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

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ABSTRACT

Background: COVID-19 has caused significant shifts in the management of newly diagnosed cancer. We sought to quantify the pandemic impact on the modality of first cancer treatment (surgery, chemotherapy, radiation, or no treatment).

Methods: In this population-based study using administrative databases of Ontario, we identified adults diagnosed with cancer during January 2016-November 2020 and their modality of first cancer treatment received within 1-year post-diagnosis. Segmented Poisson regressions were applied to each modality to estimate the change in mean service volume per thousand patients (rate) at the start of the pandemic (the week of March 15, 2020) and change in the weekly trend in rate during the pandemic (March 15, 2020-November 7, 2020) relative to pre-pandemic (January 3, 2016-March 14, 2020).

Results: Among 313,499 persons with cancer, 29,602 (9.4%) were diagnosed in the pandemic. During the first week of COVID-19, mean upfront surgical rate declined by 14% (95% CI: 10%-18%), while chemotherapy and radiation rose by 38% (95% CI: 30%-46%) and 12% (95% CI: 5%-18%). The mean rate of no treatment decreased by 10% (95% CI: 4%-16%). Afterwards until November 7, 2020, upfront surgical rate increased at 0.7% for each week (95% CI: 0.5%-1.0%), while chemotherapy and radiation rates were decreasing at 1.5% (95% CI: 1.2%-1.8%) and 0.5% (0.2%-0.8%) per week.

Interpretation: Non-surgical therapy was adopted as first-line cancer treatment to compensate for reduced surgical capacity at the start of COVID-19. Future studies need to elucidate the impact of these practice changes on patient safety, treatment outcomes, and quality of life.

INTRODUCTION

The COVID-19 pandemic has put cancer treatment systems around the world under immense pressure, forcing redefinitions of care processes to cope with resource shortages and social distancing policies.[1] For patients who received a cancer diagnosis during the pandemic, decisions on treatment became more complex, now taking into account risks of COVID-19 infection, travel restrictions, and reduced inpatient capacity in addition to other patient, disease and system factors.[2] In anticipation of significant delays in elective cancer surgery, physicians were directed to give surgical priority to a small group of patients (such as those with an immediate threat to life or limb; with obstructions, bleeding or perforations; or with progressive disease under neoadjuvant systemic therapy) and utilize non-surgical therapy to a larger extent for others.[3] However, evidence is scarce on the real-world impact of those polices at the population level, particularly if physician preference on how to treat newly diagnosed cancer has altered.[4] Hence, in this study, we used data from Ontario, Canada, a universal healthcare system with a population of 14.7 million, to contribute to better understanding on the shifts in first cancer treatment modalities used during the pandemic. This information is needed for recovery planning and to guide policy decisions in future health system emergencies.

METHODS

Study design and population

This was a retrospective population-based cohort analysis based in Ontario, Canada where all permanent residents are insured under a universal healthcare system.[5] The study cohort comprised Ontario residents age 18 or above who were diagnosed with cancer between January 3, 2016 and November 7, 2020 (**Appendix 1**). Only first cancer diagnosis over this period was

considered. Each patient was followed for 1 year after the date of cancer diagnosis (the date of specimen taken[6]), or until the date of death, or to June 26, 2021, whichever occurred first. Patients with multiple types of cancer diagnosed on the same day, those who were non-Ontario residents at diagnosis, or who were younger than 18 at diagnosis were excluded. We also excluded patients with certain cancer diagnoses; specifically, we excluded melanoma and skin cancer to ensure a reliable capture of hospital-based cancer-directed surgical procedures, as these cancers are frequently treated in the outpatient setting. We also excluded patients with cancers primarily labelled as ophthalmologic and paraneoplastic neurological syndromes as these cancers accounted for less than 0.04% of our cohort (**Figure 1**).

Data sources

Records of cancer diagnoses were retrieved from the Ontario Cancer Registry (OCR) that captures 98% of all cancer cases across the province.[7] At the time of the present analysis (January 2022), the OCR was updated to December 31, 2021 with reliable data available until November 7, 2020.[8] Receipt of cancer-directed surgery was determined from hospital abstract databases of the Canadian Institute for Health Information, and confirmed with the diagnosis records from OCR to ensure the surgical procedure matched with the cancer site and that the procedure was a resection rather than a biopsy.[9] Radiation and chemotherapy visits were determined using physician billing from the Ontario Health Insurance Plan (OHIP) claims database. Individuals who immigrated to Ontario between January 1985 to May 2017 were identified from the Immigration, Refugee and Citizenship Canada (IRCC) Permanent Resident Database (with data from that period). Rurality was determined from Statistics Canada's Postal Code Conversion File and defined as living in rural areas or small towns with an urban

population of less than 10,000.[10] Material deprivation was calculated using the Ontario Marginalization Index with data from the latest Canadian census.[11] These datasets were linked using unique encoded identifiers and analyzed at ICES.

Outcome – the modality of first cancer treatment

For each patient, we determined the modality of first cancer treatment received within a maximum of 1-year after date of diagnosis to be either surgery, chemotherapy, or radiation. A separate "untreated" category was created for those who did not receive any cancer treatment during the follow-up period (**Appendix 2**). For patients receiving hormonal therapy as the first cancer treatment, we also classified them as "untreated" since this procedure was not fully captured in the OHIP claims database. We handled patients receiving more than one modality of first cancer treatment on the same day (n=880, less than 0.3% of the cohort) with the following: if one of those modalities was surgery, we assumed the other modality (chemotherapy or radiation) had been administered prior to surgery on that day, and thus considered the non-surgical modality to be the first. If chemotherapy and radiation occurred on the same day, we assigned radiation as the first modality.

Statistical analysis

We used March 15, 2020, when all hospitals in Ontario were directed by the province's Chief Medical Officer of Health to halt non-emergent or elective procedures, to create a pre-pandemic period (January 3, 2016 to March 14, 2020) and a pandemic period (March 15, 2020 to November 7, 2020).[12] Comparisons of patient characteristics were conducted between the two periods, where a standardized difference exceeding 0.10 indicated a significant imbalance.[13]

For each modality of first cancer treatment, we conducted separate segmented Poisson regression analyses to examine trends in crude rates, defined as the weekly number of recipients per thousand patients. Three parameter estimates were of interest: the pre-pandemic weekly trend (slope) in the rate, the immediate change in mean rate at the start of the pandemic (relative change in intercept), and further change in slope during the pandemic. This method has been previously used by our group to study the trends in the volume of cancer incidence and cancer-directed surgery and the rate of virtual physician visits in Ontario amid the pandemic.[8,9,14] All regression analyses were 2-sided and statistical significance was set at p-value<0.05. Analyses were performed on SAS Enterprise Guide 7.15 (SAS Institute).

Ethics approval

The use of the data in this study is authorized under section 45 of Ontario's Personal Health Information Protection Act and therefore does not require review by a Research Ethics Board.

RESULTS

A total of 313,499 persons with cancer were included in the study cohort (**Table 1**). Among them, the vast majority (n=283,897, 90.6%) were diagnosed in pre-pandemic period, while less than 10% (n=29,602, 9.4%) of patients received a cancer diagnosis during the pandemic. We did not detect any significant difference of sociodemographic and clinical characteristics between the two groups of patients (all standardized differences<0.05).

During the first week of COVID-19, the mean rate of upfront surgery (i.e., number of patients receiving surgery as first cancer treatment per thousand patients) dropped immediately by 14% (rate ratio [RR]: 0.86, 95% confidence interval [CI]: 0.82-0.90). At the same time,

chemotherapy and radiation mean rates were both increasing by 38% (RR: 1.38, 95% CI: 1.30-1.46) and 12% (RR: 1.12, 95% CI: 1.05-1.18). This caused the mean rate of any treatment received within 1-year after diagnosis to rise by 3% (RR: 1.03, 95% CI: 1.01-1.05) and the rate of no treatment to decrease by 10% (RR: 0.90, 95% CI: 0.84-0.96) at the start of the pandemic.

During the pandemic period (March 15 to November 7, 2020), the rate of upfront surgery increased further by 0.7% (RR: 1.007, 95% CI: 1.005-1.010) for each week, and during the week of July 26, 2020 (i.e., the 20th week since the start of COVID-19), surgical rate had fully recovered to pre-pandemic weekly levels (**Figure 2**). Upfront chemotherapy and radiation rates decreased (after their initial rise), with a weekly decrement of 1.5% (RR: 0.985, 95% CI: 0.982-0.988) and 0.5% (RR: 0.995, 95% CI: 0.992-0.998). For chemotherapy, we found that after its 38% rise in rate at the beginning of the pandemic, its rate has fully reduced to pre-pandemic levels 21 weeks after the start of COVID-19 (during the week of August 2, 2020). We found no further change in the rate of no treatment (RR: 1.003, 95% CI: 0.9997-1.007) or any treatment (RR: 0.999, 95% CI: 0.998-1.000) during the pandemic.

INTERPRETATION

This population-based cohort study examines the COVID-19 pandemic impact on the modalities of first cancer treatment. Using records of over 310,000 persons with cancer in Ontario, Canada, we found that with the arrival of the pandemic, upfront surgical rate decreased by 14% with a corresponding rise in the rate of non-surgical therapy, especially chemotherapy. It took 20 weeks for both surgery and chemotherapy to return to pre-pandemic weekly utilization level. At the start of the pandemic, the number of untreated patients per thousand cancer diagnoses declined by 10%.

Consistent with an early work from our group[9], we found an immediate decline in use of surgery as initial cancer therapy when pandemic control measures first launched. Furthermore, we went beyond the examination of weekly surgical volume to assessing the rate of upfront surgery per thousand cancer diagnoses, and thereby, accounted for the pandemic-related reduction in cancer incidence (in the denominator). Due to the suspension of cancer screening and disruptions in other care services that are key in cancer diagnosis and staging (such as in-person oncologist visits)[1,15], cancer incidence has dropped by 34% in Ontario.[8] Hence, our results imply that even when facing a much smaller volume of new persons with cancer, the surgical system was unable to provide upfront surgery at pre-pandemic capacity, which emphasizes the extent to which the pandemic impacted cancer services. It is also possible that because the case-mix of incident cancers has shifted, particularly more were presented with advanced-stage cancer[16], the rate of upfront surgery has dropped correspondingly. Future studies need to quantify the proportion of patients who would have had surgery first but received neoadjuvant therapy instead during the pandemic. These data are required to identify potentially at-risk persons with cancer who might suffer the negative consequences of surgical delays so that physicians can plan care accordingly to mitigate those repercussions.

The rate of chemotherapy use as initial cancer treatment increased by 38% when the pandemic started, and for the next 20 weeks chemotherapy utilization remained higher than its pre-pandemic levels. These results contribute to existing evidence on the expanded use of neoadjuvant chemotherapy for patients who would have received surgery upfront during the pandemic.[15–17] This speculation is at least partially corroborated by our observation that at around the same time after the arrival of COVID-19, surgery and chemotherapy rates have simultaneously recovered to pre-pandemic levels. Another possibility is due to stage migration,

persons with cancer diagnosed in the pandemic were more likely to require palliative chemotherapy or chemotherapy combined with radiotherapy.[18] In Ontario, the increased uptake of chemotherapy may also be attributed to the expanded public insurance coverage for hospital-administered cancer drugs that was introduced shortly after the start of COVID-19.[19] Because of the removal of financial disincentives, more patients may have been willing to choose chemotherapy as their initial and continued modality of care. Still, a closer examination of if, and how soon, patients who had initiated chemotherapy in the early pandemic were assessed for and eventually received surgery is warranted. Furthermore, having an influx of newly diagnosed patients initiating chemotherapy has patient safety implications, as a meta-analysis study found chemotherapy to be the only cancer treatment modality whose past-month use to be associated with elevated risk of COVID-19-related death.[20] Further study that reports on outcomes among patients receiving chemotherapy during the pandemic is required to guide clinical and drug funding policies.

We observed a 10% decrease in the mean rate of no treatment over the first post-diagnosis year at the beginning of COVID-19. A potential explanation is that due to the drop in cancer incidence volume at the start of COVID-19[8], the demand for initial cancer therapy was lowered, which, coupled with the large-scale cancelation of elective surgeries, preserved capacity within the cancer system for non-surgical care delivery.[21] Additionally, we used a conservative definition for "no treatment" by not counting hormonal therapy which may result in an underestimation for treatment delivered as bridging therapy prior to definitive treatment. With nearly 2,000 incident breast cancer cases and 1,600 incident prostate cancer cases in Ontario being unidentified due to COVID-19[8] and a possible rise in use of hormonal therapy as first-line

treatment for both cancers[16,22], this would translate to an increased rate of "untreated" persons with breast or prostate cancer in our results.

From a clinical practice perspective, it is important to examine to what extent these temporary shifts in care revealed in our study will impact future oncologic practice. In the UK, oncologists are considering short-course radiotherapy, rather than the conventionally favored long-course chemoradiotherapy, as the first treatment for rectal cancer before surgery even before the pandemic.[2,23] Further studies are required to assess if physicians plan to use the same strategies to cope with the current ramp down of hospital services related to subsequent waves[24] and if they will adopt the practice changes after the pandemic has ended. This type of analysis was beyond the scope of our project and would require a different set of methods.

Limitations

As we aimed to provide a high-level description of pandemic-related shifts in first cancer treatment modalities, analyses were not stratified by cancer type or stage. Further, this study only concerns the modality of treatment without deeper evaluation of wait times, an established risk factor for patient outcomes.[25,26] These unaddressed objectives need to be examined using large administrative datasets with rich patient-level data. Next, we assumed patients who received chemotherapy and radiation on the same day (without prior surgery) to always have initiated radiation first. Although this simplification applies to most patients, some recipients of concurrent chemoradiotherapy were given chemotherapy as a radiosensitizer on the day of first dose of radiotherapy. Future study should examine these nuances of combined modality treatment. Finally, a 1-year follow-up duration after date of cancer diagnosis was not observable for those diagnosed between June 26, 2020-November 7, 2020. Thus, we may have

overestimated the proportion of the "untreated" group in this sub-cohort. However, due to its small number (n=16,338, 5.2% of the cohort), we believe the impact to be low. Furthermore, there were more patients receiving treatment during the pandemic than before and therefore if we are missing some treatment, our effect sizes will only be larger. Nonetheless, future time-to-event analysis that accounts for censoring should further investigate the pandemic impact on the probability of and the wait times for receiving each modality of first cancer treatment.

CONCLUSION

During the first week of COVID-19 in Ontario, there was a 14% decrease in the volume of upfront surgery per thousand persons with cancer (rate), accompanied by a 38% and 12% rise in the rate of chemotherapy and radiation as first-line treatment. Meanwhile, the mean rate of no treatment over the first post-diagnosis year decreased by 10%, largely due to a significant drop in cancer incidence. Around 20 weeks into the pandemic, both surgery and chemotherapy rate returned to pre-pandemic utilization levels. The findings of this study highlight a deviation from the standard of care for many patients with unknown impact on outcomes including recurrence, quality of life, and survival. Healthcare systems should work towards preserving resources to manage newly diagnosed cancer according to standard of care by creating capacity in the system even during subsequent COVID-19 waves and for future pandemics.

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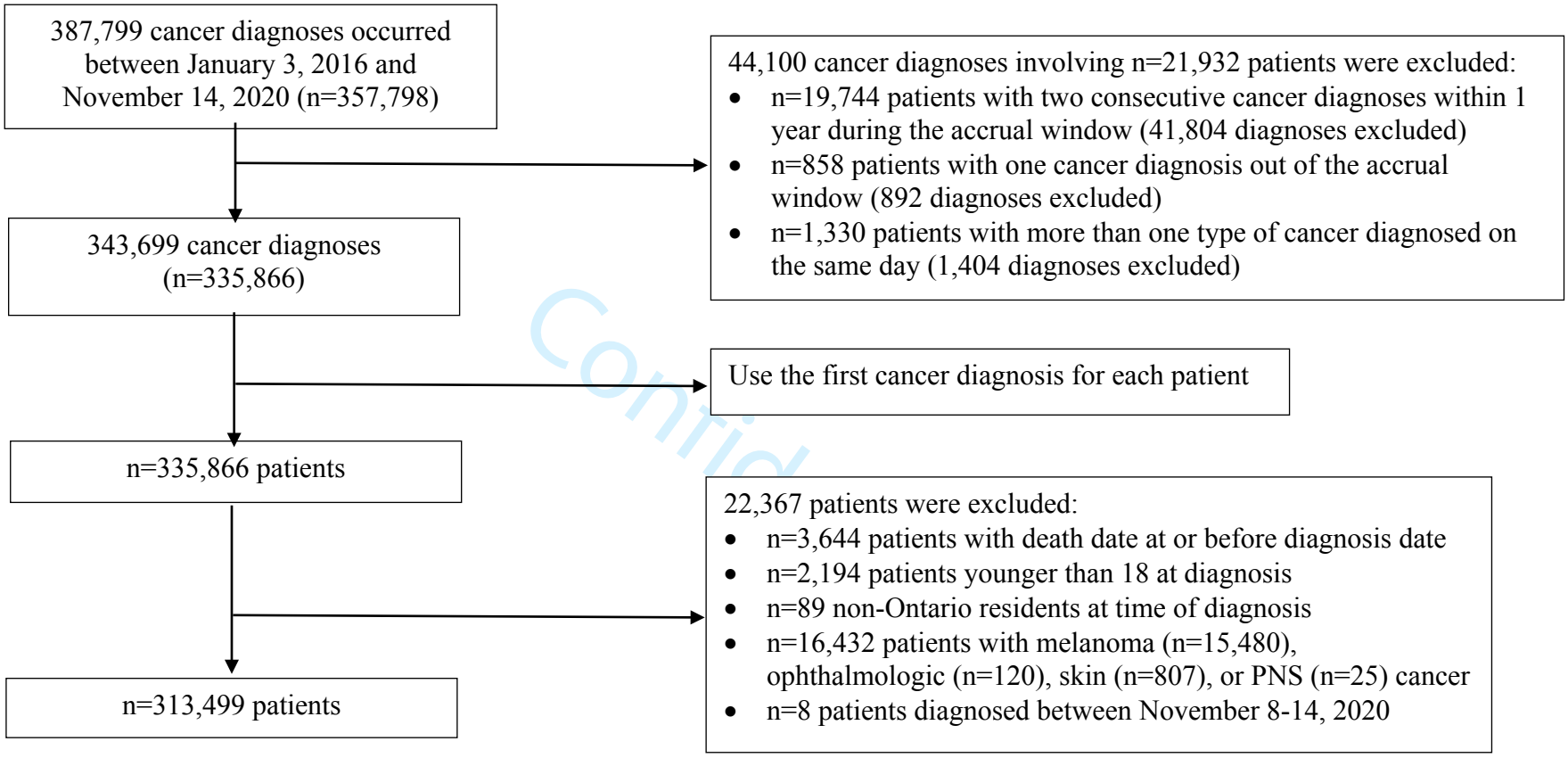
Figure 1 Flow diagram showing the creation of study cohort



Notes: The number of patients (n) at each stage of exclusion is reported in the parentheses. We excluded patients with a diagnosis of melanoma or skin cancer to ensure a robust capture of cancer-directed surgical procedures performed at hospital since these cancers are frequently treated in a clinic setting. We also excluded persons with ophthalmologic and paraneoplastic neurological syndromes (PNS) cancer due to their small numbers. Because the Ontario Cancer Registry (OCR) database had reliable data until November 7, 2020 at the time of this analysis, we used November 7, 2020 to be the last date of the accrual window and thus excluded the 8 patients who were diagnosed in November 8-14, 2020.

Table 1 Comparing the characteristics of patients diagnosed with cancer during pre-pandemic and pandemic periods (n=313,499)

Characteristics	Pre-pandemic (n=283,897, 90.6%)	Pandemic (n=29,602, 9.4%)	Standardized difference[1]
Age at diagnosis, mean ± SD, year	66.38 ± 14.09	66.17 ± 14.16	0.01
Female	144,755 (51.0%)	15,065 (50.9%)	0
Rural residents[2]	35,712 (12.6%)	3,941 (13.3%)	0.02
Immigrants	35,152 (12.4%)	3,714 (12.5%)	0
Material deprivation quintile[2,3]			
1, least deprived	60,230 (21.2%)	6,450 (21.8%)	0.01
2	58,065 (20.5%)	6,065 (20.5%)	0
3	54,770 (19.3%)	5,783 (19.5%)	0.01
4	54,509 (19.2%)	5,577 (18.8%)	0.01
5, most deprived	53,969 (19.0%)	5,465 (18.5%)	0.01
Region of residence			
Central	82,566 (29.1%)	8,631 (29.2%)	0
East	73,073 (25.7%)	7,553 (25.5%)	0.01
North	20,000 (7.1%)	2,185 (7.4%)	0.01
Toronto	22,965 (8.1%)	2,217 (7.5%)	0.02
West	85,271 (30.0%)	9,014 (30.4%)	0.01
Cancer type			
Breast	44,135 (15.5%)	4,546 (15.4%)	0.01
Central nervous system	3,796 (1.3%)	467 (1.6%)	0.02
Cervical	2,297 (0.8%)	239 (0.8%)	0
Colorectal	32,249 (11.4%)	3,352 (11.3%)	0
Endocrine	11,468 (4.0%)	1,075 (3.6%)	0.02
Esophagus	2,938 (1.0%)	380 (1.3%)	0.02
Genitourinary	20,866 (7.3%)	2,417 (8.2%)	0.03
Gynecologic excluding cervical	15,681 (5.5%)	1,739 (5.9%)	0.02
Head and neck	8,843 (3.1%)	979 (3.3%)	0.01
Hepato-pancreatic biliary	14,438 (5.1%)	1,523 (5.1%)	0
Lung	36,431 (12.8%)	3,780 (12.8%)	0
Lymphoma	15,924 (5.6%)	1,523 (5.1%)	0.02
Prostate	35,200 (12.4%)	3,448 (11.6%)	0.02
Sarcoma	4,205 (1.5%)	445 (1.5%)	0
Stomach	5,132 (1.8%)	536 (1.8%)	0
Other	30,294 (10.7%)	3,153 (10.7%)	0
Comorbidity[4]			
0	27,086 (9.5%)	3,091 (10.4%)	0.03
1	22,647 (8.0%)	2,367 (8.0%)	0
2	16,832 (5.9%)	1,533 (5.2%)	0.03
3 or more	24,422 (8.6%)	2,190 (7.4%)	0.04
No hospitalization	192,910 (68.0%)	20,421 (69.0%)	0.02

[1] We used 0.1 as the threshold to declare a statistically significant and clinically meaningful imbalance in the distributions of the characteristics.

[2] Missing data were between 0.2%-0.9% of the study cohort. Missing pattern did not differ between the two groups (standardized differences ranging from 0 to 0.01).

[3] Material deprivation encompasses the proportion of a population that is without a high school diploma, lone-parent families, receiving government transfer payments, unemployed, low-income, and living in dwellings needing major repair. This measure was derived from the material deprivation dimension of the Ontario Marginalization Index.

[4] We used the Elixhauser Comorbidity Index to measure comorbidities using a 5-year look-back window in administrative data for any hospitalization.

SD, standard deviation.

Table 2 Impact of COVID-19 on the weekly number of first cancer treatment recipients per thousand persons with cancer

Parameters[1]	Surgery	Chemotherapy	Radiation	Untreated	Treated[2]
Relative change in rate (pre-pandemic slope[3])	0.99995 (0.9999-1.0000) p-value = 0.32	1.0008 (1.0007-1.0010) p-value < 0.01	1.0006 (1.0004-1.0007) p-value < 0.01	0.9992 (0.9990-0.9993) p-value < 0.01	1.00027 (1.00023-1.00032) p-value < 0.01
Relative change in mean rate at the start of COVID-19[3] (relative change in intercept)	0.86 (0.82-0.90) p-value < 0.01	1.38 (1.30-1.46) p-value < 0.01	1.12 (1.05-1.18) p-value < 0.01	0.90 (0.84-0.96) p-value < 0.01	1.03 (1.01-1.05) p-value < 0.01
Relative change in rate (further change in slope from pre-pandemic to the pandemic[4])	1.007 (1.005-1.010) p-value < 0.01	0.985 (0.982-0.988) p-value < 0.01	0.995 (0.992-0.998) p-value < 0.01	1.003 (0.9997-1.007) p-value = 0.08	0.999 (0.998-1.000) p-value = 0.09

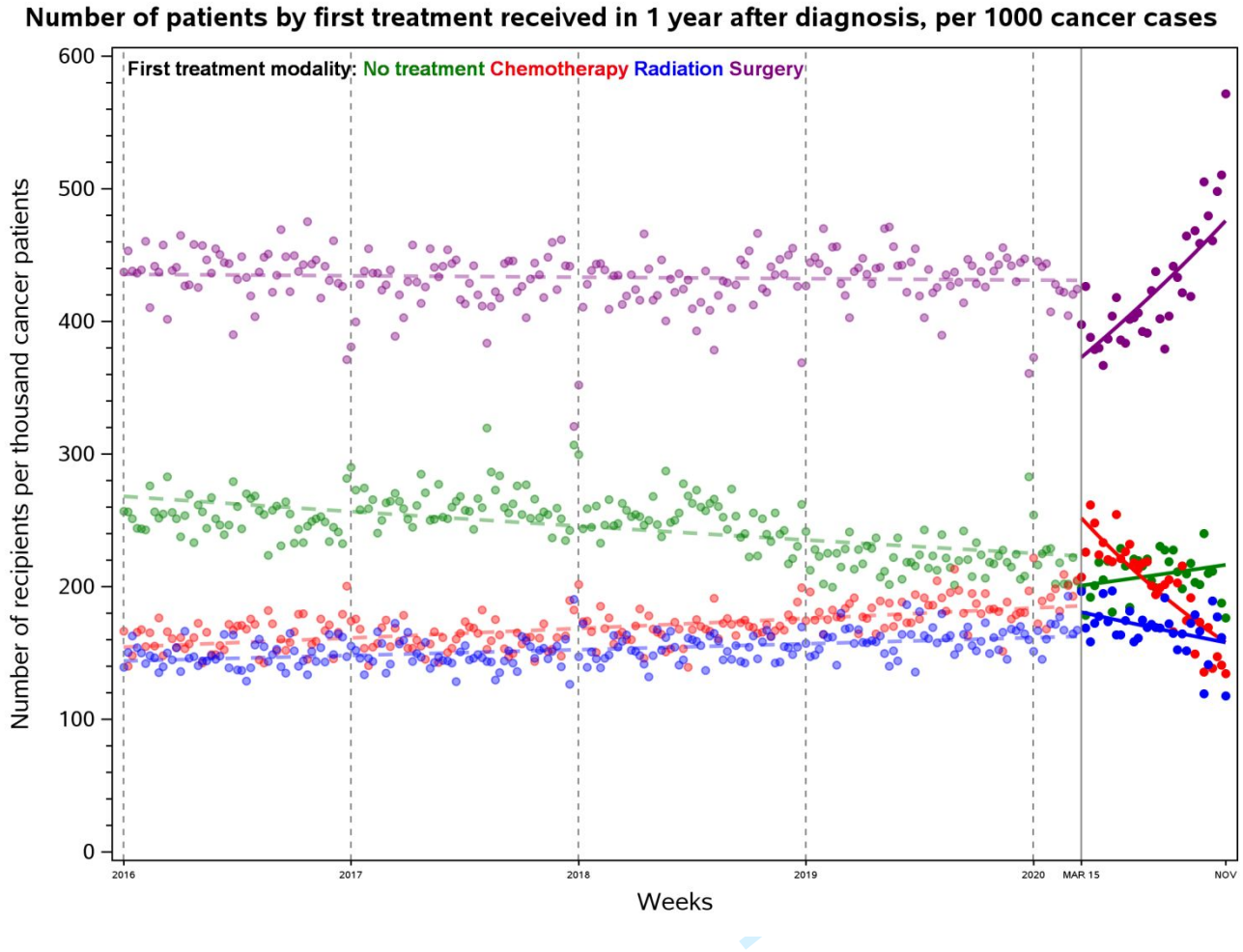
[1] Parameters were estimated from segmented Poisson regression using the standard parameterization. For each parameter, we report the ratio, the associated 95% confidence interval (in parenthesis) and the p-value testing whether the ratio equals to 1. The regression coefficients can be interpreted as followed: the weekly number of patients receiving surgery as first cancer treatment per thousand patients (rate) was initially stable (p-value=0.32) in pre-pandemic, followed by a decline in mean rate of 14% at the start of the pandemic, then a weekly rise of 0.7% (i.e., 1.007 * 0.99995 = 1.00695 or an 0.7% overall weekly increase) during the pandemic.

[2] These are patients who were treated by one of surgery, chemotherapy, or radiation therapy within 1-year after the date of cancer diagnosis.

[3] We use March 15, 2020 to proxy the start of the COVID-19 pandemic in Ontario, Canada as hospitals across the province were advised to halt non-emergent or elective procedures. Pre-pandemic period is from January 3, 2016 to March 14, 2020.

[4] The pandemic period is from March 15, 2020 to November 7, 2020.

Figure 2 Trends in the modality of first cancer treatment during pre-pandemic and pandemic periods in Ontario, Canada



We used dots and lines to denote the observed and predicted weekly recipient volume per thousand persons with cancer. Upfront surgical and chemotherapy rates have both fully recovered to pre-pandemic levels at the week of July 26, 2020 – August 1, 2020 and the week of August 2 – 8, 2020, respectively.

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

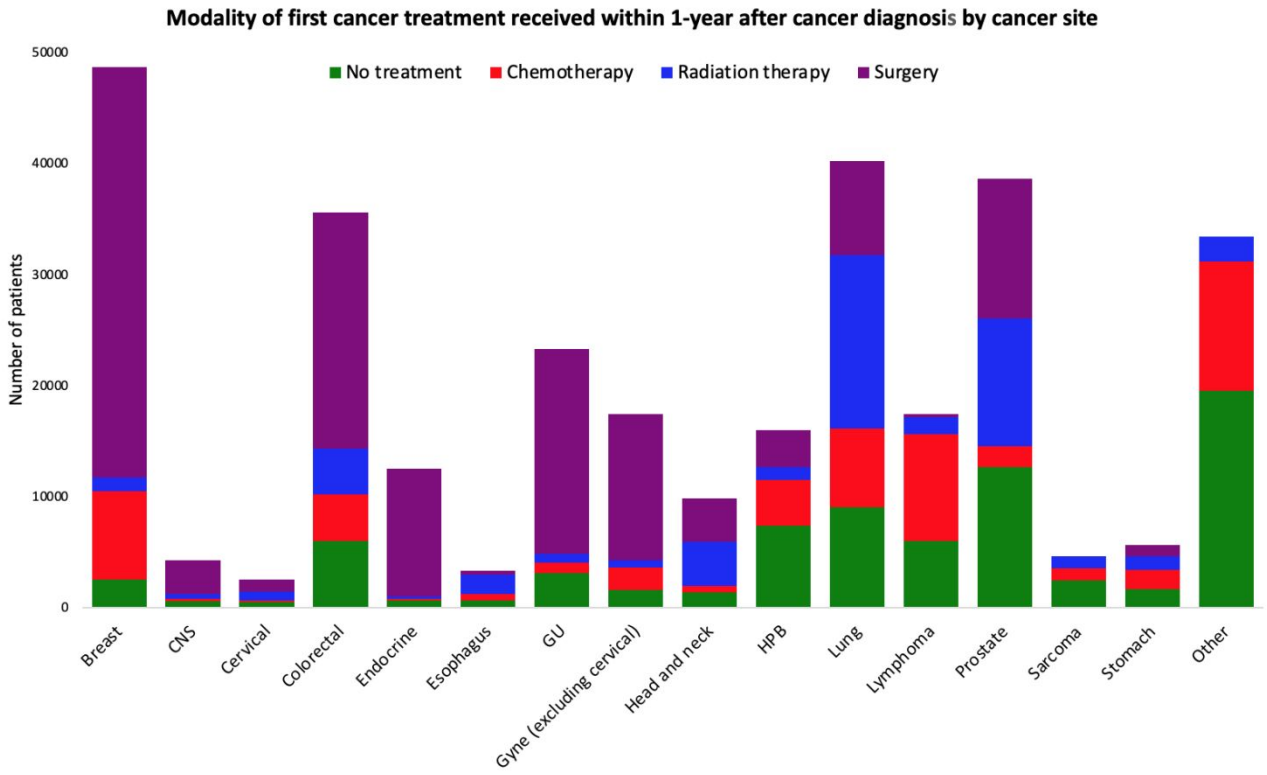
Appendix 1. Identifying cancer types from the Ontario Cancer Registry (OCR)

Cancer site	ICD-O-3 code
Breast	C50
Central nervous system	C70.0, C70.1, C70.9, C71, C72
Colorectal	C17, C18, C19.9, C20.9, C21.0, C21.1, C21.2, C21.8
Cervical	C53.0, C53.1, C53.8, C53.9
Endocrine	C73.9, C74.0, C74.1, C74.9, C75
Esophagus	C15
Genitourinary	C60, C62, C64, C65, C66, C67, C68
Gynecological exclude cervical	C51, C52, C54, C55, C56, C57
Head and neck	C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.9, C01.9, C02.0, C02.1, C02.2, C02.3, C02.4, C02.8, C02.9, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C05.1, C05.2, C05.8, C05.9, C06.0, C06.1, C06.2, C06.8, C06.9, C07.9, C08.0, C08.1, C08.8, C08.9, C09.0, C09.1, C09.8, C09.9, C11.0, C11.1, C11.2, C11.3, C11.8, C11.9, C12.9 , C14.0, C14.2, C14.8, C76.0, C06.9, C14.8, C32.0, C32.1, C32.3, C32.8, C32.9, C13.0, C13.1, C13.2, C13.8, C13.9, C00.0, C00.1, C00.2, C00.3, C00.4, C00.5, C00.6, C00.8, C00.9, C14.8, C44.0
Hepatic, pancreatic or biliary	C22.0, C22.1, C23, C24, C25
Lung	C34
Lymphoma	C77
Prostate	C61.9
Sarcoma	C00.0, C00.1, C00.3, C00.5, C00.9, C01.9 to C02.3, C02.8 to C03.1, C03.9, C04.0, C04.9, C.05.0, C05.1, C05.9, C06.0, C06.2, C06.9, C07.9, C08.0, C08.9, C09.0, C09.9, C10.3, C10.9, C11.0 to C11.3, C11.8, C11.9, C13.0, C13.1, C13.8, C13.9, C14.0, C14.8, C15.0, C15.3, C15.4, C15.5, C15.9, C16.0 to C16.6, C16.8 to C17.3, C17.8 to C18.9, C19.9, C20.9, C22.0, C22.1, C23.9 to C24.1, C24.9 to C25.2, C25.9, C30.0, C30.1, C31.1 to C31.3, C31.8 to C32.3, C32.9, C33.9 to C34.3, C34.8, C34.9, C37.9 to C38.3, C40.1 to C40.3, C40.8 to C41.4, C41.9, C42.1 to C42.4, C44.0 to C44.9, C47.0 to C47.9, C49.0 to C49.9, C50.0 to C512, C51.8, C51.9, C52.9 to C53.1, C53.8 to C54.3, C54.8, C54.9, C56.9 to C57.4, C57.7 to C57.9, C60.0 to C60.2, C60.9, C61.9 to C62.1, C62.9 to C63.2, C63.7 to C63.9, C649., C65.9, C66.9 to C68.0, C68.8, C69.0, C69.3, C69.6, C69.8, C70.0, C70.1, C70.9 to C72.0, C72.5, C72.9, C73.9 to C74.1, C74.9, C75.5, C77.0 to C77.9 with morphology code 803*, 831*, 871*, 880*-

Cancer site	ICD-O-3 code
	885*, 890*-900*, 912*, 914*, 917*-919*, 922*-924*, 926*, 933*, 944*, 948*, 953*, 958*, 974*-975*, 993*
Stomach	C16
Other	C26.0, C26.8, C26.9, C30, C31, C32.2, C33.9, C37.9, C38, C39, C40, C41, C42.0-C42.4, C44.1, C48, C49, C58.9, C63, C76, C80.9

We did not include melanoma and skin cancer to ensure a reliable capture of hospital-based cancer-directed surgical procedures as these cancers are frequently treated in the outpatient setting. We also excluded ophthalmologic and paraneoplastic neurological syndromes as these cancers were extremely rare in our cohort (<0.04% of the cohort).

Appendix 2. Modality of first cancer treatment received within 1 year after cancer diagnosis stratified by cancer type



Abbreviations: CNS, Central nervous system; GU, Genitourinary; HPB, Hepato-pancreatic biliary.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	i, iii
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1
Objectives	3	State specific objectives, including any prespecified hypotheses	1
Methods			
Study design	4	Present key elements of study design early in the paper	1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	1-2
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	2
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	2-3
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	Fig 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	3-4
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	4, Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	4, Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	4

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	4-5, Table 2, Fig 2
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	5
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8-9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	ii

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.