Peer Review File

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Reviewer Comments

Comment 1: The authors state "Diagnosing and managing locally recurrent prostate cancers after primary RT presents unique challenges stemming from the biochemical alterations in tissues that have been exposed to radiation (4)". While it is possible (and likely) that there are biological alterations post-radiotherapy which do present challenges to management of local recurrences, the authors provide a mouse study with an atypical fractionation for a course of prostate radiotherapy. This may have substantial impacts on the biological response to ionizing radiotherapy. While not mandatory, the authors may consider providing a citation of human tissue post-radiotherapy.

Reply 1: We acknowledge the importance in providing a study containing human tissue post radiotherapy in this context. Here we have instead replaced the citation with the following citation: Crook JM, Malone S, Perry G *et al*. Twenty-four-month postradiation prostate biopsies are strongly predictive of 7-year disease-free survival: results from a Canadian randomized trial. *Cancer* 2009;**115**:673–679.

Where the group looked at prostate biopsy specimens 24 months post external beam radiation therapy with 20% of biopsies have indeterminant classification given post radiation changes (such as cystoplasmic swelling and chromatin smudging).

Changes in the text: Citation changed to

"4. Crook JM, Malone S, Perry G *et al*. Twenty-four-month postradiation prostate biopsies are strongly predictive of 7-year disease-free survival: results from a Canadian randomized trial. *Cancer* 2009;**115**:673–679."

Comment 2: The authors state that there is a 63% rate of patients having a 'rise in PSA' after EBRT. This is a deceptive statement because a rise in PSA is expected and not an indicator of treatment failure. I am not sure this is indicative of modern practice. For instance in RTOG 0521 (PMID: 37179241) the Kaplan-Meier estimated rate of biochemical failure (phoenix definition) was approximately 40%. This is a cohort of high-risk / very-high risk patients so this would be the upper boundary and the actual estimate is probably much lower for the entire population.

Reply 2: We agree with the more up to date reference and have accordingly changed that line in the text.

Changes in the text: We agree with the more up to date reference and have accordingly changed that line on page 3 to:

"10 year follow-up of patients in the phase III RTOG 0521 trial looking at a combination of deprivation therapy with docetaxel and EBRT with deprivation therapy and EBRT alone demonstrated that in a population of high risk prostate cancer patients, 40% of patients experience a rise in PSA post radiation. It is important to note that this over-represents the actual rise in PSA post radiation in the general population and that this is not directly indicative of treatment failure as PSA rise is to be expected (5)."And have changed the citation to

"5. Sartor O, Karrison TG, Sandler HM, et al.. Androgen Deprivation and Radiotherapy with or

Without Docetaxel for Localized High-risk Prostate Cancer: Long-term Follow-up from the Randomized NRG Oncology RTOG 0521 Trial.Eur Urol. 2023 Aug;84(2):156-163."

Comment 3: I am having difficulty validating the statement "60-72% of patients with escalating PSA levels and a negative metastatic evaluation post external beam radiation therapy (EBRT) are confirmed to still harbor local disease upon biopsy (6)." With the data in reference 6. Perhaps the authors may kindly provide the area of this manuscript which references this. There is an issue with post-treatment biopsies which is that many patients with positive post-treatment biopsies may eventually go on to clear their disease at later time points and not all patients with post-treatment biopsies eventually manifest with biochemical recurrence (or. more accurately, this could be true but there is insufficient evidence to conclude this from the available literature). The authors do cite one of the fundamental studies which discuss the former (ref 15 by Crook et al. IJROBP 2000). Overall these rates are somewhat deceptive since it seems to imply that the rates of local failure are quite high (> 20%) which is not consistent with reported rates in clinical trials (e.g.., RTOG 0815, PCS IV which reported rates 20 years ago. In the modern era a large proportion of patients who undergo EBRT will be expected to have a post-treatment rise PSA from the simple recovery of testosterone. Furthermore, it is possible that post-treatment biopsies within the first 1-1.5 years may come at higher risk of non-healing rectal ulcers if done via a TRUS approach.

Reply 3: We agree that the reported numbers may have overstated the degree to which biochemical recurrence may manifest post RT. Insteadly we have cited the RTOG 0815 study which at 10 years demonstrated a 25% recurrence rate. We have also re-iterated that rise in PSA may not be indicative of local recurrence and thus is an area of further control before transitioning in to the remainder of the paragraph discussing the variability in the management and recognition of radiorecurrent prostate cancer.

Changes in the text: In Page 3 "Additionally, studies such as RTOG 0815 looking at patients with long and short courses of ADT after radiation therapy have demonstrated a biochemical recurrence rate of 25% in 10 years. Together, data such as these demonstrate that although PSA rise can be present post radiation from the recovery of testosterone, it is not entirety indicative of biochemical recurrence, thereby posing a difficult challenge for urologists in regards to determining when to treat"

Comment 4: The authors may wish to discuss the combined analysis of TOAD and ELAAT at ASCO 2018, although they may wish to avoid this as I am uncertain this has been published in manuscript form. Nevertheless, part of the discussion that is missing here is an evaluation of competing risks which heavily relies on age and comorbidity burden.

Reply 4: We acknowledge the need to discuss the competing risks on age and comorbidity and have therefore incorporated this into the text and included the reference involving the combined analysis mentioned above.

Changes in the text: Page 6 "It is important to note that for the use of salvage ADT, patient selection is critical and may help identify those that would receive a benefit in initiation of deprivation therapy. Trials such as the ELAAT trial and TOAD trial investigated the optimal timing of ADT initiation in post-RT PSA rise. Combined pooled analysis demonstrated no difference in all cause mortality but improvement in time to local progression with immediate ADT. One important notion to consider is that ELAAT involved significantly older with a higher comorbid all mortality risk while TOAD

incorporated higher risk patients that may have benefited from immediate ADT (30% of paatients with a relapse free intervnal of less than 3 years) together leading to no difference in all cause mortality demonstrated. Thus, when deciding when to use salvage ADT it is important to balance the benefit of initiating deprivation with the competing risks of age and comorbidities particularly in those with a high risk of all-cause mortality".

Comment 5: "Establishing a reasonable PSA threshold for ADT initiation requires additional studies." The authors may wish to edit this sentence for clarity as this paragraph appears to refer to PSA doubling time threshold and not absolute PSA threshold.
Reply 5: We agree with the editing for further clarity and have changed the sentence as seen below.
Changes in the text: Page 14 "Establishing a reasonable threshold for PSA doubling time for ADT initiation requires additional studies"

Comment 6: On lines 318-319, I believe there is a typographical error where the authors write "self-limiting" although they may have meant "self-limited"
Reply 6: We have accordingly changed the text.
Changes in the text: The text on page 14 has changed to "Seven patients (19%) reported self-limited urgency, frequency, or hematuria (grade 1-2). Seven patients (19%) developed grade 3 adverse events"

Comment 7: On line 152 the patients refer to NRG RTOG 0526 as "RG/RTOG 0526", I believe this is a typographical error
Reply 7: We have accordingly changed the text.
Changes in the text: The text on page 8 has changed to "The NRG RTOG 0526 phase 2 trial led by Crook, investigated transperineal ultrasound-guided LDR BT for patients with local recurrence post-EBRT"

Comment 8: The authors fail to include mention of the prospective studies in this paragraph which are discussed in part below. This list is lacking several publications but at least prospective studies should be mentioned including NCT03253744 which has 2 publications (PMID: 37442430, 38428681) in addition to the studies mentioned in Table 4.
Reply 8: We acknowledge the importance of this prospective study and have included it in the table and text as mentioned below.
Changes in the text: Page 11 It is also important to note the ongoing prospective studies actively being done in order to investigate the utilization of SBRT in the salvage setting for radiorecurrent prostate cancer. NCT03253744 is a phase 1 trial aimed to identify the maximum tolerated dose of SBRT for radiorecurrent prostate cancer with 40, 42.5, and 45 Gy in 5 fractions delivered > 48 hours apart. A maximum tolerated dose of 40 Gy in 5 fractions was identified with 8 patients with a 100% 2 year biochemical progression free survival and no grade 3 toxicities at this dose (Patel citation). Further follow-up demonstrated a maximum tolerated dose of 42.5 Gy in 5 fractions with an 86% 2 year biochemical free survival rate with 9 patients (Patel citation 2). Prospective studies such as these add to the literature regarding both the feasibility of SBRT in the setting of the oncologic outcomes that can be achieved.

Comment 9: Although follow-up is ongoing for NCT03253744, since the primary endpoint has been reported for both cohorts of this study it may be better discussed in the SBRT section as previously noted

Reply 9: We have accordingly also mentioned this in the SBRT section and mentioned in the trials section that this was previously described in our text as well.

Changes in the text: Page 15: As previously discussed, NCT03253744 was designed as a phase 1 trial with the goal of determining the maximum tolerated dose (MTD) when using image-guided, focal, salvage stereotactic body radiation therapy (SBRT) for patients with locally radio-recurrent prostate cancer (61). The identified MTD for this salvage SBRT, intended for treating isolated intraprostatic radio-recurrences, was established at 40 Gy delivered across 5 fractions. This dose achieved a 100% biochemical progression-free survival rate over 24 months, although there was one poststudy failure noted at the 33-month mark. Similarly, a follow-up study identified the MTD as 42.5 Gy delivered in 5 fractions with a 86% biochemical progression free survival over 24 months. The overarching goal is to refine and enhance the SBRT regimen for this specific patient population. This trial is actively obtaining further follow-up to provide additional information.

Comment 10: I believe the authors have summarized Pasquier et al. 2019 incorrectly. I believe they utilized a dose of 30Gy in 5 fractions for some patients and 36Gy in 6 fractions for other patients.

Reply 10: We have accordingly changed the text.

Changes in the text: The text in the table 4 has been changed to state: “6Gy/36Gy in 63 patients, 5Gy/35Gy in 37 patients.

Comment 11: The authors discuss the results of NCT03253744 in the discussion (ref 61), although do not mention it in their table 4. There are now two publications (PMID: 37442430 [included] PMID: 38428681 [not mentioned]) associated with this trial, both of which are prospective clinical trials which report on toxicity and efficacy of salvage SBRT. While small, given the prospective nature, these should be included

Reply 11and Changes in the text: These have now been included in the text in table 4.