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Title: Evaluating stage migration of testicular germ cell tumours in Alberta, Canada during the COVID-19 pandemic: a retrospective cohort study

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Reviewer 1

General comments (author response in bold)

Thank you for allowing me to review this very interesting manuscript. It is very well written and contains very important information which I hope reaches a large audience. I will make 2 major comments and then minor ones below.

Major:

1. TGCT are unique in that there are only 3 stages I,II,III and so some CMAJ readers who do not regularly see TGCT pts, may not realize that stage III are metastatic and stage II are often treated like stage II (versus lung and breast cancer for eg) . So, you may need a bit more educational information in the paper regarding this. But my question is: why did you separate pts out into stage I/II versus III when from a treatment point of view, we usually think it terms of stage I versus II/III? It looks like most of the stage II patients were treated with chemotherapy (although it would be helpful to have it explicitly stated how the stage II pts were treated...eg. maybe these were all the radiation patients for stage II seminoma?)

This has been clarified as per editor comment #2. Additional information has been added in the second Introduction paragraph to provide clarification on the differences between staging, management and prognosis. This has also been clarified in the first paragraph of the Results.

2. Methods, outcome, sentence 4: when you indicate the timing of tumor marker collection as “pre orchiectomy or as close to date of first presentation”, I am assuming you used these tumor marker values to determine if a patient is a poor, intermediate, or good risk pt. If so, this is incorrect. The tumor markers that should be used for determining risk category are the ones right before chemotherapy starts, not pre orchiectomy. If you didn't use this timing, some of your prognostic groupings may be incorrect and this is one of your significant secondary outcomes. It may also be why tumor markers alone didn't have more prognostic significance.

Thank you for identifying this oversight. We have revised the data to use tumour markers after orchiectomy to determine IGCCC risk group. However, we have kept the original analysis of tumour markers at presentation to be better capture the “disease burden at presentation” as all stage I patients would otherwise have normal tumour markers post-orchiectomy and be non-contributory to the analysis. An explanation and acknowledgement of this as a limitation has been added to the Methods: Outcomes and Discussion second paragraph.

Minor comments:

3. Abstract, methods, first sentence: “A retrospective review of all incidental TGCT”...what do you mean by the word incidental? In other areas of GU oncology, the term incidental means that the cancer was found incidentally while investigating for other symptoms or signs. I don't think that is what you mean here. Also, you don't mention the word “incidental” in the Methods section of the body of the paper. I think simply delete the word.

Incidental as opposed to prevalent cases, this has been removed to avoid confusion.

4. Abstract, methods, results: when talking about poor risk disease you should clarify here or in the methods section that this refers to advanced pts, some of the readers may not be aware.

This has been clarified in the Methods: Outcomes.

5. Methods, outcomes, sentence 2: “patients treated with primary chemotherapy”...I think you are referring to patients with advanced disease treated with chemotherapy but there can be patients with Stage I disease who are occasionally treated with chemotherapy. I would just make it more clear by noting advanced pts or explicitly say no Stage I patients were treated with adjuvant chemotherapy.

This has been clarified in the first paragraph of the Results. No patients in our cohort received adjuvant chemotherapy for stage I disease.

6. Methods, outcome, sentence 3: when you refer to “largest tumor dimension” I assume you are talking about the testicular primary? And not a metastatic lesion? If so, state this.

This includes the testicular primary but could also be a distant metastatic lesion if it is larger. This has been clarified in the Methods: Outcomes.

7. Methods, statistical analysis, sentence 1: Since treatment is often different between stage I (usually active surveillance) and then II(surgery, RT, chemo)/III(chemo), is it possible to also report your results as I vs II/III – even as a sensitivity analysis?

This has been added. I vs II/III is not statistically significant, as the majority of the shift has occurred from stage II to III, this has been expanded upon in the Results second paragraph and Discussion third paragraph as well.

8. Interpretation: first paragraph, last sentence: “...several were identified since the pandemic”. You report on 2 cases which I don't think is several. Perhaps there were other pts that ended up in ICU later on, if so clarify this. Otherwise, I think you have to delete several and insert two.

This has been changed.

9. Interpretation: second paragraph, sentence 6 referring to tumor markers. Did you look at tumor marker levels in just the advanced pts? It has more prognostic relevance and meaning advanced pts versus stage I patients. The fact that you looked at them preorch may have also influenced your results.

This has been commented on further in the Methods: Outcomes and Discussion second paragraph.

10. Interpretation: third paragraph, sentence 3 and sentence 6: “delays in presentation are more likely a reflection of patient education and care-seeking behaviour” and “more prone to avoiding health care professional engagement” – A lot of the comments in this

paragraph seem to put the delay all on the patient. Obviously, this is a factor for some, but you don't spend an equal amount of time on the shortcomings of the "system" – ie. access to primary care during the pandemic, virtual appointments instead of in person appointments where physical exams were not performed, that face to face interaction that might have elicited the history of a testicular mass from a reluctant patient.

This is a great point. The Discussion third paragraph has been broadened to balance the discussion and suggest further rationale. Perhaps there is a differential impact on patients with different levels of pre-pandemic engagement with the health care system.

11. Table 1. T stage: I am assuming that is a mixture of pathological and clinical? Should specify. And N stage must be predominantly clinical? Should state cN or cT.

Yes N is clinical, T was pathologic. This has been added to Table 1.

12. Table 1. Upfront radiation: are you able to clarify if that was for Stage I/II or III disease?

This was only for stage II disease. "Upfront" has been removed and this has been clarified in the Results first paragraph.

13. Table 1: In the Covid period column, 15 pts were stage II/III and you categorize all 15 into good/interm/poor risk but only 14 are accounted for in the systemic therapy setting. What happened to the other advanced pt?

This has been corrected with the updated analysis.

14. Figure 2 – I think refers to nonsem data. Figure 3 I think refers to seminoma data. If this is the case, Figure 2 under (B), I think you accidentally have the incorrect label "the proportion of stage III pure seminoma". I think you mean nonseminoma. With this mislabelling, please ensure that your graphs represent the correct data in figures 2 and 3. Figure 2 labels, you explicitly state and a 3 month lag period. You don't do the same in the labelling under Figure 3 – I am not sure why the difference, and if you do include that lag period, should it be 6 months for the seminoma?

The labelling and order have been corrected to avoid confusion. Seminoma data is now presented first for consistency and non-seminoma data presented subsequently. The lag-time references have also been removed.

Reviewer 2

General comments (author response in bold)

The study is interesting, well written and definitely a hot topic.

1) The first paragraph in the results section reports the incidence of TGCT in Alberta. However, I presume that not all cases (especially stage 1 cases) are referred to a tertiary care center. I would then assume that the authors report the incidence at the tertiary care centers. Could this decrease be explained by a referral bias? (i.e. higher number of patients treated locally to avoid travelling to higher populated centers)
Generally, pandemic restrictions were greater at the municipal level rather than the provincial level in Alberta so this was an overlooked limitation. Ultimately, this has been addressed by incorporating data from the Alberta Cancer Registry, so the methods are no longer reliant on referrals alone. Changes have been incorporated throughout the paper.

2) The authors state their study is a population-based one. As per the methods, only 2 tertiary centers were included. Please edit accordingly.

The study has been broadened to become population-based, as above and as in the Editor's comments.

3) The statement on ICU (interpretation, line 41) is misleading. Only 2 ICU cases were identified in the pandemic era and this could be entirely due to chance. Please consider stating two as opposed to several.

This has been corrected. Originally there was a limitation in the minimum number of cases that could be described.

4) Limitation: Can the authors present any evidence supporting their claim that all cases, even stage 1, are referred to a tertiary center. I suspect that many community urologists do not refer stage 1 cases and I presume that there are oncologists outside of tertiary centers that do treat advanced cases...

Thank you for the insightful comment. This has been addressed with additional registry data. The registry primarily identified patients from rural sites, not all of which were referred to an associated cancer centre for stage I disease, as above.