

Peer Review File

Article Information: <https://dx.doi.org/10.21037/tcr-21-1757>

Major criticism

Comment 1: The principle of HIFU, it is not impossible to treat the lesion located in the anterior urethral zone without urethra. Please explain in the introduction as short sentence.

Reply:

Dear reviewer, thank you for your comment.

You are right that HIFU with a focal strategy could achieve the goal of treating anterior urethral lesions and have added a sentence demonstrating that in the Introduction part as you recommended. We also cite the reference (Hanada I, et al, J Endourol. 2021; 35: 951-960) in comment 6 here.

Changes in the text:

Page 5, Line 13-16

Comment 2: The authors mentioned that the result of mp-MRI at the 3 month follow-up visit showed no signs of recurrence. For the evaluation of the effect to the urethra, dynamic contrast-enhanced MRI is useful. Please show the dynamic contrast enhanced MRI at 3 months after the treatment.

Reply:

Dear reviewer, thank you for your comment.

We agree with you that a DCE-MRI which show good perfuse would be a better proof for the preservation of urethral activity; however, it's a pity that the DCE-MRI was not acquired on the 3rd month follow-up visit, as it was not mandatory according the study protocol and the patient also minded the injection of contrast agent.

For all this, we considered that the conclusion that our method was a safe and efficient way for a urethra-sparing surgery still made sense. That is because when we found a non-perfusion area immediately after the treatment on DCE-MRI (for instance, the treatment area for tumor), we assumed that the lesion was destroyed but we needed to test that by comparing the non-perfusion area on DCE-MRI in the follow-up visit to make sure the area was fully destroyed. But when we found there was a good perfusion in an area on the post-treatment DCE-MRI in contrast, we considered the area was preserved with activity, and generally it would keep active which is just the case we presented here.

Even though we don't have data of DCE-MRI on 3rd month visit, we do find the urethra enhanced on the post-treatment DCE-MRI. Moreover, the urinary function was kept well according to IPSS and QoL collected from the patients. Therefore, we considered that our conclusions still make sense although there was no follow-up DCE-MRI.

Changes in the text:

None.

Comment 3: In early effect on urinary function, prostatic swelling induces the BOO after HIFU for prostate cancer. On the other hand, urethral stricture occurred after 2 or 3 months after the HIFU due the urethral injury, and regarded as late effects on urinary function. Therefore, the early changes on urinary function should be discussed mainly prostatic swelling.

Reply:

Dear reviewer, thank you for your comment.

We agree with you that the obstruction developed early after MRgFUS are mainly due to transient prostatic swelling. The late effects are mainly related to urethral strictures caused by urethral injury. We have added information on that in the discussion part. Meanwhile, only 3-month follow-up data was provided, we believe that the patient would not developed BOO due to urethral strictures because the patient had no symptoms of dysuria at all. Therefore we concluded that our method will be a safe way for a urethra-sparing surgery for patients with lesions anterior to the urethra, and have added content in the discussion part.

Changes in the text:

Page 10, Line 140-146, under revision mode

Comment 4: The authors' technique of "the sequence of sonication of the macro spots, starting from the midline to one side, followed by the other side to the midline..." is unclear. Please refer the basis of previous literatures.

Reply:

Dear reviewer, thank you for your comment.

We have reviewed the treatment procedure for this patient and confirmed the sonication sequences and rationale for the regime with the engineer, and we felt very sorry there was a mistake for the sonication strategy described in the original manuscript. We have corrected the mistake in the revised manuscript (see Page, Line). The regime of the sonication is as follows:

Generally, after ROT declination (Fig 2B), the workstation will generate a treatment plan automatically (Fig 2C), which could be manually adjusted later. Then the sonication will be started from one side to the other side of the ROT, plane by plane, usually from the left side to the right side on the screen.

In this treatment, we chose to start from the lateral side, a side farthest from the urethra (specifically, starting from the left side of the patient for this case), and then moved towards the midline of the prostate. The reason for this strategy is that the first spots are usually the ones with the most power (The exposure temperature and time under the temperature are two key parameters associated with cell necrosis²⁰. Therefore, less energy would be needed for the subsequent spots than the first spots, as there would be accumulated heat from the previous spots). Therefore, by starting sonication from the lateral side (far from the urethra), spots with the most power could be far away from the urethra, and as we move towards the urethra, less power would be administered thanks to the accumulated heat from the previous sub-spots.

Hence, by using the strategy, we could minimize the direct delivered energy to/via urethra and eventually reduce the damage.

As previous published literatures did not report the sonication sequences or the operating procedure in detail, we did not find any basis in previous studies. We corrected the error in previous manuscript on the sonication sequence and add some explanation of the rationale in the case presentation and discussion part.

Changes in the text:

Page 7, Line 53-61 and Page 10, Line 126-132, under revision mode,

Comment 5: Single evaluation of IPSS is insufficient to evaluate the urinary effect after HIFU for

prostate cancer. Further, IPSS QOL, maximum urinary flow rate, and residual urine are needed at least.

Reply:

Dear reviewer, thank you for your comment.

Based on your suggestions, we have added the data of IPSS QoL in the revised manuscript in the result part; however, as there is no requirement for Qmax and residual urine test in the clinical trial protocol, it is a pity that we did not have the relative data on those two parameters.

Changes in the text:

Page 7, Line 74 and Page 8, Line 77-78 under revision mode

Comment 6: Previous literature reported that there was a greater risk of urinary dysfunction with treatment in the anterior TZ portion than in the other portion at 1 month after focal therapy with HIFU (Hanada I, et al, J Endourol. 2021; 35: 951-960). The previous literature would contribute to the discussion.

Reply:

Dear reviewer, thank you for your comment.

As you suggested, we have added some discussion in the Introduction and Discussion part in the modified manuscript, citing the latest study on lesion in the anterior TZ portion (Hanada I, et al, J Endourol. 2021; 35: 951-960).

Changes in the text:

Page 5, Line 13-16; Page 9, Line 110-112, under revision mode

Comment 7: In abstract and introduction, prostate cancer is the most common malignancy among men not only in the United States. The United States should be changed to other words.

Reply:

Dear reviewer, thank you for your comment.

As you suggested, we have replaced the phrase “in the United States” by worldwide.

Changes in the text:

Page 2, Line 26-27; Page 5, Line 2-3

Comment 8: In Figure 2 (C), please explain the means of colors, such as red, blue, and green.

Reply:

Dear reviewer, thank you for your comment.

We have added some explanation on the meaning of different colors in Fig 2C.

Changes in the text:

Figure legends-Page 16, Line 14-17

Comment 9: Figure 2 (D), (E), (F) are not clear. Please replace to the more clear figures.

Reply:

Dear reviewer, thank you for your comment.

We have adjusted the brightness and contrast of the figures to make it clearer to see and replaced the original figure with clearer ones for Fig 2D, E, F, as you suggested.

Changes in the text:

Fig. 2

Comment 10: In discussion, “Sunao” should be changed to “Shoji”.

Reply:

Dear reviewer, thank you for pointing out the mistake. We felt so sorry for the careless, and we changed it in the right way.

Changes in the text:

Page 9, Line 107