

## Peer Review File

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### Reviewer A

**Comment 1:** This manuscript needs to undergo major proofreading. Unfortunately, there are numerous confusing statements, including line 45 “the fact that local therapy only treats lesions which can be seen on imaging or be proved by puncture biopsy” (should be proven by biopsy etc) or line 53 “ADT is a systemic treatment that can not only treat the invisible lesions located in the prostate, but also treat the potential early distant metastases” (should be ADT is a systemic treatment that can potentially treat not only the invisible lesions etc” or line 79 when the authors are probably referring to “neoadjuvant” rather than “adjuvant”? when they stated “Although it is supposed that ADT could be used as adjuvant therapy before HIFU to increase its efficacy, there was no comparative study of the tissue structural changes after ADT for prostate cancer”. These are but examples, there are too numerous to count or name here.

**Reply 1:** Local therapy only treats lesions that can be seen on imaging and confirmed as prostate cancer by needle biopsy. We also think that it belongs to the neoadjuvant endocrine therapy for prostate cancer before HIFU treatment. We have modified it one by one according to your opinion.

#### Changes in the text:

Delete: ADT were the test group. Twenty patients without ADT => changes: NET were the test group. Twenty patients without NET (see Page 1, line 10) .

Delete: There was a significant increase in the number of calcifications after ADT and the area of calcification after ADT => changes: There was subtle increase in the number and the area of calcification after NET (see Page 1, line 15)

Delete: higher than before ADT ( $P < 0.01$ ). => changes: higher than that before NET ( $P < 0.01$ ). (see Page 1, line 16)

Delete: ADT resulted in significantly fewer veins and blood vessels than were present before ADT ( $P < 0.01$ ). There was a significant difference in the number of arteries after ADT ( $P = 0.01$ ). => changes: NET resulted in significantly fewer veins compared to those before NET ( $P < 0.01$ ). There was a little increase the number of microarteries and arteries after NET ( $P < 0.01$ ). The number of veins decreased was much greater than the number of arteries increased resulting in significantly less total vessels after NET ( $P < 0.01$ ). (see Page 1, line 17-20)

Delete: or be proved => changes: and be proved PCa (see Page 2, line 44)

Delete: androgen deprivation therapy (ADT) => changes: neoadjuvant endocrine therapy (NET) (see Page 2, line 49)

Delete: ADT is a systemic treatment that can not only treat the invisible lesions located in the prostate => changes: NET is a systemic treatment that can potentially treat not only the invisible lesions etc (see Page 2, line 52)

Delete: ADT => changes: NET (see Page 2, line 53)

Delete:ADT => changes:NET(see Page 2, line 55)

Delete:ADT => changes:NET(see Page 2, line 57)

Delete:ADT => changes:NET(see Page 2, line 58)

Delete:ADT => changes:NET(see Page 2, line 60)

Delete: Although it is supposed that ADT could be used as adjuvant therapy before HIFU to increase its efficacy, there was no comparative study of the tissue structural changes after ADT for prostate cancer. Therefore, This retrospective study was to observe and analyze the tissue structural changes of PCa after ADT =>changes: There has been no comparative study of AET changes after NET for prostate cancer. Therefore, this retrospective study aimed to analysis of the pathological changes in tissue components and structures, (see Page 2, line77-79)

Delete: significantly => changes:little (see Page 4, line 160)

Delete:ADT => changes:NET(see Page 4, line162)

Delete:we observed and analyzed the tissue structural changes of PCa before and after ADT, and an impact on the efficacy of HIFU treatment.(see Page 5,Line195-197)

Delete:ADT => changes:NET(see Page 5, line205)

Delete:ADT => changes:NET(see Page 5, line215)

Delete:ADT => changes:NET(see Page 6, line 243)

Delete:ADT => changes:NET(see Page6, line 247)

Delete:ADT => changes:NET(see Page 6, line 248)

Delete:ADT => changes:NET(see Page 6, line 252)

22. Delete: in PCa tissue structure after ADT => changes: of AET in PCa after NET(see Page 6, line 262)

Delete:ADT => changes:NET(see Page 9, line354)

Delete:ADT => changes:NET(see Page 9, line361)

Delete:ADT => changes:NET(see Page 10, line 367)

Delete:ADT => changes:NET(see Page10, line 375)

Delete:ADT => changes:NET(see Page 11, line 386)

Delete:ADT => changes:NET(see Page 11, line 389)

Delete:ADT => changes:NET(see Page 12, line 395)

Delete:ADT => changes:NET(see Page 12, line 402)

**Comment 2:** The biggest drawback of this manuscript is the ambiguity of the study procedure itself. Did the 40 patients actually receive (or not) HIFU before prostatectomy? The title suggests the possible effects of ADT on HIFU but without actually receiving HIFU, this who manuscript is speculative in terms of vascular, smooth muscle and calcification effects. Furthermore, if they did receive HIFU, was this considered standard of care in the respective institution? Since it is a retrospective study, the understanding is there is consent obtained to trace and obtain such specimens. If patients did not receive HIFU, the title of this manuscript must be altered to just reflect changes of vascular and calcifications with ADT but no further extrapolation towards benefit in combination with HIFU can be made.

**Reply 2:** The patient was not receiving HIFU and we have revised the title of the manuscript while also revising the corresponding content. We have modified it one by one according to your opinion.

**Changes in the text:**

1. Delete: The possible effect of androgen deprivation therapy on high-intensity focused ultrasound in patients with prostate cancer => the title changes: Effect of Neoadjuvant Endocrine Therapy on the Acoustic Environment in tissue of Prostate Cancer: a study of histopathological characteristics (see Page 1, line 1-2)

2. Delete: To examine the change in tissue structure of prostate cancer (PCa) after androgen deprivation therapy (ADT), and whether ADT influences the efficacy of high intensity focused ultrasound (HIFU) => changes: To analysis of the pathological changes in tissue components and structures, focusing on calcifications, smooth muscle cells, and blood vessels, which may affect the tissue acoustic environment (AET) of prostate cancer after neoadjuvant endocrine therapy (NET). (see Page 1, line 5-7)

3. Delete: ADT leads to tissue structural changes in PCa, and it is beneficial to HIFU therapy followed by ADT. => changes: NET can lead to changes in calcifications, smooth muscle cells, and blood vessels within prostate cancer tissues, which may subsequently cause alterations in the local tissue acoustic environment. (see Page 1, line 21-23)

4. Delete: androgen deprivation therapy; high intensity focused ultrasound; prostate cancer; tissue structural change => changes: neoadjuvant endocrine therapy; prostate cancer; tissue acoustic environment; pathology (see Page 1, line 25)

5. Delete: acoustic environment in tissue => changes: tissue acoustic environment (AET) (see Page 2, line 68)

6. Delete: Although it is supposed that ADT could be used as adjuvant therapy before HIFU to increase its efficacy, there was no comparative study of the tissue structural changes after ADT for prostate cancer. Therefore, This retrospective study was to observe and analyze the tissue structural changes of PCa after ADT => changes: There has been no comparative study of AET changes after NET for prostate cancer. Therefore, this retrospective study aimed to analysis of the pathological changes in tissue components and structures, (see Page 2, line 77-79)

7. Delete: the efficiency of HIFU treatment. => changes: AET. (see Page 2, line 80)

8. Delete: we observed and analyzed the tissue structural changes of PCa before and after ADT, and an impact on the efficacy of HIFU treatment. (see Page 4, Line 195-197)

9. Delete: in the efficiency of HIFU. We speculate that this adverse effect may be ignored => changes: in the ultrasonic energy deposition (see Page 5, line 215-216)

10. Delete: FUAS may be more efficient if sound attenuation is increased after AET compared to normal prostate tissue => changes: sound attenuation may increase after AET compared to normal prostate tissue (see Page 6, line 233)

11. Delete: In HIFU treatment, the reduction of blood supply would result in more heat deposition in the PCa. As a result of these changes, we anticipated an improvement in the efficiency of HIFU => changes: As a result of these changes, the reduction of blood in AET supply would result in more heat deposition in the PCa after AET (see Page 6, line 253-254)

12. Delete: From our findings, it was demonstrated that the benefits of HIFU combined with ADT might outweigh the disadvantages. As a result, the tissue acoustic pathway might be optimized and the ablation rate of lesion/target area might be consequently increased. In addition, the HIFU treatment time could be shortened, with the improvement of treatment efficiency and reduction of adverse reactions during and after treatment, thereby patients' survival, including both overall survival and progression-free-survival might be prolonged. the results. Further study with large sample size should be conducted to confirm the results or obtain new findings. => changes: Our study has a relatively small sample size, which cannot fully explain our research findings. Therefore, we must enlarge the sample size to consolidate the existing discoveries or obtain new findings. Additionally, we can continue researching the acoustic characteristic changes in prostate cancer tissues after NET. By analyzing changes in tissue velocity, acoustic impedance, acoustic attenuation, and other factors, we can further validate our research findings.(see Page 6, line 255-259)

13. Delete: in PCa tissue structure after ADT => changes: of AET in PCa after NET(see Page 6, line 262)

14. Delete: decreasing density of venous vessels and overall blood vessel. HIFU could benefit from the characteristics of the tissue structural changes of PCa after ADT. => changes: significantly decreasing numbers of venous vessels and overall blood vessel. The pathological changes may have an impact on the local tissue acoustic environment(see Page 7, line 263-265)

## **Reviewer B**

1. Please double check the P value in **Figures 5 and 8, main text, Abstract** and make sure they are **correct and consistent**.

**Reply:** We have modified and checked the P value in Figures 5 and 8, main text, Abstract.

### **Changes in the text:**

Delete: and the area of calcification after NET( $P < 0.01$ ) => changes: ( $P = 0.001$ ) and the area ( $P = 0.000$ ) of calcification after NET. (see Page 2, line 49-50).

Delete:  $P < 0.01$  => changes:  $P = 0.000$  (see Page 2, line 51).

Delete:  $P < 0.01$  => changes:  $P = 0.000$  (see Page 2, line 52).

Delete: microarteries and arteries after NET ( $P < 0.01$ ) => changes: arteries after NET ( $P = 0.001$ ). (see Page 2, line 52).

Delete:  $P < 0.01$  => changes:  $P = 0.000$  (see Page 2, line 54).

2. If available, please update your reference list by including related literatures published within a year.

**Reply:** We have modified these to be the latest references by including related literatures published within a year.

### **Changes in the text:**

[3] Mathieu R, Doizi S, Bensalah K, et al. Complications in urological surgery: Prostate surgery. Prog Urol. 2022 Nov;32(14):953-965.

- [4] Henderson RH, Bryant C, Nichols RC Jr, et al. Local salvage of radiorecurrent prostate cancer. *Prostate*. 2023 Aug;83(11):1001-1010.
- [5] Fujihara A, Ukimura O. Focal therapy of localized prostate cancer. *Int J Urol*. 2022 Nov;29(11):1254-1263.
- [6] Westhoff N, Ernst R, Kowalewski KF, et al. Medium-term Oncological Efficacy and Patient-reported Outcomes After Focal High-intensity Focused Ultrasound: The FOXPRO Trial. *Eur Urol Focus*. 2023 Mar;9(2):283-290.
- [7] Gómez Rivas J, Fernandez L, Abad-Lopez P, et al. Androgen deprivation therapy in localized prostate cancer. Current status and future trends. *Actas Urol Esp (Engl Ed)*. 2023 Sep;47(7):398-407.
- [10] Chu KF, Dupuy DE. Thermal ablation of tumours: biological mechanisms and advances in therapy. *Nat Rev Cancer*. 2014 Mar;14(3):199-208.
- [11] Elhelf IAS, Albahar H, Shah U, et al. High intensity focused ultrasound: The fundamentals, clinical applications and research trends. *Diagn Interv Imaging*. 2018 Jun;99(6):349-359.
- (see Page 9, line 342-353, line 360-363)