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Title: Impact of the COVID-19 pandemic on first cancer treatment modality: a population-based cohort study

Authors: Rui Fu PhD, Rinku Sutradhar PhD, Qing Li MMath, Timothy P. Hanna MD PhD, Kelvin KW Chan MD PhD, Jonathan C. Irish MD MSc, Natalie Coburn MD MPH, Julie Hallet MD MSc, Anna Dare MBChB PhD, Simron Singh MD MPH, Ambica Parmar MD MSc, Craig C. Earle MD MSc, Lauren Lapointe-Shaw MD PhD, Monika K. Krzyzanowska MD MPH, Antonio Finelli MD MSc, Alexander V. Louie MD PhD, Nicole J. Look Hong MD MSc, Ian J. Witterick MD MSc, Alyson Mahar PhD, David R. Urbach MD MSc, Daniel I. McIsaac MD MPH, Danny Enepekides MD MPH, Antoine Eskander MD ScM

Peer review comments:

Reviewer 1: Dr. Garth Nicholas, The Ottawa Hospital Cancer Centre

The authors are to be commended for writing a very clear paper that is easily comprehensible. The question is set out clearly, and the description of the data sources and analysis is lucid.

The authors identify two quite large groups of patients where the determination of their first treatment within a year after diagnosis may be problematic. These are patients with hormone-sensitive cancers (close to 90,000 patients), and patients diagnosed after 26 June 2020 (55% of the patients in the pandemic group). Given that this is the primary outcome measure of the study, I thought both required more comment:

i. Given that the primary outcome is the first treatment modality of patients with newly diagnosed cancers, one might quibble with the inclusion of patients with breast and prostate cancers. These cancers may be treated with hormones as the first line of therapy, and the authors acknowledge that the data about hormone treatments are not complete. The authors plausibly speculate that this may increase the number of patients captured as "untreated". This question might be well addressed with a sensitivity analysis, seeing if the major results of the study change when hormone-sensitive cancers are excluded.

RESPONSE R1-1: Thank you for this important suggestion. A sensitivity analysis excluding patients newly diagnosed with 1) breast cancer or 2) breast or prostate cancer has been added to the paper with results reported in Appendix 3 and on page 6. Exclusion of these hormone-sensitive cancers did not change the regression parameter estimates at all. As such, none of our conclusions changed on the basis of this sensitivity analysis but we think it's a great addition to the manuscript.

ii. The fact that patients diagnosed after 26 June 2020 had necessarily less than one year of follow up is acknowledged, but I think passed over a bit quickly. While these patients may comprise only 5.2% of the total cohort, they comprise 55% of those patients diagnosed during the pandemic (16338 of 29602). That more than half of patients in the study group have follow up shorter than the duration specified as the primary outcome of the study (first treatment, within one year of diagnosis) probably warrants more discussion to convince the reader that it's not a big problem. What was the median follow up of this group? In the pre-pandemic group, how often did first treatments come early in the year vs late in the year post-diagnosis? Again, the

authors speculate plausibly that this might increase the untreated fraction, and because this fraction ultimately decreased, there is not much further consideration.

RESPONSE R1-2: We have expanded the dataset to ensure all patients in the cohort were followed for one full year after date of cancer diagnosis. Furthermore, as we now have the complete cancer incidence data from the OCR between July-Nov 2020 (previously data completion was only up to June 2020), we expanded the cohort from 313,499 to 321,535. This represents a complete capture of incident cancer patients that meet our inclusion criteria between Jan 2016 to Nov 2020.

I thought there was an excellent discussion of the next set of questions to be answered when considering the impact of the pandemic on cancer care. Thank you very much for your efforts to describe and understand this still-unfolding chapter of cancer treatment in Ontario.

RESPONSE R1-3: Thank you for this comment.

Reviewer 2: Dr. Heather Bryant, Canadian Partnership Against Cancer

This paper provides a window into the change in cancer treatment that occurred over the early days of the pandemic, which is an important topic of concern. I do have a couple of questions about some of the data cited and interpretations.

1. The important factor of the dramatic reduction in incidence until the interpretation section of the paper. This is a significant enough variable that it needs to be included in the results and abstract as a significant contributing factor.

RESPONSE R2-1: Thank you for this comment. Because we didn't explicitly study cancer incidence volume in the current analysis, we chose not to present it in the Results or Abstract. In our previous publication, we have assessed the fluctuation of weekly cancer incidence in Ontario during the first wave of COVID-19. On page 6-8, we discuss our results on rates of first cancer treatment while accounting for the changing cancer incidence, the directed ramping down of cancer surgeries, and the potential stage migration that might have occurred during the pandemic. On page 8, we further suggest future study to examine if adopting the various practice changes physicians have made in the pandemic (such as expanded use of neoadjuvant therapy) will help the cancer system to tackle the incoming tsunami of new cancer patients who may be sicker, presented with more advanced-stage cancer, and would be more challenging to treat.

• Eskander A, Li Q, Yu J, et al. Incident cancer detection during the COVID-19 pandemic. *Journal of the National Comprehensive Cancer Network*. 2022;20(3):276-284. doi:10.6004/jnccn.2021.7114

2. The reference that the authors use to describe what was directed for treatment in the pandemic (3) was not published until a year after the end of the study period, so would not necessarily describe the treatment during the study period. Reference 12 would be the relevant one here.

RESPONSE R2-2: Thank you for the careful review. We have replaced that reference with the two initial clinical guidelines developed by Cancer Care Ontario in March 2020. We

have also added a new “Setting” subsection on page 1-2 to provide a focused description of the initial set of pandemic control policies related to cancer treatment.

- Ontario Health-Cancer Care Ontario. Pandemic Planning Clinical Guideline for Patients with Cancer. Published online March 10, 2020.

https://obgyn.utoronto.ca/sites/default/files/oh-cco_pandemic_planning_clinical_guideline_final_2020-03-10_002.pdf

- Ontario Health-Cancer Care Ontario. COVID-19 Supplemental Clinical Guidance for Patients with Cancer. Published online March 29, 2020.

https://www.ontariohealth.ca/sites/ontariohealth/files/2020-04/Ontario%20Health%20Cancer%20Care%20Ontario%20COVID-19%20Supplemental%20Clinical%20Guidance%20for%20Patients%20with%20Cancer_29Mar20%20PDF.pdf

3. The analysis is done per 1000 cancer patients, which obscures the fact that cancer surgeries are still dramatically reduced. This is alluded to in the text, but if an additional figure looking at absolute numbers of treatments could be added, that would be helpful.

RESPONSE R2-3: We have previously reported the trends in weekly volume of cancer surgery and cancer incidence in Ontario during COVID-19 in 3 publications. In the present analysis, we aim to investigate a per-patient rate outcome to assess the potential shift in physician treatment behaviour in response to the provincial pandemic policy. This has been clarified in the Abstract, the last sentence of the new “Setting” subsection, and throughout the Interpretation. This analysis takes into account fluctuations in surgery and cancer incidence together. It provides a more complete picture compared to our prior work on this topic and also provides an expanded data set.

- Eskander A, Li Q, Hallet J, et al. Access to cancer surgery in a universal health care system during the COVID-19 pandemic. *JAMA Netw Open*. 2021;4(3):e211104.

doi:10.1001/jamanetworkopen.2021.1104.

- Fu R, Kamalraj P, Li Q, et al. The Changing Face of Cancer Surgery during Multiple Waves of COVID-19. *JNCI Cancer Spectrum*. Published online August 18, 2022.

doi:10.1093/jncics/pkac062.

- Eskander A, Li Q, Yu J, et al. Incident cancer detection during the COVID-19 pandemic. *Journal of the National Comprehensive Cancer Network*. 2022;20(3):276-284.

doi:10.6004/jnccn.2021.7114

4. In the interpretation, the authors state that the surgical system was unable to provide surgery, even with the lower incidence rate. Yet it appears that perhaps it wasn't that it was unable -- it had been directed not to provide this service. There is a difference between actual capacity and directed capacity.

RESPONSE R2-4: Thank you for this suggestion. This is a really important point. We have rewritten this entire paragraph on page 6-7 to discuss the observed drop in upfront surgical rate in relation to the provincial pandemic control policy.

5. The decrease in the rate of no treatment is interesting, but the authors don't consider the fact that this may be because, with the drop in incidence, only the most severe/advanced cases were presenting -- and therefore would have a greater need for treatment potentially. (And those that would have had no treatment because they declined it would be less likely to even bother presenting, potentially.) I think it is an overstatement in the conclusions to attribute this due to the reduction in incidence.

RESPONSE R2-5: We concur with this reviewer. The discussion paragraph (page 8) and Conclusion (page 9) were both revised to soften our language and to address this comment. Further work will be required to elucidate how stage at presentation may have impacted the cancer treatment trends identified. Unfortunately, the data for this will not be available in Ontario until April 2023.

6. I don't understand on page 9 the statement "there were more patients receiving treatment during the pandemic than before" in light of the reduction in incidence.

RESPONSE R2-6: This statement has been deleted since the incomplete follow-up issue has been resolved by expanding the cohort in the new analysis.