Peer Review File

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Reviewer A

Comment 1: I recommend authors to cite the latest guidelines of NCCN and AUA. Please, consider citing these papers:10.1097/JU.0000000000003491, 10.6004/jnccn.2023.0014

Reply 1: *We thank the Reviewer for the suggestion. We have updated the references.*

Changes in the text: Please see Page 13, Reference.

Comment 2: This study is registered in clinicaltrials.gov as NCT03479359 to investigate the learning curve of DRE for prostate cancer among internship and not as cited in the manuscript "the diagnostic value and adjunctive role of DRE". Can the authors explain the difference between the two protocols and why they change the subject?

Reply 2: *We thank the reviewer for raising this question. The two protocols are consistent in terms of patient inclusion and exclusion criteria and intervention, which require doctors to perform DRE on patients with clinically suspected prostate cancer before biopsy, without knowing the results of PSA and MRI examinations. The difference is that the original registered protocol was designed to analyze the differences in DRE performance by internship under different interventions, while this study focused more on the diagnostic efficacy of DRE itself in this setting, which we believe is a more valuable sub-study under the original protocol.*

Comment 3: Is the location of the tumor is also evaluated on the region as explained in the text in case of <12 core biopsies?

Reply 3: *We thank the reviewer for bringing up this issue. In clinical practice, we routinely perform a systematic biopsy on patients, which is the 12-core or 20-core ultrasound-guided transperineal biopsy, but some of the patients we included also underwent targeted biopsy, and the number of biopsy cores for these patients was often <12. For the tumor locations in these patients, we also had experienced urologists conduct independent reviews and evaluation based on positive biopsy core locations, DRE, and MRI results.*

Changes in the text: Please see Page 5, line 176-177.

Comment 4: Are authors using, in the abstract and the text, diagnostic efficacy and diagnostic accuracy interchangeably?

Reply 4: *We thank the reviewer for bringing up these issues. In our context, diagnostic efficacy and diagnostic accuracy are distinct terms. Diagnostic accuracy refers specifically to the ability of a diagnostic test to correctly identify or rule out disease, whereas diagnostic efficacy is a broader concept that depends not only on diagnostic accuracy but also on the added value of a diagnostic test for the clinician or patient. We do not mix these two terms in the abstract or the text.*

Reviewer B

Comment 1: An explanation why the of the number of biopsies is so wide 4-24, and whether those patients who underwent small number of biopsies had surely prostate cancer. Please explain and add to methods.

Reply 1: *We appreciate the reviewer's suggestions. The number of biopsy needles often depends on the patient's prostate size. Usually, patients undergo a 12-core or 20-core systematic biopsy. Patients with larger prostates may need up to 24 cores. Some patients have a targeted biopsy based on mpMRI images with fewer needle cores. mpMRI is more sensitive to small lesions. According to the PRECISON study, the targeted biopsy group with an average of 4 needles per patient was more effective in detecting clinically significant prostate cancer than the systematic biopsy group with an average of 12 needles per patient (38% vs 26%, P=0.005). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9084630/*

Changes in the text: Please see Page 5, line 171-174.

Comment 2: Examiners were blinded to PSA values; do they were also blinded to MRI finding?

Reply 2: *Yes, the examiner did not know anything about the patient's PSA and MRI results before performing the DRE procedure.*

Changes in the text: Please see Page 5, line 171.

Reviewer C

Comment 1: English language should be improved in both grammar and syntax

Reply 1: *We thank the reviewer's comment and have fully polished the English language of this article.*

Comment 2: The article does not consider the total prostate volume and its correlation to tumor pathology; the use of magnetic resonance imaging could help correlate these two factors. At this regard I suggest the following article: https://pubmed.ncbi.nlm.nih.gov/34247169/

Reply 2: *Thanks to the reviewer for his suggestion. We recognize that the correlation between total prostate volume and tumor pathology is an important factor, and magnetic resonance imaging can help analyze the relationship between these two factors. We have read the articles recommended by the reviewer, which helped inspire us to further refine our experimental plan. We again thank the reviewer for his valuable comments and assistance.*

Changes in the text: Please see Page 13, line 397-399.

Comment 3: The study does not take into consideration patients with PSA<4 ng/ml and digital rectal evaluation of these patients, which may create bias

Reply 3: *We appreciate the reviewer's suggestion and we have acknowledged this limitation in the Discussion section. Due to ethical constraints, we generally do not advise prostate biopsy under the gold standard for patients with PSA <4ng/ml. Therefore, it is challenging to obtain evidence for the diagnosis of prostate cancer in these patients, and it is also hard to assess the diagnostic value of DRE in these patients, although this is an important topic.*

Changes in the text: Please see Page 12, line 367-370.

Comment 4: The article does not analyze the pathologies affecting the recruited patients, and how these pathologies could influence the study. At this regard, this article could be useful: https://pubmed.ncbi.nlm.nih.gov/32570240/

Reply 4: *We appreciate the reviewer's suggestions. We carefully read the references recommended by the reviewer and added this limitation in the text discussion section.*

Changes in the text: Please see Page 13, line 397-399.

Reviewer D

Comment 1: Important topic, conclusions need further investigation

Reply 1: *Thanks to the reviewer's suggestion, we have further improved the conclusions.*

Changes in the text: Please see Page 13, line 412-415.

Reviewer E

Comment 1: In the introduction, the authors contextualize and delimit the object of their study and raise controversies about the use of the rectal examination. In this context, it is noted that the Ministry of Health of some countries, in line with the scientific evidence available to date, has not recommended screening for prostate cancer in men without symptoms. We recommend making a note of this in the introduction.

Reply 1: *We thank the reviewer for the comment and we have added a note in the introduction about the Ministry of Health guidelines of some countries that do not recommend screening for prostate cancer in men without symptoms. We have cited the source from https://pubmed.ncbi.nlm.nih.gov/35974245/ that support this statement. We appreciate the reviewer's valuable feedback and help.*

Changes in the text: Please see Page 4, line 97-99.

Comment 2: In the method, it is recommended that the authors better describe the type of study, the data collection and analysis techniques, using theoretical support and citing references on the subject. We recommend that the authors make their inclusion and exclusion criteria clearer, as well as the type of study.

Reply 2: *We appreciate the reviewer's suggestions. We have specified patient inclusion criteria (patients with positive mpMRI (PI-RADS≥3) or elevated PSA (PSA≥4 ng/ml) in the Department of Urology of Changhai Hospital from February 2020 to May 2021) and exclusion criteria (Patients who did not ultimately undergo DRE or biopsy) in our methods, and our study type is a prospective cohort analysis.*

Changes in the text: Please see Page 6, line 177-178.