

Peer Review File

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Review Comments

Reviewer A

Comment 1: The aim of the manuscript is very broad and I request the authors to disclose how many manuscripts met the inclusion criteria and then how many finally made it to the review and why were others excluded. I feel that at least all recent systematic reviews on various aspects of FT should at least find mention as they all act as useful reference for readers to find all information in one place.

Reply 1: Thank you for your response. We have modified the text as advised to better clarify how our selection process for inclusion/exclusion was decided (see pages 5-6, lines 125-138). Given the introductory nature of this review, our aim was to better familiarize readers with specific focus on selective focal therapy. While many systematic reviews exist, those that captured outcomes with a majority of patients that were included for analysis (i.e. whole-, hemi-gland ablation, etc.) were left out of our review.

Comment 2: I request the authors to also consider including the following recent references in the main text and possibly briefly discuss them.

Reddy D, Peters M, Shah TT, van Son M, Tanaka MB, Huber PM, Lomas D, Rakauskas A, Miah S, Eldred-Evans D, Guillaumier S, Hosking-Jervis F, Engle R, Dudderidge T, Hindley RG, Emara A, Nigam R, McCartan N, Valerio M, Afzal N, Lewi H, Orczyk C, Ogden C, Shergill I, Persad R, Viridi J, Moore CM, Arya M, Winkler M, Emberton M, Ahmed HU. Cancer Control Outcomes Following Focal Therapy Using High-intensity Focused Ultrasound in 1379 Men with Nonmetastatic Prostate Cancer: A Multi-institute 15-year Experience. *Eur Urol.* 2022 Apr;81(4):407-413. (this is the largest series with the longest follow-up data on HIFU)

Reply 2: Excellent and recent publication. We have added this reference and discussed their outcomes in the HIFU section (see pages 8-9, lines 209-221).

Comment 3: I request the authors to also consider including the following recent references in the main text and possibly briefly discuss them.

Jaipuria J, Ahmed HU. Clinical and pathologic characteristics to select patients for focal therapy or partial gland ablation of nonmetastatic prostate cancer. *Curr Opin Urol.* 2022 May 1;32(3):224-230. (latest review talking about case selection for focal therapy).

Reply 3: We have now included this reference in the introduction section to emphasize the need for adequate patient selection process (see page 4, lines 108-112).

Comment 4: I request the authors to also consider including the following recent references in the main text and possibly briefly discuss them.

Bakavicius A, Marra G, Macek P, Robertson C, Abreu AL, George AK, Malavaud B, Coloby P, Rischmann P, Moschini M, Rastinehad AR, Sidana A, Stabile A, Tourinho-Barbosa R, de la Rosette J, Ahmed H, Polascik T, Cathelineau X, Sanchez-Salas R. Available evidence on HIFU for

focal treatment of prostate cancer: a systematic review. *Int Braz J Urol.* 2022 Mar-Apr;48(2):263-274. doi: 10.1590/S1677-5538.IBJU.2021.0091.

Reply 4: As above (comment 3) article outlines, we included this reference to help identify predictors for disease recurrence after primary treatment. (see page 4, lines 105-107).

Comment 5: I request the authors to also consider including the following recent references in the main text and possibly briefly discuss them.

Khoo CC, Miah S, Connor MJ, et al. A systematic review of salvage focal therapies for localised nonmetastatic radiorecurrent prostate cancer. *Transl Androl Urol* 2020; 9:1535–1545

Reply 5: We have modified the text to address the role of salvage focal therapy and the need for future data/outcomes. Added in the “Future Directions” section (See page 18, Lines 467-470).

Reviewer B

Comment 1: I would add and discuss this reference: future of focal therapy?

Ehdaie B, Tempany CM, Holland F, Sjoberg DD, Kibel AS, Trinh QD, Durack JC, Akin O, Vickers AJ, Scardino PT, Sperling D, Wong JYC, Yuh B, Woodrum DA, Mynderse LA, Raman SS, Pantuck AJ, Schiffman MH, McClure TD, Sonn GA, Ghanouni P. MRI-guided focused ultrasound focal therapy for patients with intermediate-risk prostate cancer: a phase 2b, multicentre study. *Lancet Oncol.* 2022 Jun 14:S1470-2045(22)00251-0. doi: 10.1016/S1470-2045(22)00251-0. Epub ahead of print. PMID: 35714666.

Reply 1: Phenomenal study that was recently published regarding intermediate-risk prostate cancer. While we do not go into the mechanism of MR-focused ultrasound therapy, it is important to acknowledge and we included this study in the context of future studies to expand the inclusion criteria for focal therapy (intermediate and beyond) (See page 19, Lines 494-502).

Congratulations

Reviewer C

Comment 1: Please add some details as to how discretion was used to include or exclude papers after searching. One would expect a narrative review like this to include many more references given the broad scope and inclusion of several different focal therapies.

Reply 1: We have modified the text as advised to better clarify how our selection process for inclusion/exclusion was decided (see pages 5-6, Lines 125-138). Given the basic introductory nature of this review, our aim was to better familiarize readers with specific focus on selective focal therapy. While many systematic reviews exist, those that captured outcomes with a majority of patients that were included for analysis (i.e. whole-, hemi-gland ablation, etc.) were left out of our review.

Comment 2: For instance, for IRE, the following paper is one of the most comprehensive. Please consider including it in this manuscript:

<https://doi.org/10.1371/journal.pone.0215093> April

Reply 2: The authors encountered this review in their search. While an exhaustive and thorough report of IRE outcomes, the decided to exclude this paper given the heterogeneous population in

which the majority of cases included high-risk patients treated with techniques that were not necessarily focal/selective treatments (i.e. whole-gland).

Comment 3: Page 10, line 258: please change the units of “ms” to “μs” – IRE uses pulses on the order of 70-100 microseconds.

Reply 3: We have modified our text to reflect this change, thank you!

Comment 4: Page 17, line 440: please double check the grammar of this sentence.

Reply 4: We have modified our text to edit the grammar and allow for more concise reading of the text.

Reviewer D

Comment 1: - In the table 1:

* Date of Search : I don't understand what means "2021-2022"

* Inclusion and exclusion criteria: basic-science, book chapter don't seem to be "study type". What did you consider the case reports and thesis work? Were they included? For "book chapter", how did you proceed to guarantee the exhaustivity?

* Selection process: "By Interventional Urologist attendings and fellows, board members of the Focal Therapy Society." Could we have more information about their experience (how many years etc.)

Reply 1: Thank you for your comments. We have modified this text to allow the table to address the comments. As you mentioned, the basic-science and book-chapter delineations were confusing and removed. Selection process members were better clarified (See pages 4-5, line 118).

Comment 2: - In the chapter of HIFU: the authors should discuss the result of this systematic review :

Ramsay, C.R., et al. Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation. *Health Technol Assess*, 2015. 19: 1.

<https://pubmed.ncbi.nlm.nih.gov/26140518/>

Reply 2: We have now included this reference in our section “Future Directions” which addresses the clinical effectiveness as it relates to the balance of cost-efficiency. While this study did not have any clear recommendations or findings regarding a superior technology to treat PCa in regards to the mentioned balance, it is important to reference that this is a special consideration when consulting patients (see page 20, lines 518-530).

Comment 3: In the chapter of Vascular-Activated Photodynamic Therapy : the authors should discuss the result of this RCT:

Azzouzi, A.R., et al. Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial. *Lancet Oncol*, 2017. 18: 181.

<https://pubmed.ncbi.nlm.nih.gov/28007457/>

Reply 3: Thank you for this mention, after reviewing this paper, we have modified our text to include the above reference (see page 14, Lines 365-370).

Comment 4: It will be welcome to have more figures.

Reply 4: Given the nature of our review and the deadline/timeframe for publisher access request, we decided to focus on a primarily narrative review.

Reviewer E

Comment 1: Line 134-136. The authors mentioned "...few studies have looked at treating intermediate-high risk disease..." I disagree with this opinion. According to a systematic review recently published by Hopstaken et al., not a few studies and physicians currently provided cryotherapy to treat intermediate risk disease

Eur Urol. 2022 Jan;81(1):5-33. doi: 10.1016/j.eururo.2021.08.005. Epub 2021 Sep 4.

Reply 1: We agree with your above comment and have modified the text to better clarify our sentiment. In regards to initial wording, we wanted to express our thoughts that the need for long-term outcome data, specifically in atypical focal candidates (high-risk disease)) in this subgroup is needed. (see page 6, lines 152-155).

Comment 2: Line 205. The authors described "Failure-free survival" for HIFU. Since the definition of "Failure" has no consensus between studies, it would be better to explain how "Failure" was defined when the authors refer to "Failure-free survival".

Reply 2: We have modified the text to elucidate the definition of failure (see page 9, lines 238-240).

Comment 3: Line 259-262. The authors evaluated residual disease on follow-up biopsy. Detection of insignificant PCa and clinically significant PCa (CSPCa) on follow-up biopsy have different importance. Therefore, I suggest that any PCa detection or CSPCa detection should be clarified when follow-up biopsy results are evaluated. The same applies to some sentences regarding other FT modalities. In field CSPCa recurrence on follow-up PBx is important outcome for FT. Therefore, it would be more useful if the authors described in-field CSPCa detection rate on follow-up PBx after each FT modality.

Reply 3: The authors agree with you that: 1) CS prostate cancer detection has a largely different implication and in the majority of papers, insignificant cancer detection on f/u was not determined to be "treatment failure." 2) In-field CSPCa detection rate is an important marker of clinical treatment success; however, some of the mentioned studies largely describe their outcomes/results without explicitly including whether this was in-field or out-of-field detection.

Comment 4: Patient selection and ablation method (focal, hemi, quadrant, and whole-gland) can influence FT success. There is no consensus which patient and ablation method are optimal for FT. Could the authors comment on this?

Reply 4 This is a point well taken and have modified our text to address that inclusion for focal therapy differs from whole-gland etc. (see page 4, Lines 99-103).