

## Peer Review File

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### Reviewer A

I commend the authors on this effort. Overall, an excellent and concise review of how to approach this challenging clinical dilemma. The information was organized in a logical way.

Please see some comments below.

#### Comment 1:

Abstract -Introduction: I don't understand how miRNA can increase compliance with surveillance. Telemedicine and MRI as of the TRISST trial may have a role, but miRNA we are not there yet.

**Reply 1:** We agree entirely that we are not there yet with miRNA. Therefore, the language throughout the manuscript and in the abstract has been updated to reflect that we are optimistic about the potential but cautiously so and will study things accordingly.

**Changes in text:** We have modified our text in the abstract (see Page 3, lines 51-54): "miRNA may potentially be a helpful biomarker for men with localized disease, but further research on diagnostic accuracy and marker kinetics are needed before implementing it into routine surveillance strategies or using it to deviate from long-standing surveillance regimens." We have also modified our text throughout the manuscript (see Pages 15-16, lines 302-305): "Additional research on how new diagnostic approaches, including miRNA as an STM and alternative surveillance schedules, will be implemented are necessary to ensure that there is no compromise in the ability to detect relapse, particularly in the first two years of surveillance when patients are at greatest risk."

#### Comment 2:

-Telehealth has been studied for testicular cancer in the WATCHman trial; please rephrase this sentence: "Telemedicine is a safe and acceptable platform for urologic cancer follow-up care but has not been explicitly studied among men with testicular cancer."

**Reply 2:** Thank you for this comment. We do highlight this excellent study in the main text of the manuscript (see Page 10, lines 171-187), but the language has been changed to reflect that although the study is not complete (to our knowledge), it is underway. This is expanded upon more in the main text as well.

**Changes in text:** We have modified our text in the abstract as advised (see Page 3, lines 47-49): “Telemedicine is a safe and acceptable platform for urologic cancer follow-up care, but it requires further study specifically among men with testicular cancer.” Additionally, we have expanded upon the need to further study telemedicine by revising our text (see Pages 9-10, lines 164-170): “However, patients with testis cancer tend to be young and are likely to have extensive experience with mobile platforms, thus making this a feasible path forward. Telehealth may also improve access for certain rural populations where experienced specialists would not otherwise be available due to location (14). Telehealth “second opinion” consultations or even regional virtual tumor board conferences are potential avenues to centralize expert care for a rare diagnosis and deserve exploration.”

**Comment 3:**

Line 81. Are clinical visits disruptive of patients’ quality of life or just a burden?

Line 93 - This phrase is confusing “we believe can address less than optimal aspects of the current surveillance paradigm”

**Reply 3:** Thank you. We feel that clinic visits are burdensome and also disruptive of patients’ quality of life. Our text has been edited for clarity.

**Changes in text:** We have modified our text as advised (see Page 6, lines 94-98): “In this narrative review, we highlight three recent developments that we believe can address aspects of the current surveillance paradigm that are less than optimal for patients, and we discuss how these approaches may be used to redesign and improve the surveillance of men with early-stage testicular cancer in the years ahead.”

**Comment 4:**

141 – I would dare to say that telehealth also has the potential to increase physician satisfaction, as It helps to overcome the burden of the growing demands of survivorship care.

Line 158: I agree that telehealth can increase disparities in other types of tumors, but in testicular cancer, most patients are young and therefore tech-savvy. Probably worth mentioning this.

Line 181 – Aside from satisfaction, it may be worth mentioning that most patients trust the virtual care clinic, and 82% of the patients answer they can have access to the same excellence of care as in-person appointments.

**Reply 4:** Thank you. We agree entirely with these comments and have edits/added to the text to reflect these excellent points.

**Changes in text:** We have modified our text as advised (see Pages 8-9, lines 141-143): “In addition, most studies have shown high levels of satisfaction with video visits among patients and clinicians, at times even more so than in person.” Additionally, we have added the following to our main text (see Pages 9-10, lines 164-166): “However, patients with testis cancer tend to be young and are likely to have extensive experience with mobile platforms, thus making this a feasible path forward.”

**Comment 5:**

I would suggest reviewing and discussing Garisczak paper “Safety of Minimizing Intensity of Follow-up on Active Surveillance for Clinical Stage I Testicular Germ Cell Tumors” as it is in line with your discussion of minimizing the intensity of follow-up in CSI surveillance.

**Reply 5:** Thank you for this important comment. This citation and a description of the study results has been added to the text.

**Changes in text:** We have added the following to our main text, with this reference cited at the end of the sentence (see Page 11, lines 208-210): “Recently, a report from The Princess Margaret Cancer Center in Toronto over four decades demonstrated that relaxing the intensity of surveillance imaging results in a significant reduction in imaging frequency and is safe (18).”

**Comment 6:**

Line 245 – I would say a more sensitive biomarker of relapse could help to guide a surveillance strategy.. As the biomarker itself is not going to reduce the axial imaging tests required.

**Reply 6:** Thank you. We agree and have revised our text accordingly.

**Changes in text:** We have revised our text as advised (see Page 13, lines 251-254): “A more sensitive circulating biomarker of relapse could help to guide a risk-adapted surveillance strategy, and thus potentially decrease the number of axial imaging tests required or completely obviate the need for routine cross-sectional imaging.”

**Comment 7:**

Line 27 – I agree miRNA371 has a potential future role in surveillance, however, there is not enough clinical data to support this right now. Saying that patients with seminoma may avoid cross-sectional imaging if the miRNA is negative is misleading, and it is way too early to reach that conclusion.

**Reply 7:** Thank you for this important comment. We agree and believe the optimal use of miRNA would be to adjudicate the need for imaging or allow for a better risk-adapted

use of imaging intensity. Although the data do not currently support this approach, there are several ongoing studies, including studies at our institution and multi-center studies, that aim to study the potential for this approach.

**Changes in text:** We have revised our text as advised (see Page 15, lines 285-287): “A potential example is that for patients with pure seminoma, cross-sectional imaging may be reserved for patients suspected of a relapse based on detectable circulating miR-371a-3p.” In addition, we have revised our text on Page 15, lines 290-295: “Ultimately, in the future, the frequency of cross-sectional imaging may potentially be safely decreased for patients with CSI NSGCT. Although outstanding issues related to the assay cutoff values, interpretation, and reproducibility do exist, circulating miR-371a-3p may potentially transform surveillance programs for patients with early-stage GCTs with a tremendous reduction on cost, need for axial imaging, and patient inconvenience.”

**Comment 8:**

In the conclusions section you only discuss telehealth, despite the fact that that half of your manuscript discussed the frequency and different imaging modalities and miRNA371. I would suggest addressing this issue.

**Reply 8:** Thank you for this important comment. We have updated our text to reflect the importance of miRNA and surveillance intensity.

**Changes in text:** We have revised our text as advised (see Pages 15-16, lines 302-305): “Additional research on how these new diagnostic approaches, including miRNA as an STM and alternative surveillance schedules, will be implemented are necessary to ensure that there is no compromise in the ability to detect relapse, particularly in the first two years of surveillance when patients are at greatest risk.”

**Reviewer B**

I'd like to congratulate the authors on an excellent narrative review that addresses three factors that may improve adherence to active surveillance in men with stage 1 TGCT.

**Comment 9:**

The section on telehealth was nicely presented and summarised existing literature well. The section on imaging was also nicely presented. One citation was missing, although this may be due to the time of the pubmed search: <https://cancerimagingjournal.biomedcentral.com/articles/10.1186/s40644-02200496-w> However, this manuscript was also presented in abstract form in 2021: [https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15\\_suppl.5027](https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.5027) It may be worthwhile including this, as it is the most up to date paper on PET in testicular cancer.

**Reply 9:** Thank you. A citation to the Conduit et al. article (Cancer Imaging, 2022) has been added to the manuscript.

**Changes in text:** We have added this citation (see reference 21 on Page 13, line 241).

**Comment 10:**

The section on miR is also nicely written. However, I think it can be improved by addressing issues relating to type of assay used, and cut-off for positive/negative... and future directions for new assays, such as digital droplet PCR?

**Reply 10:** Thank you for this important comment. We agree entirely that these issues are of critical importance to the interpretation and widespread use of miRNA.

**Changes to text:** We have modified our text as advised (see Page 15, lines 292-295):“Although outstanding issues related to the assay cutoff values, interpretation, and reproducibility do exist, circulating miR-371a3p may potentially transform surveillance programs for patients with early-stage GCTs with a tremendous reduction on cost, need for axial imaging, and patient inconvenience.”

**Comment 11:**

Well written review by respected authors. If narrative reviews remain in the scope of TAU, then this should be accepted with minor revisions as suggested.

**Reply 11:** We thank the reviewer for these important comments and feel that these suggestions have further strengthened our paper.

**Reviewer C**

This is a well organized, well written thought exercise reflecting on three contemporary developments that might positively influence testicular cancer surveillance protocols in the near future. The authors have chosen to consider the potential role of a more "sophisticated" tumor marker, miRNA, imaging strategies that lead to less ionizing radiation exposure, and modern communication approaches that could all potentially increase patient adherence to surveillance, with the attendant benefits of such improved adherence. The methodology (a web-based literature review and narrative summary) appears appropriate for this review.

**Comment 12:**

One consideration for the authors to reflect on relates to the section on "Telehealth". This is perhaps the one strategy that could be (and has been) readily adopted today

without a lot of debate. In many centres the phrase "Virtual Medicine" is substituted to more broadly encompass the strategies that can be employed to communicate with patients who are not attending in person. The focus here is primarily on video appointments (and perhaps that is what is reimbursed in the USA), but for many, phone appointments are more commonly used. An unpublished review of the literature in the second year of the pandemic identified that for many patients and clinicians phone appointments were preferred over video appointments because of their ease and flexibility of use. Regulators, on the other hand, generally endorse video appointments. The authors might want to comment on the relative merits of phone versus video virtual appointments.

**Reply 12:** We agree with the reviewer and agree that video vs. phone visits is a point of continued debate within the US health care community and among regulators. However, the nuances and differences between telehealth and virtual medicine are beyond the scope of this paper and we consider “telehealth” as analogous to what you are describing. The introduction was updated to make this clear.

**Changes to text:** We have revised our text as advised (see Page 5, lines 86-88): “Recent developments including more widespread availability and uptake of telehealth in its various forms (video visits, telephone visits, asynchronous communications),...”

**Comment 13:**

I found this an informative and thought provoking review. It should be of interest to those who care for such patients.

**Reply 13:** We thank you for your review and helpful comments.

**Reviewer D**

A very nicely written narrative review on follow up in testicular cancer CS1.

**Comment 14:**

The topic is very important for young men. It may be of interest to discuss the cumulative dose of radiation with a regular follow-up that the patient is exposed to and its potentially associated risks. Furthermore, it remains important to outline that there is need to follow-up patients with testicular cancer a lifetime as very late relapses are reported.

**Reply 14:** Thank you. We agree entirely, and this is highlighted in the introduction as a significant risk of repeat and unnecessary imaging studies (see Page 5, lines 78-80):

“Current surveillance strategies call for serial imaging with ionizing radiation, frequent blood draws for STM assessment, and a significant number of clinic visits.”