

## Peer Review File

Article information: <https://dx.doi.org/10.21037/tau-22-191>

### Reviewer A

General comments: This is a retrospective dataset to compare the charges between chemical vs surgical castration in one hospital system in Iowa

Specific comments:

1. Was infusion chair, nurse injection charges accounted for in the chemical castration arm?
  - a. Reply: For the chemical castration arm, we included the charges of the medication itself as well as the nursing injection charge. We did not include an infusion chair charge.
  - b. Changes in text: None, this is included in Methods, Endpoints section. (Page 6, Lines 12-16)
2. While responses and outcomes are known to be similar based on early VA studies, it would be nice to compare in this contemporary cohort (albeit numbers are so very few) regarding differences
  - a. Reply: Unfortunately, our cohort's data collection did not include treatment outcome measures. However, more recent work from Tan, et. Al. demonstrated similar oncologic outcomes between medical and surgical ADT. They found equivalence in PSA response, androgen suppression, time to castrate resistance, and prostate cancer-specific mortality.
  - b. Changes in text: We have added citation to Tan, et. Al (Citation #6). Additionally, we added their findings of comparable PSA response, time to castrate resistance, and prostate cancer-specific survival to the Introduction, paragraph 1 (Page 3, Lines 8-9)
3. Is there a particular challenge and perhaps ideal to do a follow-up in terms of barriers for men choosing surgical castration (given only n=7)
  - a. Reply: Yes, the lack of men choosing surgical castration is notable. Our group has previously analyzed the potential reasons for this in another paper, which we have now referenced in this text. In our survey study, only 33% of men recall having a discussion of orchiectomy as an option for permanent ADT. While this is limited by recall bias, even if the option was brought up to men it is notable that they do not remember it. It is also important to note that surgical castration is not appropriate for some men, particularly those who require a limited duration of ADT or prefer intermittent administration. Our study would not be generalizable to these situations.
  - b. Changes in text: In Discussion, paragraph 5, (Page 12, Lines 10-17) we included reference to our previous work on attitudes regarding surgical orchiectomy. The prior work was cited as reference #29.

4. Perhaps a discussion of safety or risks/complications entailed with surgical castration/orchiectomy
  - a. Reply: We agree that risks and complications are an important part of the discussion and consideration for patients.
  - b. Changes in text: We have specifically stated the most frequently occurring post-operative complications, as well as rates of complications from recent work. These have been added to the Introduction, paragraph 2. (Page 4, Lines 1-5)
5. Recommend adding on the breakdown of men in each disease characteristic ie., low-risk, intermediate-risk, high-risk, or locally advanced, local vs metastatic prostate cancer (ie., the understanding of choice with surgical castration would be in men with metastatic disease vs chemical castration for intermediate- or high-risk disease for whom there is a finite time to receive ADT and the understanding is stopping it)
  - a. Reply: All of the patients in our cohort had been diagnosed with metastatic prostate cancer and were at minimum known to have N1 or M1 disease. Therefore, we do not have any distribution of risk stratification (for clinically localized disease) to include. We agree that this study is not generalizable for patients who only require a define course of ADT (such as those receiving ADT with radiation therapy) or to those who might prefer intermittent ADT.
  - b. Changes in text: No changes made in the text. We acknowledge the inclusion criteria of metastatic disease in the Methods, paragraph 1 (Page 5, Line 22). In our limitations section, we describe the generalizability of the analysis, and how it is would not be appropriate to apply to patients needing a limited course of ADT or intermittent administration. This is included in the Discussion, paragraph 7. (Page 14, Lines 12-14)

#### **Reviewer B**

1. The cost-effectiveness of SO over medical ADT is not new. Yet most patients would still choose SO over medical ADT. The reasons for such ironical observation should be explored.

Below is a useful article: 18. YG Tan, R Poon, L Pang, A Villanueva, HH Huang, K Chen, TK Ng, KJ Tay, H Ho, JSP Yuen. Comparative Study of Surgical and Medical Castration in Treatment Efficacy, Adverse Effects and Cost Based on a Large Prospective Metastatic Prostate Cancer Registry. *Urologic Oncology*; 2020 Aug; 38: 682e1-9

- a. Reply: Thank you for including this excellent, recent article, which we have included in the paper and citations. From this work and recent survey work done at our institution, it would seem that more men voice more interest in orchiectomy than those that follow through with surgery. Potentially, orchiectomy is more desirable as an "idea," but not desirable enough to make

the permanent decision to proceed with surgery.

- b. Changes in text: We have added citation to Tan, et. Al (Citation #6). We also provide a more thorough discussion of attitudes towards surgical orchiectomy in the Discussion, paragraph 5. (Page 12, Lines 10-17)
2. The SO has only 7 patients which lacks meaningful comparisons. The authors would attempt to include SO from other centres.
    - a. Reply: We agree that our surgical orchiectomy patient cohort is smaller than would be ideal for analysis. However, this is actually a representative number of patients who choose orchiectomy for permanent ADT. The range of surgical charges were relatively predictable, and adding additional patients to the surgical cohort would be unlikely to change the mean/median surgical charge figures to a large extent. We agree that a multi-institutional analysis would provide a broader context, but it is beyond the scope of the current study.
    - b. Changes in text: No changes in text.
  3. The cost-analysis would be better off discussed in months rather than weeks, as ADT are often prescribed at 3-6 monthly interval
    - a. Reply: We elected to frame our time in weeks, rather than months, as weeks are a fixed amount of time (7 days), where months will vary to a small degree (28-31 days). While we agree that colloquially ADT agents are prescribed by monthly interval, the package inserts for these agents typically instruct dosing based on number of weeks.
    - b. Changes in text: We have included our rationale for weekly analysis in Methods, paragraph 5. (Page 7, Lines 7-10). We have also referenced the United States FDA package insert for Lupron as an example of weekly dosing instructions, included as reference #21 and also linked here:  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/020517s036019732s041lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020517s036019732s041lbl.pdf)
  4. The authors should highlight that in this day and age, monotherapy with ADT is not the SOC, there needs to be treatment intensification with chemo/NHA. The added costs need to be emphasized.
    - a. Reply: We agree that systemic treatment beyond simply ADT is the norm in this day and age and will add a large treatment cost in addition to what we analyze in this study. Guidelines recommend continuation of ADT even in the setting of castrate resistance, so even in advance disease ADT will continue to play a role. We see the ADT charges as an inevitable baseline, with additional agents to be considered on top.
    - b. Changes in text: We emphasized the need for continued ADT in the Introduction, paragraph 1 (Page 3, Lines 3-6), and discussed the context of ADT being only a component of treatment in Discussion, paragraph 7. (Page 14, Lines 14-19).

### **Reviewer C**

This article revealed the median chemical ADT patient charges were greater than surgical castration in less than a year (38 weeks) in patients with advanced prostate cancer. The NPV of electing surgery over ADT was the highest with leuprolide. Although castration has shortcomings such as cosmetic or psychological concerns, the potential cost savings by castration become more emphasized as the treatment period gets longer. Castration is the most cost-effective method as a androgen deprivation therapy.

#### Specific comments

1. In this study, 137 patients had undergone chemical ADT. Please reveal the number of patients who received each chemical ADT agent (histrelin, degarelix, goserelin, triptorelin, leuprolide) in result section and table 1. Also, please reveal the total ADT charge, total care charge, follow-up duration (weeks) of patients who received each chemical ADT agent (histrelin, degarelix, goserelin, triptorelin, leuprolide) in result section and table 1.
  - a. Reply: Patients did not necessarily receive a single agent throughout their treatment course, and in fact many patient received a variety of agents. Therefore, the time-to-equivalence calculations were performed in two different manners. For the overall group in Figure 1, we sought to see how long it took median patients to accumulate charges similar to having had surgery. The by-agent analysis, Figure 3, was a hypothetical analysis making an assumption *if* a patient only received one agent, how long it would take to surpass those charges. Therefore, we cannot provide a breakdown of demographic information by agent, as many patients would fall into several different agent groups.
  - b. Changes in text: We made the nature of the by-agent analysis clearer in Methods, paragraph 5, (Page 7, Lines 19-21) and in Results, paragraph 4. (Page 9, Lines 17-19) We also included an additional figure, Figure 4, which visually displays the heterogeneity of agents administered to patients.

### **Reviewer D**

An important updated analysis of the ongoing debate between pharmacologic versus surgical castration.

The authors, as have other papers addressing the topic, thoughtfully review and analyze the financial superiority of the latter. They address their study' limitations.

Perhaps they might also address 2 points:

1: HCP remuneration incentivizations, via Medicare parts B/D (parenteral vs oral)

- a. Reply: There is certainly historical concern as to how reimbursement

incentives affect the choice of who receives ADT and the type of treatment they may receive. As the oral agents (relugolix) are much newer, we did not include in this analysis. However, this and comparable agents are likely to be a major consideration moving forward.

- b. Changes in text: We included a more recent work from Shahinian, which analyzed incentives of ADT administration before and after Medicare modernization and substantial decrease in ADT reimbursement (Citation #28). We discussed this further in the Discussion, paragraph 4. (Page 12, Lines 5-8).

2: Payor ready acceptance of pharmacologic choice, esp. for longterm ADT requirement (metastatic patients).

- a. Reply: The payor mix, and specific payors' willingness to reimburse various treatments is sure to have some impact on selection of treatments across urology, including the use of ADT. Our data set is limited to institutional charges. Therefore, we cannot provide any data behind reimbursement for this cohort. However, we added additional commentary below as to the importance of payor influence on treatment selection.
- b. Changes in text: We added additional verbiage to our limitations section of the Discussion, paragraph 7. (Page 13, Lines 15-17). We acknowledge that the changing regulatory/payor environment will continue to play a role in treatment selection that this analysis cannot account for.