Peer Review File

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Reviewer #1

I really enjoyed reading this review article, and think that it covers a very important topic. Prostate cancer is just one of many sites where there is excitement about local therapies in the metastatic setting, but as the most common cancer in men in the U.S., there is a high impact of research on this site. I thought the authors did a good job referencing the most important and highest profile clinical trials that were relevant to the discussion. I thought it was very important to have a section on imaging, as I do agree that research on detecting metastases and accurately assessing burden of disease will go hand in hand with proper patient selection for oligometastatic directed therapy.

Comment 1: The only general thematic comment I would make is the pointed emphasis on SBRT in this paper is not fully explained. There is the section on alpha/beta and the potential advantages of extreme hypofractionation based on radiobiological principles. However, we know that at the moment, the potential improvement in prostate cancer control has not been realized in practice. Therefore, I would recommend a little more fleshing out of why SBRT may be the preferred radiation modality when treating oligometastatic patients (I don't disagree that it is, but I feel like it could use more explaining).

We would like to thank the reviewer for all their helpful comments. To address comment one we have added a couple of sentences in the section entitled "Metastasis-directed therapies in Oligometastatic Disease" to emphasize why SBRT is a better option for ablation in most cases, and thus justify why this is the focus of this paper.

A few specific nit-picky points:

Comment 2: Abstract - Is it really true that RT to the prostate in oligometastatic disease has become integrated into routine clinical practice? Not in two locations that I've worked at recently. It could be nationally, but perhaps this kind of sweeping statement could use a citation or a softer wording for the time being.

Wording has been changed slightly to reflect this, although we hope that all centres will implement prostate radiotherapy for all patients who may benefit soon.

Comment 3: No mention of Axumin scans in the body of the paper. I agree that I am most excited about PSMA-PET scans in the future, but in the last 5 years I've seen Axumin scans ordered the most in multiple sites of practice.

There is a brief sentence about Axumin in the table (18F Fluciclovine). We have expanded on this in the text within the table and have also added a sentence into the main text.

Comment 4: I would describe the RT used in HORRAD and STAMPEDE, especially since the authors put a lot of emphasis on SBRT. It should be pointed out that non-SBRT radiation treatment was used in these studies and should be considered important as well.

We have described the dose / fractionation used in each trial and have emphasised that this is standard fractionation rather than SBRT.

Comment 5: I would also mention intermittent ADT as a common treatment strategy in metastatic hormone sensitive prostate cancer. It is especially relevant to the discussion about trying to limit the impact on quality of life from ADT.

We have added a paragraph on intermittent ADT:
Intermittent ADT is an alternative to continuous ADT, with promising toxicity and QOL outcomes. However, direct comparisons between intermittent and continuous ADT have found clinically important survival differences, and importantly the SWOG trial failed to demonstrate non-inferiority. Continuous ADT is therefore recommended except for well-informed, motivated patients who are troubled by side effects, have a reliable PSA response, and undergo increased surveillance.

Overall, great job detailing out the key studies in this space. Thank you for this contribution!

Reviewer #2

This is a very well written review that provides very useful information on oligometastatic prostate cancer.

Comments:

Comment 1: Under Radiobiology, "Treatments are typically delivered >48hr and <96hr apart to minimise toxicity."- There are some centers delivering fractions QD. The authors may want to indicate that in the statement.

We have added "although some institutions treat daily ".

Comment 2: Under "Use of SBRT in Oligometastatic Disease"- *"The attempts to ablate all sites of disease as they arise has been likened to the futility of catching all Pokemon (82), although this was rebutted (83)"* should be changed to "*The attempts*

to ablate all sites of disease in metastatic prostate cancer as they arise has been likened to the futility of catching all Pokemon (82), although this was rebutted (83)".

'in metastatic prostate cancer' has been added

Comment 3: In Table 3, the authors may want to indicate that SABR-COMET included various histologies including prostate cancer.

Added specifically that prostate cancer is also included

Comment 4: The authors may also want to include the prospective clinical trial from Peter Mac as the trial showed that SBRT delayed hormone therapy in half of the patients not on ADT at 2 years.

We have already included the POPSTAR trial from Peter Mac in the "Data supporting SBRT in metachronous oligometastatic disease section" (reproduced below) – is there another similar Peter Mac trial we have missed?

"Accordant results were achieved in the POPSTAR trial, which evaluated the role of SBRT (20Gy in 1 fraction) to up to 3 bone-only (n=20), node-only (n=12) or both (n=1) oligometastases (87). Local control was again superb, 2-year local PFS of 93% (CI 84-100%), and although 67% suffered grade 1-2 side effects, grade 3 reactions were limited to 1 patient (vertebral fracture requiring spinal instrumentation). Distant progression was common (2-year distant PFS 39% (CI 25-60%)) but biased by whether patients were already on ADT (n=11); if not, 2-year freedom from ADT was 48%. A quarter of relapses were amenable to salvage SBRT. Interestingly, three quarters of patients recurring following SBRT to bone-only disease reoccurred in bone, whilst irradiated nodal disease re-occurred only in other nodes. "