 pathologists.

(page 7) and a critical reproducibility of our results regarding the level of EPE. Pathologists must re-evaluate the level of EPE.

Minor

1. Page3, line3, change to "outcome associated with PSA biochemical recurrence (BCR) and poorer outcome". The phrase "failure of the surgery" is a bit too much.
with outcome associated with prostate specific antigen (PSA) biochemical recurrence (BCR) and poor outcome

2. Page 3, line 9, it should be "maximize the remaining functioning urethra".
maximizing the remaining functioning urethra

3. Page 3, Patient selection, line 3, is should be "or were lost to follow-up"
were lost to follow-up

4. Page 6, line 16, it should be "unclear whether the tumor-behavioral ..."
unclear whether the tumor-behavioral factor