Author’s response to reviews

Title: Safety and efficacy of Holmium laser enucleation of the prostate (HoLEP) in patients with previous transperineal biopsy (TPB): outcomes from a dual-centre case-control study

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Author’s response to reviews:

Thank you for the comments. We have included the original comments below with a reply to each point in turn:

Reviewer 1

This article describes the outcomes from a dual-centre case-control study, to evaluate the surgical feasibility, safety and effectiveness of 50W Holmium Laser enucleation of the prostate (HoLEP) in patients who underwent previous template biopsy of the prostate (TPB). Authors stratify their patients in 2 groups. Authors conclude that "in patients with a previous TPB, HoLEP is surgically feasible, safe and effective and that TPB should not be considered a contraindication to HoLEP".

In Methods section, line 11, could authors specify why they did not chose "control patients" in group 2 from both 1st and 2nd center too? (when they state "Patients in group 1 were from two centers whereas "control" patients in group 2 were from the second centre only."
The control patients were chosen as they were consecutive patients from early in the learning curve of one of the surgeons. Therefore they would effectively serve as the lower end of normal (worst case scenario outcomes for template-biopsy naïve patients) enucleation and morcellation efficiency, rather than later in the surgeons experience – which could have caused some bias. We have added a comment to this effect to explain, thanks (methods section, page 5, lines 6-8).

Also when authors state "Both groups had several surgeons performing the procedure" could they specify how many? "several is not a very accurate word to use from a scientific perspective. Was it 2, 3, 5 surgeons? And furthermore any reason why they did not stratify those interventions with the same urologist? This represent a selection bias and a confounding bias.

We agree this should be clearer. There were three surgeons operating over both sites, fairly equally split in numbers operated upon. As suggested to reduce confounders we have additionally compared enucleation and morcellation efficiency between surgeons and found no significant difference. This has been added to the manuscript (results section, "Operative outcomes in biopsied versus biopsy-naive men", page 8, lines 11-13)

Some typing mistakes that authors should correct too "including" instead of "includin" line 30.

Thank you for picking this up. We have corrected this and other minor errors.

In the case group, can authors specify how many patients had bilateral v/s unilateral prostate cancer detected? And how many were Gleason 7, 8, 9 or 10? Tissue consistency and degree of urethral occlusion might be different among those patients and would have different dynamics after HoLEP too.

We agree and have added how many were uni/bilateral, and the Gleason scores of each, thank you (results section, 'Demographic and baseline data' page 7, lines 1-3). There is insufficient data to analyse within these subgroups but we have commented on complication rates between the 'malignant' and 'benign' groups elsewhere in the text (results section, "Operative outcomes in biopsied versus biopsy-naive men", page 10, lines 3-6).

In their demographic and baseline data, authors state "The median time from TPB to HoLEP was 38.6 weeks (range 7-163 weeks). It is quite impossible to set a fixed time between the TPB and the HoLEP procedure, and it all depends on patient's needs, but a patient who obviously had to wait just 7 weeks, would react differently and have different clinical expectations/outcomes from a patient who waited more than 3 years (163 weeks).

Agreed - we have added several elements to improve the manuscript on this point. Interquartile ranges have been added here to give more information on the spread of data (results section, "Demographic and baseline data", page 6, line 23). We have also added an analysis correlating time from TPBx - HoLEP and enucleation and morcellation efficiencies (results section, "Operative outcomes in biopsied versus biopsy-naive men", page 8, lines 11-13). This showed no significant difference. We agree that patients at the extremes of these times will have different expectations and outcomes, but as this was not the main aim of the paper we did not collect the
type of data necessary to draw proper conclusions on this area. We have added to the discussion regarding this point, (discussion section, 'Strengths and limitations', page 12, lines 18-20) thanks. Could authors specify the pre-op medications taken? Were some of the patients on finasteride/dutasteride? If yes, did they have to continue post-op? By doing so, in the group that did not continue the medication, their uro-dynamics/parameters would be different. An explanatory table (regarding medication, tamsulosin pre op etc..) to be added by authors is strongly recommended.

Agreed - we have added the data on pre-operative medications taken (supplementary table 1). None of the patients continued with medication for LUTS after the procedure – a note to this effect has been added to the results section (results section, 'Demographic and baseline data', page 6, lines 28-29), thanks.

Reviewer 2

Current study is a retrospective short series of patients who underwent HoLEP alone and HoLEP after transperineal biopsy. Authors aimed to assess how biopsy may influence further EEP. Topic of the paper pose scientific interest, but there is lot of major concerns about the study and it is design.

1) Endoscopic enucleation (with lasers and electrosurgery) is routinely performed in most of the clinics after transperineal biopsy (both systematic and MR-fused). One may argue that this could affect outcome of laser enucleation. If there are any effect, cohort size should be larger to estimate it. This limitation converts into statistical inaccuracy and thus the informative value drops greatly. It's worth mentioning, that the difference between group numbers is also to high which decreases significance of this research.

We agree that larger study size would be an advantage in terms of more reliable statistical estimates of effect. However, as discussed (discussion section, "strengths and limitations", page 12, lines 1-6) this is the first study to look into HoLEP post-TPBx, and we believe the numbers are sufficient to provide initial evidence for operating in this scenario.

2) There are no data on the surgeons who performed the technique. It is more likely that change in enucleation efficacy was due to different experience of the surgeons, neither previous biopsy. This limitation cancel all of author's findings.

We have performed a subanalysis to this effect to compare enucleation efficiencies between the operating surgeons and found no difference (results section, "Operative outcomes in biopsied versus biopsy-naive men", page 8, lines 11-13). We hope this shows a reduced risk of confounding effect of the operating surgeon, thank you.

3) Another major limitation of the paper is the lack of peri and postoperative results (IPSS, QoL and etc.). Some of them is absent in more than a half of the cohort. Such limitation decreases scientific interest of the paper.
We accept this point but have already acknowledged in the manuscript that this is a weakness in the study due to a retrospective study design. However, the main finding of the paper is that the HoLEP procedure is safe and efficacious after TPBx, and the data for this is complete. Although the missing data you mention does somewhat limit the interest of findings related to success as per symptomatology, it does not affect the primary finding of the study.

4) The results of biopsy are not covered at all. It would be more informative if authors describe the pathology (core involvement, number of positive core and etc.). In a current state there are almost no data on the biopsy.

Agreed, we have added this in a supplementary table (supplementary table 2), thanks.

Reviewer 3

The authors compared the perioperative outcomes of HoLEP in patient who had undergone transperineal prostate biopsy and biopsy naïve men. Overall, endpoints such as IPSS, QOL, surgery time, and complications did not differ between the groups.

In the methods section, why did the authors choose IPSS>6 and QOL>2 as success. It is also unclear why was QOL<2 defined as success for patients who did not complete a preoperative QOL questionnaire. What type of QOL questionnaire did the authors use?

It is difficult to quantify what improvement is considered successful – however there is some evidence in the literature that around a 7 point improvement is a success, a reference has been added to the manuscript regarding this, thanks. Regarding quality of life score, this is part of the IPSS questionnaire and is well validated. We would generally not operate on patients with quality of life scores of 2 or less (indicating mostly satisfied, pleased, or delighted with living with their symptoms).

Since the learning curve of HoLEP is steep, surgeon's experience is a key in success. The authors must provide the number of surgeons and their prior HoLEP experience in each group. Was this associated with a change in the perioperative outcomes?

Agreed, we have added comments as described above and showed that between the surgeons there was no difference in the perioperative outcomes (results section, "Operative outcomes in biopsied versus biopsy-naive men", page 8, lines 11-13). Thank you.

When evaluating the pathology reports, was there any histological evidence of excessive scarring/inflammation in the biopsy group?

There was no evidence of excessive scarring or inflammation, and no cases of granulomatous inflammation. For completeness we have added the histological features as a supplementary table (supplementary table 3).
The authors mention in the introduction that transperineal biopsy includes more extensive sampling of the transitional zone. Was this indeed the case with patients in group 1?

We have added to the methods section to detail the method of mapping template biopsy of 5mm of the whole of the prostate gland as per the PROMIS trial protocol (methods section "Procedure information", page 5, line 27). This includes extensive sampling of the transitional zone.

There is a typo in the methods section- "includin" Missing units for creatinine in table 1 Missing range of QOL score in table 1 It is advised not to start a sentence with a number. Please make the necessary corrections.

Thank you for picking these up. We have corrected these and other minor problems in the text.