Peer Review File

Article information: http://dx.doi.org/10.21037/tau-20-1031

Reviewer #1

The authors have performed a detailed and interesting review of possible treatment approaches to node-positive PCa. The review is based on up-to-date papers and poses a significant interest for urologists.

Comment 1: It is suggested to authors adding data regarding intermittent hormonal therapy and its possible use in node-positive patients.

Response 1: A discussion of intermittent ADT has been added to the ADT without local therapy section.

Comment 2: It is suggested to expand section regarding novel modalities for immune and chemotherapy in prostate cancer (clinical studies and etc.).

Response 2: We expanded our discussion of future directions in the conclusions section. We have added a brief discussion of NRG GU008, an ongoing clinical trial assessing the addition of abiraterone acetate and apalutamide to salvage RT for patients with pN1 disease after prostatectomy with a detectable PSA. We believe this is the only current large randomized trial specifically focused on node-positive patients. We had included a discussion of chemotherapy in section II. To our knowledge, there is no data or current large clinical trial on the use of immune therapy in node positive patients.

Reviewer #2

I would like the congratulate the authors on this extensive review of which the topic is very interesting. I do however have some urgent remarks which have to be considered:

Major concerns:

Comment 1: Detailed information about the search strategy is missing. For a review article this is the most important part of the article, because it helps readers to determine if the authors could have missed important articles. Please provide the strategy.

Response 1: We would like to note that this manuscript was not intended to be a systematic review, but rather was an invited expert review on this topic. Therefore, we have not included a search strategy. Further, the various subtopics in this review do not lend themselves easily to a systematic search.

Comment 2: Two topics are described, the treatment strategy of newly diagnosed cN1 prostate cancers and the treatment strategy of pN1 patients. Please insert the view of the most used guidelines (among others AUA en EAU) recommendations for these patients in a table.

Response 2: A table has been added which summarizes current recommendations from EUA-ESTRO-SIOG, FROGG (Australia), and NCCN. Of note, AUA guidelines do not have specific recommendations on N1M0 prostate cancer.

Comment 3: The second part of the review focuses on pN1 patients. This is a quite extensive group. My advise would be to focus on patients with BCR after pN1 RP and PLND and make this more clear in the introduction. This makes the article more clear for readers.

Response 3: We have specifically included "adjuvant" treatment for pN1 patients (patients with undetectable PSA after surgery) in this review article because this is relevant for clinical practice, and adjuvant treatment for pN1 patients is a recommended option by the NCCN and EAU guidelines, with supportive literature as we summarized in the manuscript. Therefore, this is an important section to keep in the manuscript.

To address the reviewer's comment, we have included a section on timing of post-prostatectomy therapy to clarify adjuvant and salvage therapy.

Minor revisions:
Part 2 cN1 patients:
Comment 4: Make clear to the reader that it is about cN1M0 patients, so no distant metastases.

Response 4: The title of section II has been updated to reflect cN1M0 and edits have been made within section II to clarify this distinction.

Comment 5: Start all paragraphs on what we do know out of studies describing the cN1M0 patient group. Then continue and make clear that there is information about high risk patients or patient with distant metastases which you would like to extrapolate.

Response 5: Modifications have been made to section II to alert readers when the evidence to be discussed is extrapolated from other settings.

Comment 6: Describe in cN1 patients if RT is on the prostate only or on the prostate and pelvic lymph nodes. Same for RP, RP only or RP with ePLND.

Response 6: A statement has been added to the Androgen Deprivation Therapy + Radiation Therapy discussion in section II. The title of the ADT + RP section has been adjusted to include extended PLND, which is recommended when considering RP (Table 4).

Part 3:
Comment 7: Describe what the treatment options are for pN1 patients after RP + PLND

Response 7: We added a line at the end of this section to clarify.

Comment 8: wait and see --> possible salvage treatment either sPLND, RT fossa, RT fossa and lymph nodes, all with or without ADT.

Response 8: We have included a discussion of adjuvant versus early salvage in response to comment 3. We specifically discuss the role of adjuvant vs. early salvage.

Comment 9: Adjuvant treatment --> same as above.

Response 9: We have included a discussion of adjuvant versus early salvage in response to comment 3. We specifically discuss the role of adjuvant vs. early salvage.

Comment 10: Overall try to reduce the number of words to make it easier to read. Also try to prevent a summary of all articles, but make it more about the treatment options and what is known. Maybe it will be interesting to insert the improvements in imaging (PSMA) and therefore that cN1 might be more often seen.

Response 10: We include a statement on PSMA PET in the conclusion.