

# Peer Review File

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## Reviewer A

1. In the introduction authors stated in line 60 that the current standard technique of prostate biopsy is the TRUS-GB, this is actually changing now everywhere and the transperineal biopsy is taken over, even the EAU guidelines in the last edition have changed that, in the UK all centers are avoiding TRUS biopsy due to the sepsis rate so I think this need to be updated and changed.

## Response:

We thank the reviewer for pointing out this important update. We have revised the following sentences on Page 4, line 17 as per the reviewer's suggestion:

TRUS-guided systemic biopsy (TRUS-GB) through the transperineal route is one of the standard techniques for detecting PCa and avoiding PB-related infectious complications. The technique can help collect 10–14 template cores of the prostate (10-12).

We have added the following new references in the revised manuscript.

11. Roberts MJ, Bennett HY, Harris PN, et al. Prostate biopsy-related infection: A systematic review of risk factors, prevention strategies, and management approaches. Urology 2017;104:11-21.
12. Pilatz A, Veeratterapillay R, Köves B, et al. Update on strategies to reduce infectious complications after prostate biopsy. Eur Urol Focus 2019;5:20-8.

2. In the methodology, I wonder if the author could explain more their exclusion criteria and why for example patients with Finasteride was excluded, it is known that Finasteride role in decreasing prostate cancer is questionable, and actually high-risk cancer can be detected more with Finasteride accroding to the PCPT.

## Response:

We have deleted the following part on page 6, line 9:

Patients who had urinary tract infections, ~~those who received finasteride or~~

~~dutasteride before PB~~, those who underwent PB before 2014,

**3. In the prostate biopsy protocol the Trinity system has gained FDA approval in 2016 so i don't know what system was used in this study before that.**

**Response:**

We have revised the following part on page 8, line 11:

Transrectal PB, including TRUS-GB and FUS-TB, was performed by an experienced single urologist (HU) using Urostation® between February 2015 and March 2018 or using TRINITY® between April 2018 and February 2020 (Koelis, Meylan, France) with the three-dimensional (3D)-TRUS-based biopsy mapping technique.

**4. Also in the same point, more details are needed in the 10-12 cores sampling details, if they were systematic, did they included the target again, or contralateral PZ only, and TZ samples included as all of these points will make much difference in the utility of these samples and the results gained from them.**

**Response:**

We have revised the following sentence on page 9, line 8:

Subsequently, we obtained 10–12 cores—including medial and lateral cores from bilateral sextant prostate regions where no indications of PCa were noted on mpMRI were biopsied—for TRUS-GB.

**5. For the results about the comparison of the cancer detection rates, I got very confused about the details of csPCA between the FUS TB and TRUS-GB so i wonder if this could be detailed more and explained more.**

**Response:**

We have delete Table 2.

We have revised the following sentence on page 11, line 16:

Of these, 113 patients (37.7%) were diagnosed with PCa using FUS-TB alone, while 43 patients (14.3%) who tested negative in FUS-TB were left undiagnosed.

The PCDR of csPCa was 46% for those who underwent combined FUS-TB and TRUS-GB.

We have deleted the following sentence on page 12, line 4:

The comparison between FUS-TB and TRUS-GB based on PI-RADS v2 is shown in Table 2. PCDRs after FUS-TB were significantly higher than those after TRUS-GB at PI-RADS v2 score of 3, 4 or 5.

### **Reviewer B**

1. How many unique cancers were found on targeted biopsy which were not found on TRUS?
2. Does the combination of targeted plus TRUS maximize CS cancer detection? How many CSs would be missed if only targeted biopsy was done?

### **Response:**

We have added the following sentence on page 11, line 16:

Of these, 113 patients (37.7%) were diagnosed with PCa using FUS-TB alone, while 43 patients (14.3%) who tested negative in FUS-TB were left undiagnosed. The PCDR of csPCa was 46% for those who underwent combined FUS-TB and TRUS-GB.

3. Based on your data could any of these men safely avoided a biopsy?

### **Response:**

We have added the following sentences on page 14, line 12:

PI-RADS plays an essential role in detecting csPCa using mpMRI in order to select appropriate candidates for PB (17). Pooled meta-analyses with random-effect models demonstrated that the positive predictive value for csPCa was 8%, 13%, 40%, and 69% for PI-RADS 2, PI-RADS 3, PI-RADS 4, and PI-RADS 5, respectively (34). Han et al. reported that the PCDR is 0% in patients with PI-RADS 1 and 4.6% in those with PI-RADS 2 (35). In our series, patients with PI-RADS 1 or 2 underwent TRUS-GB due to high PSA. The PCDR in these patients was 14.3% (data not shown). Additionally, approximately 90% of the patients did not undergo PB because they were diagnosed with PI-RADS 1 or 2 based on mpMRI findings. Indeed, PCa was undiagnosed in 30%-48% of patients as it was not visible on MRI (36). However, on the contrary, unnecessary PB was avoided

in several patients with PI-RADS 1 or 2 in our series.

We have added the following references.

34. Mazzone E, Stabile A, Pellegrino F, et al. Positive predictive value of Prostate Imaging Reporting and Data System Version 2 for the detection of clinically significant prostate cancer: A systematic review and meta-analysis. Eur Urol Oncol 2020; S2588-9311(20)30212-1.
35. Han C, Liu S, Qin XB, et al. MRI combined with PSA density in detecting clinically significant prostate cancer in patients with PSA serum levels of 4~10ng/mL: Biparametric versus multiparametric MRI. Diagn Interv Imaging 2020;101:235-44.
36. Zhu K, Qin Z, Xue J, et al. Comparison of prostate cancer detection rates between magnetic resonance imaging-targeted biopsy and transrectal ultrasound-guided biopsy according to Prostate Imaging Reporting and Data System in patients with PSA  $\geq$ 4 ng/mL: a systematic review and meta-analysis. Transl Androl Urol 2019;8:741-53.

### **Reviewer C**

Uno et al. investigated the value of MRI fusion biopsy in biopsy naive men, relative to transrectal biopsy without prior MRI. The authors found that higher cancer detection rates were observed in MRI fusion biopsy.

The study repeats findings from several previous publications and does not bring anything new to the medical literature. Moreover, the study is retrospective and lacks of sample size.

### **Response:**

We completely agree with the reviewer's comment. However, PCDR was relatively high in the present case, compared with that reported previously. In particular, approximately 90% of the patients who had PI-RADS 4 or 5 based on MRI findings were diagnosed with PCa in this study. Thus, we considered that MRI accuracy for PCa identification might differ among institutions depending on the experience of the radiologists and interpretation techniques employed. Therefore, we recommended that patients with elevated PSA should undergo mpMRI before prostate biopsy. In addition, FUS-TB might improve risk stratification and reduce the need for repeat biopsy.