

Peer Review File

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Review Comments

Reviewer A

It was a pleasure reviewing the manuscript "THE PAST, PRESENT AND FUTURE OF NON-METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (NMCRPC): A NARRATIVE REVIEW" by Vidal et al.

The authors mention an increased incidence in prostate cancer diagnosis with PSA screening but do not mention the change in incidence with change in screening recommendations. If a point is discussed it needs to be discussed in totality for clarity and completion.

Reply: Thank you for the comment. We have added the NCCN recommendations (lines 43-46).

Again in first paragraph of page 2 they mention ADT as standard therapy for biochemical recurrence. This is incorrect because it is monitoring. Please refer to NCCN guidelines.

Reply: Thank you for the observation. We have rephrased it to show that, although it is not the preferred option, it is still an option in selected patients (lines 56-59).

Need to include other important papers such as:

1. Morris et al. Phase 3 Randomized Controlled Trial of Androgen Deprivation Therapy with or Without Docetaxel in High-risk Biochemically Recurrent Prostate Cancer After Surgery (TAX3503) Eur Urol Oncol. PMID: 34020931

Reply: Excelent point. We added the reference (10) in the text (lines 68-72).

2. Sayegh et al Drug Development for Prostate Cancer with Biochemical Recurrence: Trials and Tribulations Eur Urol Oncol. PMID: 34148857

Reply: Thank you. We have added this reference (number 7, lines 52-55, 56-72)

3. Marshall CH, Chen Y, Kuo C, et al. Timing of androgen deprivation treatment for men with biochemical recurrent prostate cancer in the context of novel therapies. J Urol. PMID: 34003011

Reply: We also added this reference (9) in the text (lines 62-66).

Reviewer B

In this narrative review, the authors discuss the management of castration-resistant nonmetastatic prostate cancer. They describe previously used treatment options and detail three important contemporary trials: ARAMIS, SPARTAN, and PROSPER that lead to the use of NHT in this setting. They also report the PSMA-based imaging utilities in nmCRPC as well as the association of molecular subtyping with response to NHT.

Although very interesting, I would suggest the following modifications:

-Proof reading by a native English speaker (some minor errors concerning wording, some confusing sentence structure)

Reply: Thank you for the observation. We have proofread ourselves and asked a native English speaker to double check.

-Elaborating further on the mechanism of action of the three anti-androgen agents cited.

Reply: Thank you for the excellent observation. We have elaborated further the mechanism of action of the three drugs (lines 206-209, 268-273 and 340-344)

-Elaborating further on the health related QOL (PMID: 30213449,)

Reply: We have added the HRQOL of the PROPER (lines 243-245), SPARTAN (lines 314-315) and ARAMIS trials (lines 380-381)

-In the PSMA-based imaging section: It would be enriching to talk about the effect of ADT on PSMA-PET imaging (PMID 31732768). It would also be judicious to report the following study on 68 Ga-PSMA-11 PET/CT in nmCRPC (PMID: 32034191)

Reply: The first reference (number 61) has been added in lines 469-471. The second reference (number 59) was added in lines 465-466.

-Adding a table about ongoing clinical trials for patients with nmCRPC would be a great asset for the paper, since the title of the manuscript indicates that it talks about

the future of nmCRPC.

Reply: Excellent suggestion. We have added this information on table 3 (lines 543-544)

-Adding titles to the tables (and the references for the numbers in Table 1).

Reply: Done.

Reviewer C

This is a narrative review of treatment options for non-metastatic castration resistant prostate cancer. The authors first review negative studies done prior to 2018 and then the three pivotal studies done since.

In the introduction, the authors define castration resistance and make a distinction between metastatic and non-metastatic. While this is a valid comparison, the comparison must also be made first to non-metastatic hormone sensitive and non-metastatic castration resistant disease.

Reply: Thank you for the comment. We have added the definition of BCR (lines 52-55)

Continuous ADT is not an approved treatment for biochemical recurrent prostate cancer and has not been supported by level 1 evidence to prolong survival and this should be stated.

Reply: We have clarified this statement on lines 56-66.

Furthermore, the trials included men who had recurrence after local treatment as well as men who never had any local treatment. This should be clearly stated.

Reply: We have clarified this statement on lines 223-224, 287 and 352-353.

There is no information in this article about who would be getting continuous ADT in the first place (in order to enroll in the studies cited) or when continuous ADT should be started in the nmCRPC space.

Reply: We have clarified this statement on lines 56-66.

Darolutamide - Would argue that is not a meaningful difference - falls (4.2% versus 4.7%).

Reply: That is true. We have erased that to avoid confusion.

What is the purpose of singling out the Japanese patients in the ARAMIS study? These patients were a part of the main study and not different patients. Why were other subgroups not mentioned?

Reply: Thank you for the excellent observation. We have removed that paragraph

since it adds no new information.

Another major concern with starting these treatments early is the long-term risk of cardiovascular health. This should be discussed as there is significant real world evidence related to this and a significant concern when starting these treatments.

Reply: We have added this information on lines 59-61.

Other important papers to include:

<https://pubmed.ncbi.nlm.nih.gov/32605736/>

Reply: Thank you for the suggestion. We have included it (reference number 54, lines 405-410).

<https://pubmed.ncbi.nlm.nih.gov/34003011/>

Reply: Thank you for the suggestion. We have included it (reference number 9, lines 62-66).

There are some typos, run-on sentences, and repeated or missing words which make the article difficult to read. Line #322 – is this paragraph supposed to go there? It looks like it was inserted by mistake right there. If the readability were better it might make the article better.

Reply: We have modified it to make more sense with the rest of the text (lines 502-507).