Peer Review File

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Comment 1: Even though a narrative review is acceptable, it would be beneficial to flesh the methods of the manuscript out. For example, what time-period of literature was considered? How senior were the reviewers of the literature etc.

Reply 2: We thank the reviewer for the comments and corrections provided. The reason a narrative review was chosen as manuscript type is mostly due to the scarcity of literature available on the topic. FT is in its infancy, with sporadic adoption and little standardization. Most of the studies are retrospective and extremely heterogeneous. Guidelines are drawn on the basis of consensus conferences. Therefore, careful selection and assessment was necessary to include in chosen article in the manuscript. This means that a strict date cut-off was not possible. That said, articles from 2016 onwards were given greater emphasis, as trials and greater FT adoption was starting in those years.

Changes in text: Added a Methods section outlining methodology underlying this narrative review: "*Methods; In this study we aimed to explore and evaluate what is really needed to push forward FT from the "investigational" status to that of a valid alternative that needs to be considered and to be proposed to selected patients. To do this, we reviewed relevant literature on FT, and described and compared available studies, in order to generate a comprehensive overview of the recommendations regarding FT. No specific time-period was used to determine relevant studies, as FT is a nascent technique, and as such, characterised by numerous biases and differing methodologies. That said, most evidence provided in this review comes from studies published after 2016, as larger studies were emerging.*"

Comment 2: A major omission from this piece is the lack of discussion around "what happens if FT fails" - for patients and clinicians we must understand what the salvage options are and what they can achieve if we offer FT first and it does not work. Expert, high-volume surgeons have shown that they can perform salvage RP with the same perioperative outcomes as primary RP [1. Techniques and Outcomes of Salvage Robot-Assisted Radical Prostatectomy (sRARP) 2. Salvage robot assisted radical prostatectomy: A propensity matched study of perioperative, oncological and functional outcomes. However literature is limited to very small cohort of prospective patients (RAFT) or single-centre, retrospective analyses (Bates / De Groote]. Furthermore, only very recently has a paper compared different salvage modalities (Comparative Effectiveness Analyses of Salvage Prostatectomy and Salvage Radiotherapy Outcomes Following Focal or Whole-Gland Ablative Therapy (High-Intensity Focused Ultrasound, Cryotherapy or Electroporation) for Localised Prostate Cancer). This is one-centre, high-volume but the first to report salvage outcomes after FT. Again the quality of the evidence is limited, however it remains the only paper to assess the issue. It would be important to touch on your paper that this is also an area that needs to be better explored.

Reply 2: We thank the Reviewer for this comment. Indeed, the reviewer rightly pointed out a controversial and commonly misinterpreted aspect of FT, salvage therapies. To address this comment we added a sub-heading titled 'Salvage therapies for FT failure'.

Changes in the text: *Salvage therapies for FT failure; Notwithstanding important advances in patient selection, up to a third of patients may require further local salvage treatment after ablative therapy failure [51]. Options for patients experiencing recurrence after FT include salvage robotic-assisted radical prostatectomy (sRARP), salvage radiotherapy (sRT) and repeat FT. Literature regarding salvage therapies for FT failure is limited, mostly descriptive in nature and with small cohorts.*

In the past, sRARP was avoided as it was considered complex and unsafe, as prior FT generated peri-prostatic fibrosis, adhesions and loss of anatomical planes [52]. However, a study by Pierrard et al. [53], showed that sRARP post vascular-targeted PDT was feasible and safe without difficulty for most of the surgeons involved. In most cases the reported difficulty was due to lateral fibrosis during dissection of the nerve bundles on the PDT treated lobe. A second difficulty encountered was linked to posterior fibrosis with consequent adherence to the rectum [53]. Accordingly , in another study comparing sRARP and RARP, it was found that while operating times are longer in sRARP compared to primary RARP, and general surgical perception agrees that sRARP are more complex procedures, a matched analysis demonstrated no significant differences in post-operative Clavien-Dindo scores [54]. The same study also showed that while sRARP had a 25% increased risk of positive surgical margins and a three-fold greater incidence of PSA persistence, there was no substantial difference in BCR incidence, albeit with a short 36 month follow-up [54]. On the other hand, functional outcomes diverged significantly between sRARP and primary radical treatment. Indeed, only 55% of patients treated with sRARP recovered continence at three years, as opposed to 83% in the second group [54]. Similarly, recovery of potency was achieved only in 13% patients undergoing sRARP, half compared to primary RARP. Part of the divergence in functional outcomes may be attributed to the feasibility in performing a full or partial nerve-sparing procedure. Indeed, nerve sparing was performed less in patients undergoing sRARP, due to peri-prostatic fibrosis [54]. However, in a separate propensity score–matched analysis between sRARP after FT and primary RARP, a sub-analysis on patients who underwent a full nerve-sparing procedure showed that potency rates remained inferior in the cohort with prior FT, possibly owing to a lower quality of nerve-sparing and prior direct nerve damage from FT [55].

Salvage radiotherapy (sRT) is another possibility. Indeed, a recent single-institution study compared sRARP and sRT with concomitant hormone therapy in patients previously treated with FT [56]. The study confirmed that like sRARP, oncological and functional outcomes of sRT are inferior compared with primary radical outcomes . When compared in the salvage setting, it appears that sRT may provide better medium-term oncological control compared to sRARP, as overall BCR-free survival at 3 years was 89% and 69%, respectively [56]. A potential explaination for this outcome in this particular study was the higher prevalence of high-risk disease in the sRARP cohort (indeed, no significant oncological difference was present in patients with intermediate-risk disease) and concomitant hormone therapy in sRT, resulting in a biochemical supression. Cumulative sRT-related bowel and urinary toxicity was 25% and 61%, respectively. When comparing functional outcomes, sRT provides a similar urinary continence

rate, but a superior erectile function (EF) profile, as potency at 2 years was 21% and 73% for sRARP and sRT, respectively [56].
If FT failure is due to a low volume intermediate-risk disease, repeat FT is a viable option. Indeed, in a previously cited study looking at oncological outcomes in men treated with HIFU, patients were followed for 3 years. Twenty-six per cent required salvage treatment, of which 193 (71%) opted for a repeat focal HIFU, with 74% of these patients not requiring further treatment [32].
In conclusion, sRARP performed by experienced surgeons is a feasible treatment option in patients experiencing FT failure. Both sRARP and sRT appear to provide acceptable oncological control, albeit at the cost of worse functional outcomes when compared to a primary radical treatment. Definitive evidence of oncological control using 'hard' endpoints such as overall survival are still needed in this setting. Potency was significantly more preserved in patients which had undergone sRT, therefore careful councelling and patient preference should be performed when deciding on the ideal salvage treatment option.
However, it is worth mentioning that current data in the salvage setting are afflicted by the poor disease features of current patients candidate for salvage therapies. For instance, in the previously cited study by Bhat et al. [54], 50% of patients had at least ISUP Grade Group 3 or more disease. Furthermore, at the final pathology assessment, 66% and 9% of men had locally advanced disease and nodal metastasis, respectively. Again, this is most probably due to poor patient selection and lack of a standardized post-FT follow-up. This leads to poor outcomes in the salvage setting and consequent hesitation towards welcoming FT as a valid therapeutic alternative [57].

Furthermore, we added a table showing the main studies assessing salvage therapies after FT failure

Comment 3: Specific Points:
1) Line 55 - It would be important to differentiate between the toxicities for different radical therapy modalities, rather than group them into one. For example, RP is not significantly associated with rectal toxicity and RT has a different erectile dysfunction profile to RP.
2) Line 58 - do you mean "making complications associated with 'radical treatment' - difficult to accept"? - This I would agree with!
3) Paragraphs (Line 136 and 150) - a further issues with the definition of focal therapy is the use of bilateral or whole-gland FT energy sources? Should this still be considered FT. Even though whole-gland focal is not presently widely used, what about unilateral FT and then a further treatment of the contralateral side, should this be considered FT or whole-gland (even though FT energy sources are being used). Further it would be good to get the authors opinion on the use of whole-gland or unilateral and then further contralateral FT.
4) Line 201 - this is a key point and I agree with the authors that this is a significant issue, there are currently no well-defined definitions for failure (does this include imaging and histology and biochemical - further the current evidence for FT has no well set definitions. This undoubtedly has a key effect on salvage therapies and therefore limits the confidence of the patient and clinician in counselling.
5) Line 271 - the issue is even though PART is due to finish in 2024, recruitment may be an issue and for intermediate risk PCa we need 10+ years at least to see the effect of BCR and even longer

to assess survival...

Reply 3: Regarding the Specific Points mentioned, the following changes in the text were performed:
1) "…*functional sequelae as a consequence of neurovascular bundle and external sphincter damage, such as erectile dysfunction and urinary incontinence in RP and rectal toxicity in (RT) [2,3]…"*
2) "…*The choice to undergo radical treatment and risk the emergence of functional complications is more difficult to accept when considering available evidence suggesting that there is a marginal difference…"*
3) We thank the reviewer for this comment. We aimed at providing what should be considered a correct definition of FT ("*On the other hand, FT, as stated by its own definition, is an image-targeted, biopsy-confirmed treatment modality. In this context attention should not be so much placed on a treatment template to be respected, rather on the correct localization of the neoplastic burden and the ablation of the previously described safety margin [30]"*). Whole gland treatment should not be considered FT.
4) We thank the reviewer for this comment. This issue has also been stressed more in the added sub-heading regarding salvage therapies.
5) We thank the reviewer for this comment

Comment 4: General comments:
- line 72: Three crucial aspects are mentioned. Where do these come from? Include reference(s) if possible.
- It seems to me that the Introduction already mentions the 'conclusions' from the abstract. However, the conclusions should be based on the results obtained from the literature analysis. This should be rewritten.

Spelling/grammar/etc.:
- line 54: "radiotherapy" -> "radiotherapy (RT)"
- line 96: "80% cases" -> "80% of cases".
- line 117: "csPCa" -> "clinically significant prostate cancer (csPCa)"
- line 120: "represent" -> "represents", "selection" -> "selecting"
- line 121: "obstacle" -> "obstacles"
- line 158: "Multidisciplinar Consensus" -> "Multidisciplinary Consensus"
- line 179: "represents to" -> "represents the"?
- line 188: "QoL"-> "Quality of Life (QoL)"
- line 302: "targetetd biopsy" -> "targeted biopsy"
- table 2: "á la carte" -> "à la carte"

Reply 4: We thank the reviewer for the comments and corrections.
-We have added citations regarding the three crucial aspects mentioned
-We had originally written down the final section of the introduction in that way to summarise the findings from the survey mentioned, and use it as a foundation for the narrative review. That said, we agree with the reviewer in that the conclusions should be based on the results obtained from

the literature analysis. Therefore, we changed the text to add clarity: "*Finally, to provide strong and reliable evidence supporting the efficacy of FT, valid clinical endpoints, surrogate of treatment response, and valid salvage therapies in case of failure need to be identified, as there is currently no reliable comparable data comparing FT to RP. In this study we aimed at exploring and identifying the key factors that might push FT forward among the set of PCa therapeutic alternatives.*"

-We have corrected all spelling and grammar, and thank the reviewer for pointing them out.