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Potentially inappropriate interventions in the end of life for patients with cancer

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Running head: Potentially inappropriate interventions

Abstract

Objectives: To describe variations in the receipt of potentially inappropriate interventions in the last 100 days of life of patients with cancer according to patient characteristics and cancer site.

Methods: We conducted a population-based retrospective cohort study of cancer decedents in Ontario, Canada who died between January 1, 2013, and December 31, 2018. Potentially inappropriate interventions, including chemotherapy, major surgery, intensive care unit admission, cardiopulmonary resuscitation, defibrillation, dialysis, percutaneous coronary intervention, mechanical ventilation, feeding tube placement, blood transfusion, and bronchoscopy, were captured via hospital discharge records. We used Poisson regression to examine associations between interventions and decedent age, sex, rurality, income, and cancer site.

Results: Among 151,618 decedents, 81.3% received at least one intervention, and 21.4% received 3+ different interventions. Older patients (age 95-105 vs. 19-44 rate ratio (RR) 0.36, 95% confidence interval (CI) 0.34-0.38) and females (RR 0.94, 95% CI 0.93-0.94) had lower intervention rates. Rural patients (RR 1.09, 95% CI 1.08-1.10) individuals in the highest area-level income quintile (vs. lowest income quintile RR 1.02, 95% CI 1.01-1.04), and patients with pancreatic cancer (vs. colorectal cancer RR 1.10, 95% CI 1.07-1.12) had higher intervention rates.

Conclusions: Potentially inappropriate interventions were common in the last 100 days of life of cancer decedents. Variations in interventions may reflect differences in prognostic awareness, healthcare access, and care preferences and quality. Earlier identification of patients' palliative

care needs and involvement of palliative care specialists may help reduce the use of these interventions at the end of life.

Keywords: Neoplasms, Terminal Care, Delivery of Healthcare, Health Administrative Data

What is already known about the topic: Most people with cancer who are nearing death prefer care that is focused on symptom management and palliation, yet many receive aggressive care at the end of life. While previous research has studied end-of-life chemotherapy and ICU admissions as potentially inappropriate interventions, less is known about the use of other potentially inappropriate interventions at the end of life for patients with cancer.

What this study adds: Potentially inappropriate interventions, including major surgery, mechanical ventilation, feeding tube placement, blood transfusions, chemotherapy, and ICU admissions, are common in the last 100 days of life of cancer decedents, with over four in five receiving at least one intervention. Interventions were more frequent in younger cancer patients, males, patients residing in rural areas, individuals residing in the highest income areas, and among those who died of pancreatic cancer.

How this study might affect research, practice or policy: Variations in the receipt of potentially inappropriate interventions in the last 100 days of life may reflect underlying differences in healthcare access, prognostic awareness, quality of care, and care preferences. Goals of care discussions, informed by patients' prognosis and supported by palliative care providers, may help ensure that end-of-life care is delivered in accordance with patients' preferences and reduce the occurrence of potentially inappropriate interventions.

Introduction

The months leading up to a cancer death are a period of heightened vulnerability for patients, with increased symptom burden, psychological distress, and care needs.[1] High-quality end-of-life healthcare can improve the dying experience for patients and their families, as well as reduce healthcare costs by limiting interventions that may be burdensome and provide little benefit to patients.[2]

Routinely collected administrative health data provide an opportunity to measure population level end-of-life cancer care quality . Previous studies have examined end-of-life care quality using administrative data indicators, including place of death and palliative care receipt.[3–12] These indicators are aligned with the end-of-life preferences of patients with cancer, including less aggressive care delivered out of hospital.[13] These studies suggest that the quality of end-of-life cancer care varies, with many patients receiving care and dying in hospital and receiving potentially inappropriate interventions prior to death.[3,4,6,7,9,14–16] However, these studies have been limited in their examination of end-of-life interventions, with many focusing on hospitalizations, intensive care unit (ICU) admissions, and chemotherapy use.[7,8,17,18] Other interventions, when delivered near the end of life, may not be aligned with patients' preferences and therefore potentially inappropriate given their risks, burden to the patient, uncertain survival benefit, and resource intensity. Previous research by Quinn et al.[19] identified interventions that may be potentially inappropriate when delivered near death based on a literature review and expert opinions of geriatrics, internal medicine, and palliative medicine specialists. These included major surgery, mechanical ventilation, cardiopulmonary resuscitation (CPR), newly initiated dialysis, percutaneous coronary

intervention, bronchoscopy, feeding tube placement, blood transfusions, and ICU admissions. While these interventions have been studied as measures of end-of-life quality, little is known about their use among individuals dying of cancer. The objective of this study was to describe the receipt of potentially inappropriate interventions in the last 100 days of life of patients with cancer and explore variations by patient demographics and cancer site. We selected the last 100 days of life as the study timeframe based on evidence that individuals dying of cancer experience fairly predictable health and functional declines during this period.[20] Further, the average terminal period in which active cancer treatment is unlikely to prolong survival is just over three months, raising the likelihood that interventions delivered in the last 100 days of life were potentially inappropriate.[21]

Methods

Setting and data sources

We conducted a retrospective cohort study of cancer decedents in Ontario, Canada. Ontario (population of 14.5 million) has a publicly-funded, universal health system in which all citizens and permanent residents are eligible for coverage of physician and hospital services through the Ontario Health Insurance Program (OHIP). We used population-based health administrative data housed at ICES, an independent, non-profit research institute that is authorized to collect and use healthcare data for health system evaluation and improvement. Decedents were identified using the Ontario Registrar General Vital Statistics Database and the Ontario Cancer Registry was used to assign the cancer site. Interventions were captured via hospital discharge records in the Discharge Abstract Database, cancer clinic data in the National Ambulatory Care Reporting System, and OHIP physician claims data. The Registered Persons Database were used

to capture patient demographics. These datasets were linked using unique encoded identifiers and analyzed at ICES.

Study population

We included all individuals who died of cancer (International Classification of Diseases (ICD), 10th revision C00 to D48, excluding benign neoplasms D10-D36) in Ontario between January 1, 2013, and December 31, 2018. We excluded individuals who were age <18 or >105 at death, individuals not eligible for OHIP in the last year of life, non-Ontario residents, individuals with no healthcare system contacts in the last five years of life, those whose cause of death was not cancer or was missing in the Ontario Cancer Registry, and females whose cause of death was prostate cancer. We excluded decedents age <18 at death to exclude pediatric cancer patients, whose prognoses and goals of care often differ from adult populations. The exclusion of decedents age >105 at death is a common exclusion applied in ICES research as it is likely represents errors due to data quality issues in the health administrative data.

Study variables

The outcome was potentially inappropriate interventions in the last 100 days of life, including chemotherapy, major surgery, ICU admission, CPR, defibrillation, dialysis, percutaneous coronary intervention, mechanical ventilation, feeding tube placement, blood transfusion and bronchoscopy. Major surgical procedures included abdominal, cardiac, retroperitoneal, thoracic, and vascular procedures.[19] These interventions were captured via procedure and service codes in the Discharge Abstract Database, except for chemotherapy which was captured via physician claims and cancer clinic records. See Supplemental Methods for details.

Decedent characteristics included age at death (19-44, 45-54, 55-64, 65-74, 75-84, 85-94, 95-105), sex, rurality, and neighbourhood income quintile (1=lowest income, 5=highest income). Cancer site was categorized as breast, colorectal, prostate, pancreatic or lung, which are the top five causes of cancer death in Canada, or other sites.[22]

Analysis

We described the study population characteristics using frequencies and proportions. We reported the count of each intervention, counting one occurrence per intervention per day. The exception was chemotherapy which was captured as any or no occurrence as multiple chemotherapy records could reflect a single treatment course. We described differences in decedent characteristics according to the receipt of interventions using chi-square tests to identify statistically significant ($p<0.05$) differences. We used Poisson regression to examine differences in intervention counts according to decedent characteristics, reporting the crude and adjusted rate ratios (RRs) and 95% confidence intervals (CIs). Patients with missing covariate data are reported in the cohort description but excluded from subsequent analyses. Reference groups for the regression analysis included age 19-44, male, urban, lowest income quintile, and colorectal cancer. In sensitivity analyses, we measured potentially inappropriate interventions in the last 30 days of life, a period during which there may be more certainty about proximity to death.

Results

The study population included 151,618 cancer decedents (Figure 1). Of these decedents, 48.1% were female, 28.8% were aged 75 to 84, and 85.7% lived in an urban area (Table 1). There was a higher proportion of patients in the lowest income quintile (22.9%) than in the highest quintile

(17.5%). Of the five main cancer sites, lung cancer was the most common cause of death (23.4%), followed by breast cancer (7.1%) and colorectal cancer (7.1%). Just over half of all decedents (50.5%) had a cancer death with site classified as 'other.' Of those, the most common cause of death was 'malignant neoplasm, primary site unknown,' which accounted for 7.3% of decedents with 'other' cancer site (see Supplemental Table 1 for top 50 causes of death in 'other' cancer site).

Potentially inappropriate interventions in last 100 days of life

Of all decedents, 29.4% received chemotherapy, 17.8% received a blood transfusion, 12.9% underwent surgery, 10.5% were admitted to ICU, 5.1% received mechanical ventilation, and 2.4% had a feeding tube placed in the last 100 days of life (Table 2). Defibrillation, dialysis, percutaneous coronary intervention, CPR, and bronchoscopy were relatively rare, with each observed in no more than 1.8% of decedents.

Table 3 reports the unadjusted associations between patient characteristics and potentially inappropriate interventions. Because few patients received more than one occurrence of the same intervention, these analyses examined each intervention as a dichotomous outcome (0 vs. 1+). Further, because few patients received CPR, bronchoscopy, percutaneous coronary intervention, dialysis or defibrillation, we did not examine these interventions in relation to patient characteristics. Older patients were less likely to receive each intervention ($p<0.001$). Females were more likely to receive chemotherapy ($p=0.04$), while males were more likely to receive the remaining five interventions ($p<0.001$). Rural patients were less likely to receive each intervention, except for ICU admissions which were more common in rural patients ($p=0.01$). Individuals residing in higher-income areas were more likely

to receive chemotherapy (p<0.001) and surgery (p=0.004) compared to those residing in lower income areas. The receipt of blood transfusions varied across income quintiles, with those in the middle quintile having the highest proportion (18.4%) and those in the lowest quintile having the lowest proportion (17.2%) (p=0.001). There were no differences in the receipt of mechanical ventilation (p=0.92), feeding tubes (p=0.30), or ICU admissions (p=0.29) by income quintile. There were variations in the receipt of each intervention by cancer site (p<0.001). Patients with breast cancer had the highest proportion receiving chemotherapy (46.2%) and patients with colorectal cancer had the highest proportion receiving surgery (19.1%). Patients in the other cancer site category had the highest proportion receiving all other interventions.

Overall, 18.7% of decedents received no potentially inappropriate interventions in the last 100 days, while 33.9% received one, 26.0% received two, and 21.4% received three or more potentially inappropriate interventions (Figure 2). Intervention rates differed according to patient demographics and cancer site, with minimal change between the unadjusted and adjusted RRs (Table 4). In the adjusted model, the intervention rate was lower with older age, with patients age 95-105 having an intervention rate that was 64% lower (RR 95% CI 0.34-0.38) than that of those age 19 to 44. The intervention rate was 6% lower (RR 95% CI 0.93-0.94) in females vs. males, and 9% (RR 95% CI 1.08-1.10) higher in rural vs. urban patients. The intervention rate was 2% higher (RR 95% CI 1.01-1.04) in patients residing in the highest vs. the lowest income quintiles, but similar between residents in the middle three vs. the lowest income quintile. Patients with pancreatic cancer and other cancer sites had intervention rates that were 10% (RR 95% CI 1.07-1.12) and 9% (RR 95% CI 1.07-1.11) higher, respectively, than

patients with colorectal cancer. Intervention rates for patients with breast, lung, and prostate cancer were similar to those of patients with colorectal cancer.

Sensitivity analysis

In sensitivity analyses measuring interventions in the last 30 days of life, just under half (47.6%) of patients received no potentially inappropriate interventions in the last 30 days, and 40.8%, 9.8%, 2.1% received 1, 2, or 3+ interventions, respectively. Chemotherapy and blood transfusions remained the most common interventions, received by 12.0% and 9.4%, respectively. The patterns observed for variations in rates of potentially inappropriate interventions by age, sex, and rurality in the last 30 days of life remained consistent with those in the last 100 days of life. In contrast, the relationship between area-level income and interventions reversed, with lower rates with increasing income quintile (RR 0.96, 95% CI 0.94-0.98 for highest vs. lowest quintile). Differences by cancer site remained consistent for breast, pancreatic and other cancer sites. However, in the last 30 days of life, prostate cancer patients had lower intervention rates (RR 0.88, 95% CI 0.85-0.92) and lung cancer patients had higher intervention rates (RR 1.13, 95% CI 1.10-1.16) in contrast to those with colorectal cancer. See Supplemental Tables 2-4 for full results from sensitivity analyses.

Discussion

Main findings

This population-based study demonstrates that many individuals with cancer receive interventions that may be potentially inappropriate in their last 100 days of life. The most common interventions were chemotherapy and blood transfusions. Over four in five (81.3%) cancer decedents received at least one potentially inappropriate intervention, while over one in

five (21.4%) received three or more interventions in the last 100 days of life. These interventions varied across patient demographics and cancer site. While intervention rates were lower in the last 30 days of life, the variations across patient demographics and cancer site largely remained consistent, with the exception of those observed for income, as well as lung and prostate cancer.

What this study adds

Variations in potentially inappropriate interventions across patient demographics and disease site may point to issues with end-of-life care quality and access. Older age was consistently associated with lower rates of potentially inappropriate interventions , which is aligned with evidence from other jurisdictions.[5,16] These findings may reflect age differences in end-of-life care preferences, as younger patients have been reported to prefer more aggressive and potentially life-sustaining care at the end of life than older patients.[23,24] However, these differences may also reflect ageism in medical decision-making, as older patients with cancer have also been found to be less likely than younger patients to receive life-prolonging care, even when it was their care preference.[25]

Female cancer patients also had a lower intervention rate and aside from chemotherapy, a lower proportion receiving each intervention than males. Previous research has identified sex differences in end-of-life care that support these findings.[4,7,16] Men are more likely to receive aggressive care and be admitted to the ICU in the last weeks of life and less likely to receive hospice and supportive care and appropriate pain and symptom management.[4,7,14,16,26] These variations align with sex differences in care preferences, with women being less likely to prefer life-sustaining interventions and more likely to prefer

palliative care at the end of life.[27,28] Women with cancer have also been found to have a better understanding of their prognosis, have discussed life expectancy with their oncologist, and be more open to discussing death and dying.[29,30] Reasons for these sex differences in end-of-life care and care preferences are not well understood and warrant further study. If females' preferences for less aggressive care stems from a better understanding of their prognosis, this suggests that improved end-of-life communication, particularly tailored to males, may help reduce potentially inappropriate interventions as death approaches.

Rural patients with cancer were less likely to undergo chemotherapy, surgery, mechanical ventilation, feeding tube placement, and blood transfusions in the last 100 days of life compared to urban patients. However, this pattern was reversed when we evaluated the intervention rate, with rural patients having a higher intervention rate than urban patients in both the unadjusted and adjusted models. Together, these findings suggest that while rural patients may be less likely than urban patients to receive any intervention on its own, they are more likely to receive multiple interventions contributing to a higher intervention rate. One potential explanation is individuals in rural areas have reduced access to palliative and community-based care, which is associated with increased acute care use.[31–33] These late hospitalizations may lead to more interventions.

We observed a small increase in the potentially inappropriate intervention rate among patients in the highest vs. the lowest income quintile, although the rates in the middle three income quintiles were similar to those in the lowest quintile. Chemotherapy showed the largest variation across income quintiles, with the unadjusted proportion receiving chemotherapy in the last 100 days of life being 9% higher in the highest vs. the lowest income quintile. However,

the relationship was inversed when assessed in the last 30 days of life, with lower intervention rates in higher income quintiles. The variation in the proportion who received chemotherapy across income quintiles was also reduced. Recent systematic and integrative reviews reported that in high income and developed countries, higher socioeconomic deprivation is associated with poor quality end-of-life care, including reduced palliative care use, increased use of acute care, more aggressive care, and death in hospital.[34,35] Similar patterns have been observed in other studies of end-of-life care in Ontario.[31,36] Our findings may be contradictory to the previous research because of the time period in which we measured potentially inappropriate interventions. Care in the last 100 days of life may include life prolonging treatment, which may be more accessible for individuals with greater economic resources. The 30 days before death may be a more easily recognized terminal period, and improved access to palliative care by individuals in higher income areas may contribute to lower intervention rates in that time period. Further research is needed to understand these income-related care differences, including a consideration of whether interventions were delivered with palliative or life-prolonging intent..

Variations in potentially inappropriate interventions by cancer site are in line with previous research that has shown substantial differences in end-of-life care according to cancer site.[4,5,16] In the last 100 days of life, patients with pancreatic cancer had the highest intervention rate while patients with breast, lung and prostate cancers had intervention rates that were similar to those with colorectal cancer. In 30 days before death, patients with lung cancer had higher intervention rates while patients with prostate cancer had lower rates compared to those with colorectal cancer. However, no single cancer site was consistently

more likely to undergo each intervention. Indeed, despite having a high intervention rate, patients with pancreatic cancer were never the most likely to receive any of the six interventions studied. There may be disease-related factors driving these differences. For instance, surgery may be used for palliation in patients with colorectal cancer to provide symptom relief, while blood transfusions may be used to manage symptoms of anemia, which is relatively common in advanced colorectal and prostate cancer.[37] Variations in chemotherapy by cancer site may reflect differences in use of palliative chemotherapy across cancer sites.[14] Patients with hematologic malignancies, who were included in the other cancer sites category, have previously been reported to receive more aggressive end-of-life care when compared to patients with solid tumours, in part due to the more fluctuating illness trajectory and shorter terminal period in this group.[38] Interventions in the last 100 days of life of patients with hematologic malignancies may reflect care delivered when the cancer was still being treated with curative intent, which may partially explain the high intervention rates observed in the other cancer sites category.

The interventions we studied were defined as potentially inappropriate because they have potential risks and questionable benefits when delivered near death, may cause discomfort, and are costly. However, some of these interventions may have been appropriately delivered based on patients' health and goals. We did not have information on treatment intent, and some of these interventions may have been delivered for palliation. However, even interventions with palliative intent may have limited benefit. For instance, a 2015 study found that chemotherapy delivered in the last months of life did not improve, and in some instances worsened, the quality of life of patients with end-stage cancer.[39] Further, while blood

transfusions may be used for symptom management, the benefits of transfusion at the end of life are not well known, and there are known risks, including death in hospital and transfusion-related adverse events.[40] Second, while patient-reported end-of-life care preferences tend to focus on symptom management and palliation, some patients do prefer more aggressive care even as death approaches. We cannot be certain that the interventions captured in this study were not aligned with patient preferences. Finally, it is also possible that these interventions were delivered without the patients and clinicians recognizing that the patient was nearing death. Tools to support prognostication and the identification of palliative care needs, such as mortality prediction tools, can help support personalized decision making at the end of life. Discussions around end-of-life goals should consider patients' prognosis to allow patients to make evidence-informed care decisions. Ideally, palliative care providers should be involved in these discussions throughout the disease course which may help reduce the rates of potentially inappropriate interventions at the end of life.

Strengths and limitations of the study

This study provides a comprehensive and population-level examination of potentially inappropriate interventions at the end of life for all cancer decedents in Ontario, thereby minimizing selection bias. While this study was conducted in a single Canadian province, the findings are aligned with international evidence regarding high rates of potentially inappropriate care at the end of life, including differences in rates across patient characteristics and disease site.[5,14,16,26,35] This study expands on our understanding of potentially inappropriate interventions as we evaluated a more comprehensive set of interventions, such as mechanical ventilation and dialysis, and highlighted important variations in the last 100 days

of life. This study built on a previous definition and administrative data coding of potentially inappropriate interventions that was developed by Quinn et al. While that study used a literature review and consultations with experts to identify interventions, it did not use any formal consensus-based approaches to identify inappropriate care. Other research has more rigorously identified inappropriate interventions in cancer patients, although with considerable overlap with the interventions examined in our study.[10] Our study population included decedents who died up until December 31, 2018; more recent deaths could not be captured as cause of death was not available in the administrative data. Thus, our findings may not reflect current patterns of end-of-life cancer care. We used a decedent cohort to study end-of-life care, with interventions defined as potentially inappropriate only after death. However, prospectively identifying individuals who are expected to die and whose care could thus be considered to reflect end-of-life care in advance of death is challenging, particularly at a population-level using administrative data.

Conclusion

Potentially inappropriate interventions are common among patients with cancer who are nearing death. Variations in the receipt of potentially inappropriate interventions across patient demographics and cancer site may be partly explained by differences in patient care preferences, knowledge and awareness of prognosis, resource access, and clinical indication. They may also reflect differences in the overall quality of care provided. Earlier identification of patients' palliative care needs using prognostication tools, supported by the involvement of palliative care specialists, may help reduce the use of these potentially inappropriate interventions as death approaches.

Disclosures and Acknowledgements

Ethics approval and consent to participate

ICES is a prescribed entity under Ontario's Personal Health Information Protection Act (PHIPA). Section 45 of PHIPA authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. Projects that use data collected by ICES under section 45 of PHIPA, and use no other data, are exempt from REB review. The use of the data in this project is authorized under section 45 and approved by ICES' Privacy and Legal Office.

Consent for publication

Not applicable.

Availability of data and materials

The data set from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www. ices.on.ca/DAS. The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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Authors' contributions

CW, MH, SI, and AH conceived the study. All authors designed the study and interpreted the results. AG analyzed the data. CW wrote the manuscript. All authors revised the manuscript critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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Table 1: Decedent characteristics

		Decedents n=151,618
Age at death	19-44	3,446 (2.3)
	45-54	9,246 (6.1)
	55-64	24,909 (16.4)
	65-74	39,617 (26.1)
	75-84	43,622 (28.8)
	85-94	27,979 (18.5)
	95-105	2,799 (1.8)
Sex	Female	72,915 (48.1)
	Male	78,703 (51.9)
Rural status	Urban	129,990 (85.7)
	Rural	21,256 (14.0)
	Missing	372 (0.2)
Neighbourhood income quintile	1 (lowest)	34,673 (22.9)
	2	33,197 (21.9)
	3	29,725 (19.6)
	4	27,017 (17.8)
	5 (highest)	26,492 (17.5)
	Missing	514 (0.3)
Cancer site	Breast	10,808 (7.1)
	Colorectal	10,774 (7.1)
	Lung	35,552 (23.4)
	Other	76,573 (50.5)
	Pancreatic	10,052 (6.6)
	Prostate	7,859 (5.2)

Table 2: Receipt of potentially inappropriate interventions in the last 100 days of life

Intervention	Frequency in last 100 days	N (%) decedents
Blood transfusion	0	124,592 (82.2%)
	1	21,710 (14.3%)
	2	4,201 (2.8%)
	3+	1,115 (0.7%)
Major surgery	0	132,158 (87.2%)
	1	17,280 (11.4%)
	2	1,939 (1.3%)
	3+	241 (0.2%)
ICU admission	0	135,741 (89.5%)
	1	14,353 (9.5%)
	2	1,327 (0.9%)
	3+	197 (0.1%)
Mechanical ventilation	0	143,817 (94.9%)
	1	7,327 (4.8%)
	2	425 (0.3%)
	3+	49 (0.0%)
Chemotherapy	0	107,038 (70.6%)
	1+	44,580 (29.4%)
Feeding tube placement	0	147,920 (97.6%)
	1	3,469 (2.3%)
	2	210 (0.1%)
	3+	19 (0.0%)
Bronchoscopy	0	148,959 (98.2%)
	1	2,512 (1.7%)
	2	138 (0.1%)
	3+	9 (0.0%)
Dialysis	0	149,914 (98.9%)
	1	1,403 (0.9%)
	2	227 (0.1%)
	3+	74 (0.0%)
CPR	0	150,103 (99.0%)
	1+	1,515 (1.0%)
Defibrillation	0	151,071 (99.6%)
	1+	547 (0.4%)
Percutaneous coronary intervention	0	151,397 (99.9%)
	1	173 (0.1%)
	2	48 (0.0%)

ICU: Intensive Care Unit; CPR: cardiopulmonary resuscitation.

Table 3: Number and proportion of patients who received each potentially inappropriate intervention in last 100 days of life according to patient characteristics.

		Chemotherapy n=44,580	Surgery n=19,460	ICU admission n=15,887	Mechanical ventilation n=7,801	Feeding tube n=3,698	Blood transfusion n=27,026
Age at death	19-44	2,057 (59.7)	833 (24.2)	705 (20.5)	430 (12.5)	141 (4.1)	1,040 (30.2)
	45-54	4,836 (52.3)	1,807 (19.5)	1,420 (15.4)	765 (8.3)	355 (3.8)	2,106 (22.8)
	55-64	11,062 (44.4)	4,109 (16.5)	3,346 (13.4)	1,737 (7.0)	890 (3.6)	4,986 (20.0)
	65-74	14,376 (36.3)	6,029 (15.2)	4,949 (12.5)	2,461 (6.2)	1,136 (2.9)	7,632 (19.3)
	75-84	9,876 (22.6)	4,899 (11.2)	4,034 (9.2)	1,829 (4.2)	876 (2.0)	7,419 (17.0)
	85-94	2,302 (8.2)	1,710 (6.1)	1,388 (5.0)	567 (2.0)	287 (1.0)	3,596 (12.9)
	95-105	71 (2.5)	73 (2.6)	35 (1.3)	12 (0.4)	13 (0.5)	247 (8.8)
		p<0.001*	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Sex	Female	21,620 (29.7)	8,914 (12.2)	6,774 (9.3)	3,308 (4.5)	1,493 (2.0)	12,233 (16.8)
	Male	22,960 (29.2)	10,546 (13.4)	9,103 (11.6)	4,493 (5.7)	2,205 (2.8)	14,793 (18.8)
		p=0.04	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Rural status	Urban	38,495 (29.6)	16,927 (13.0)	13,515 (10.4)	6,929 (5.3)	3,268 (2.5)	23,414 (18.0)
	Rural	5,998 (28.2)	2,500 (11.8)	2,327 (10.9)	851 (4.0)	426 (2.0)	3,559 (16.7)
		p<0.001	p<0.001	p=0.01	p<0.001	p<0.001	p<0.001
Neighbourhood income quintile	1 (lowest)	8,680 (25.0)	4,346 (12.5)	3,728 (10.8)	1,784 (5.1)	843 (2.4)	5,949 (17.2)
	2	9,363 (28.2)	4,213 (12.7)	3,404 (10.3)	1,675 (5.0)	827 (2.5)	5,916 (17.8)
	3	8,892 (29.9)	3,785 (12.7)	3,123 (10.5)	1,534 (5.2)	765 (2.6)	5,465 (18.4)
	4	8,576 (31.7)	3,611 (13.4)	2,799 (10.4)	1,406 (5.2)	624 (2.3)	4,827 (17.9)
	5 (highest)	8,956 (33.8)	3,455 (13.0)	2,766 (10.4)	1,370 (5.2)	632 (2.4)	4,792 (18.1)
		p<0.001	p=0.01	p=0.29	p=0.92	p=0.30	p=0.001
Cancer site	Breast	4,988 (46.2)	846 (7.8)	694 (6.4)	330 (3.1)	84 (0.8)	1,139 (10.5)
	Colorectal	3,055 (28.4)	2,057 (19.1)	1,077 (10.0)	625 (5.8)	242 (2.2)	1,836 (17.0)
	Lung	8,996 (25.3)	2,848 (8.0)	3,698 (10.4)	1,706 (4.8)	389 (1.1)	3,566 (10.0)
	Other	22,382 (29.2)	12,045 (15.7)	9,329 (12.2)	4,767 (6.2)	2,759 (3.6)	17,615 (23.0)
	Pancreatic	2,872 (28.6)	1,179 (11.7)	679 (6.8)	222 (2.2)	180 (1.8)	1,267 (12.6)
	Prostate	2,287 (29.1)	485 (6.2)	400 (5.1)	151 (1.9)	44 (0.6)	1,603 (20.4)
		p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001

*All p-values from chi-square test

ICU: Intensive care unit

Table 4: Number of potentially inappropriate interventions received in last 100 days of life according to patient characteristics

		0 interventions n=28,416	1 intervention n=51,338	2 interventions n=39,426	3+ interventions n=32,438	Unadjusted RR (95% CI)	Adjusted* RR (95% CI)
Age at death	19-44	362 (10.5)	733 (21.3)	995 (28.9)	1,356 (39.3)	1.00	1.00
	45-54	1,016 (11.0)	2,365 (25.6)	2,852 (30.8)	3,013 (32.6)	0.91 (0.89, 0.94)	0.92 (0.89, 0.94)
	55-64	3,215 (12.9)	7,062 (28.4)	7,363 (29.6)	7,269 (29.2)	0.85 (0.83, 0.87)	0.85 (0.83, 0.87)
	65-74	5,811 (14.7)	12,343 (31.2)	11,400 (28.8)	10,063 (25.4)	0.79 (0.77, 0.81)	0.79 (0.77, 0.81)
	75-84	8,633 (19.8)	15,768 (36.1)	11,130 (25.5)	8,091 (18.5)	0.67 (0.65, 0.68)	0.67 (0.65, 0.68)
	85-94	8,192 (29.3)	11,920 (42.6)	5,336 (19.1)	2,531 (9.0)	0.49 (0.48, 0.50)	0.49 (0.48, 0.51)
	95-105	1,187 (42.4)	1,147 (41.0)	350 (12.5)	115 (4.1)	0.35 (0.34, 0.37)	0.36 (0.34, 0.38)
Sex	Female	14,837 (20.3)	25,071 (34.4)	18,553 (25.4)	14,454 (19.8)	0.92 (0.92, 0.93)	0.94 (0.93, 0.94)
	Male	13,579 (17.3)	26,267 (33.4)	20,873 (26.5)	17,984 (22.9)	1.00	1.00
Rural status	Urban	24,571 (18.9)	44,555 (34.3)	33,965 (26.1)	26,899 (20.7)	1.00	1.00
	Rural	3,745 (17.6)	6,646 (31.3)	5,382 (25.3)	5,483 (25.8)	1.10 (1.09, 1.12)	1.09 (1.08, 1.10)
Neighbourhood income quintile	1 (lowest)	6,406 (18.5)	12,189 (35.2)	8,986 (25.9)	7,092 (20.5)	1.00	1.00
	2	6,241 (18.8)	11,328 (34.1)	8,566 (25.8)	7,062 (21.3)	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)
	3	5,515 (18.6)	10,040 (33.8)	7,746 (26.1)	6,424 (21.6)	1.02 (1.01, 1.03)	1.01 (1.00, 1.03)
	4	5,118 (18.9)	8,923 (33.0)	7,108 (26.3)	5,868 (21.7)	1.02 (1.01, 1.04)	1.01 (1.00, 1.02)
	5 (highest)	5,003 (18.9)	8,663 (32.7)	6,907 (26.1)	5,919 (22.3)	1.03 (1.02, 1.04)	1.02 (1.01, 1.04)
Cancer site	Breast	2,336 (21.6)	3,470 (32.1)	2,967 (27.5)	2,035 (18.8)	1.01 (0.99, 1.04)	0.98 (0.96, 1.00)
	Colorectal	2,340 (21.7)	3,734 (34.7)	2,744 (25.5)	1,956 (18.2)	1.00	1.00
	Lung	6,555 (18.4)	12,866 (36.2)	9,283 (26.1)	6,848 (19.3)	1.04 (1.02, 1.06)	0.99 (0.97, 1.01)
	Other	13,596 (17.8)	25,136 (32.8)	19,879 (26.0)	17,962 (23.5)	1.13 (1.11, 1.15)	1.09 (1.07, 1.11)
	Pancreatic	1,653 (16.4)	3,423 (34.1)	2,667 (26.5)	2,309 (23.0)	1.14 (1.12, 1.17)	1.10 (1.07, 1.12)
	Prostate	1,936 (24.6)	2,709 (34.5)	1,886 (24.0)	1,328 (16.9)	0.94 (0.92, 0.97)	0.98 (0.96, 1.01)

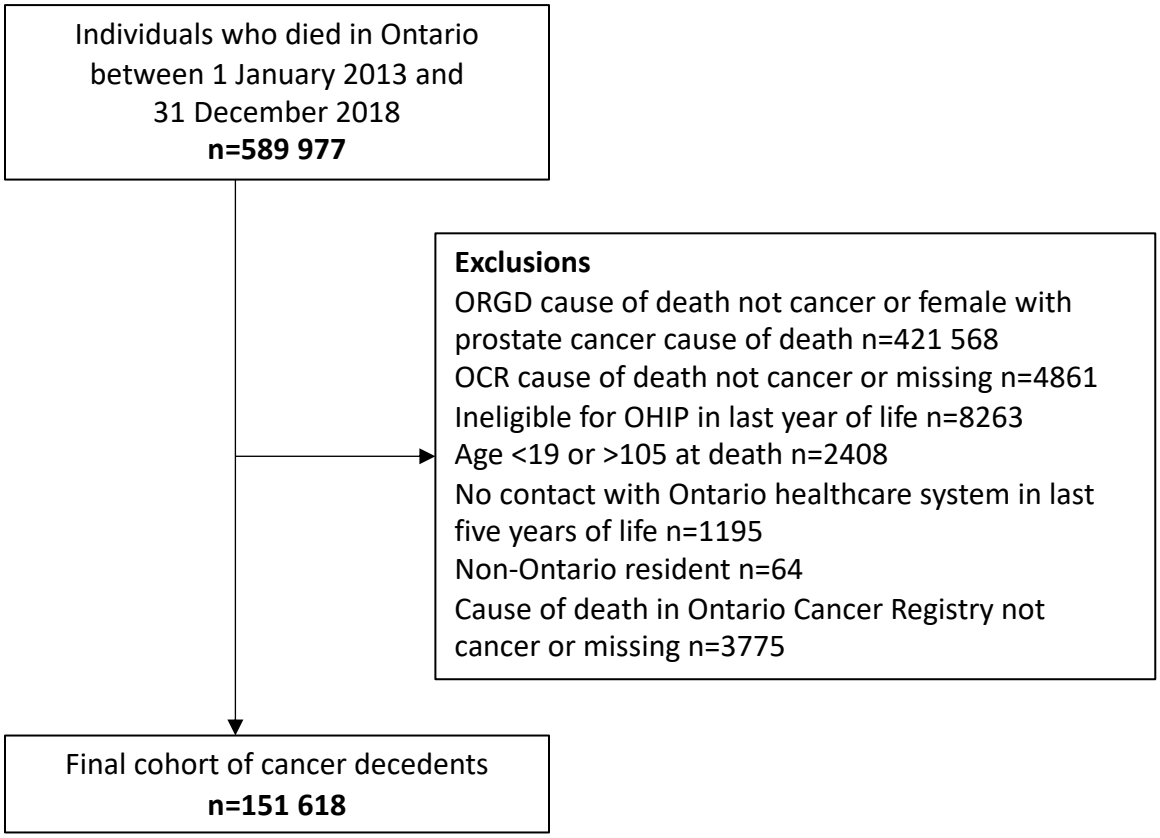
RR: rate ratio; CI: confidence interval

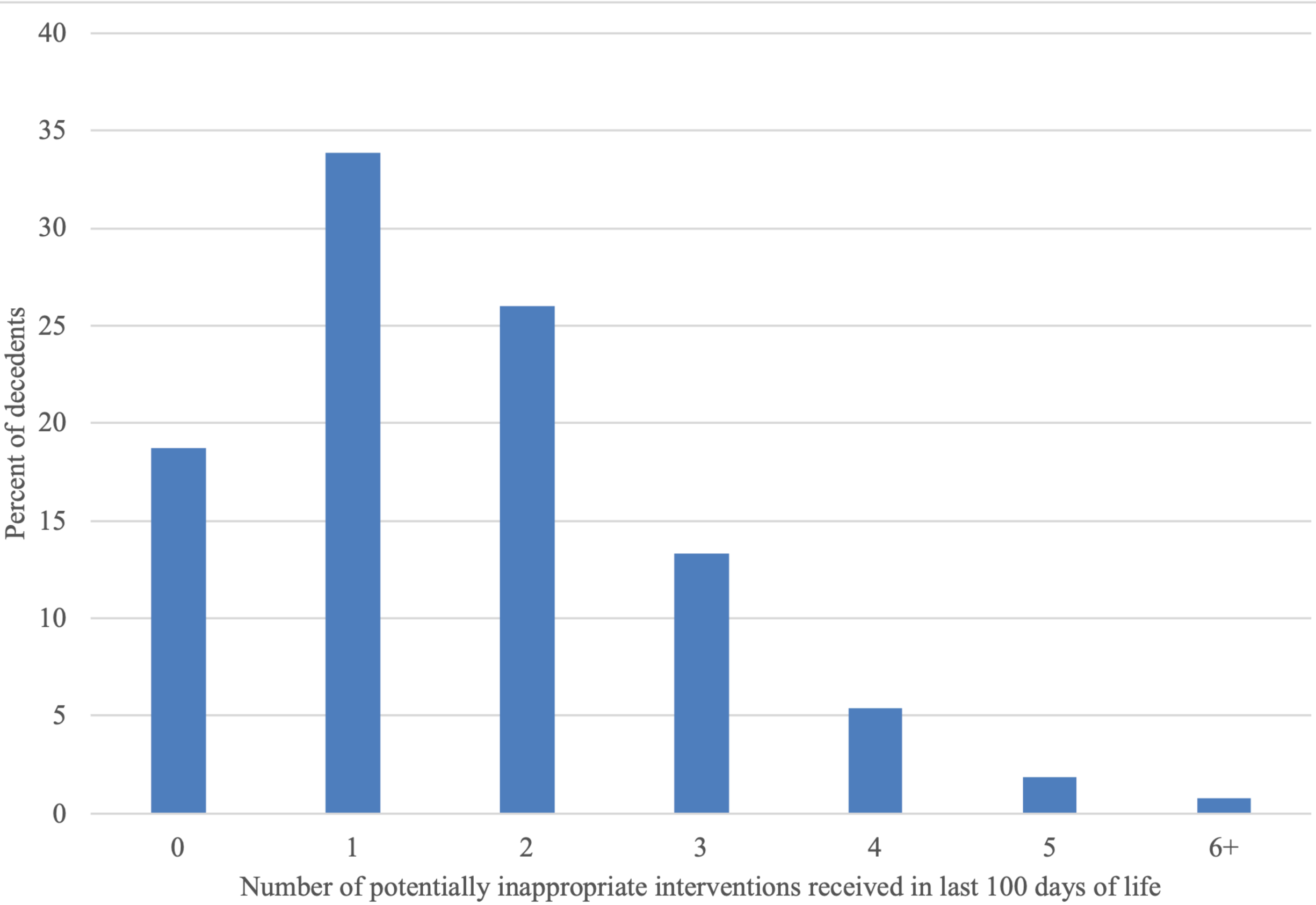
*Adjusted for all variables in Table 4

Figure legend:

Figure 1: Study population flow diagram. ORGD: Ontario Registrar General Vital Statistics Database. OCR: Ontario Cancer Registry. OHIP: Ontario Health Insurance Program.

Figure 2: Distribution of the number of potentially inappropriate interventions in the last 100 days of life


Individuals who died in Ontario between 1 January 2013 and 31 December 2018
n=589 977
Exclusions
ORGD cause of death not cancer or female with prostate cancer cause of death n=421 568
OCR cause of death not cancer or missing n=4861
Ineligible for OHIP in last year of life n=8263
Age <19 or >105 at death n=2408
No contact with Ontario healthcare system in last five years of life n=1195
Non-Ontario resident n=64
Cause of death in Ontario Cancer Registry not cancer or missing n=3775
Final cohort of cancer decedents
n=151 618


40
35
30
25
20
15
10
5
0
Percent of decedents
0
1
2
3
4
5
6+
Number of potentially inappropriate interventions received in last 100 days of life

Supplemental Methods

Administrative data codes to identify potentially inappropriate interventions

Intervention	Data source	Administrative data codes
Chemotherapy	OHIP NACRS	OHIP fee code: G345, G359, G381, G388, G382, G281 NACRS source=cancer clinic, diagnosis type=main diagnosis
Intensive care unit admission	CIHI-DAD	Service provider: 00055 (Critical Care Medicine)
Major surgery	CIHI-DAD	Identified by CCI codes. Includes abdominal, cardiac, retroperitoneal, thoracic, and vascular surgical procedures. See full details in: Quinn et al. Association between high cost user status and end-of-life care in hospitalized patients: A national cohort study of patients who die in hospital. *Pall Med.* 2021;35(9):1671-1681.
Cardiopulmonary resuscitation	CIHI-DAD	CCI code: 1.HZ.30.^^
Defibrillation	CIHI-DAD	CCI code: 1.HZ.09.^^
Dialysis	CIHI-DAD	CCI code: 1.PZ.21.^^
Percutaneous coronary intervention	CIHI-DAD	CCI code: 1.IJ.50, 1.IJ.54, 1.IJ.57.GQ
Mechanical ventilation	CIHI-DAD	CCI code: 1.GZ.31.^^
Feeding tube placement	CIHI-DAD	CCI code: 1.NF.53.^^
Blood transfusion	CIHI-DAD	CCI code: 1.LZ.19.^^
Bronchoscopy	CIHI-DAD	CCI code: NEC 2.GM.70.^^

OHIP: Ontario Health Insurance Program
NACRS: National Ambulatory Care Reporting System
CIHI-DAD: Canadian Institute of Health Information Discharge Abstract Database
CCI: Canadian Classification of Interventions

Supplemental Table 1: Top 50 causes of death for 76,573 cancer decedents with cancer site classified as 'other'

ICD-10 cause of death recorded in Ontario Cancer Registry	Count	Percent
Malignant neoplasm, primary site unknown, so stated	5,606	7.3
Malignant neoplasm of bladder, unspecified	4,219	5.5
Malignant lesion oesophagus unspecified	4,121	5.4
Malignant neoplasm of brain unspecified	3,974	5.2
Malignant neoplasm of ovary	3,727	4.9
Malignant neoplasm stomach unspecified	3,591	4.7
Malignant neoplasm of kidney, except renal pelvis	3,179	4.2
Multiple myeloma	2,730	3.6
Non-Hodgkin's lymphoma, unspecified type	2,702	3.5
Malignant melanoma of skin, unspecified	2,677	3.5
Intrahepatic bile duct carcinoma	2,569	3.4
Malignant neoplasm of rectum	2,540	3.3
Acute myeloid leukaemia	2,353	3.1
Malignant neoplasm of rectosigmoid junction	2,156	2.8
Liver cell carcinoma	1,747	2.3
Malignant neoplasm, unspecified	1,618	2.1
Malignant neoplasm of endometrium	1,519	2.0
Myelodysplastic syndrome, unspecified	1,152	1.5
Large cell (diffuse) Non-Hodgkin's lymphoma	1,096	1.4
Malignant neoplasm intestinal tract, part unspecified	1,035	1.4
Malignant neoplasm of uterus, part unspecified	995	1.3
Chronic lymphocytic leukaemia	991	1.3
Malignant neoplasm of connective and soft tissue, unspecified	884	1.2
Malignant neoplasm cervix uteri, unspecified	850	1.1
Malignant neoplasm urinary organ unspecified	829	1.1
B-cell lymphoma, unspecified	821	1.1
Malignant neoplasm of liver unspecified	778	1.0
Malignant neoplasm tongue unspecified	739	1.0
Mesothelioma, unspecified	732	1.0
Malignant neoplasm of gallbladder	613	0.8
Malignant neoplasm larynx unspecified	561	0.7
Malignant neoplasm of thyroid gland	485	0.6
Leukaemia, unspecified	466	0.6
Malignant neoplasm of cardia	461	0.6
Malignant neoplasms of other & Ill-defined sites within the digestive system	437	0.6
Malignant neoplasm of vulva unspecified	433	0.6
Malignant lesion oropharynx unspecified	407	0.5
Acute leukaemia of unspecified cell type	390	0.5
Malignant neoplasm of mouth unspecified	374	0.5
Malignant neoplasm of skin, unspecified	333	0.4
Malignant neoplasm pharynx unspecified	294	0.4
Malignant neoplasm skin of scalp & neck	292	0.4
Malignant neoplasm of duodenum	289	0.4
Peripheral T-cell lymphoma	279	0.4
Small cleaved cell (diffuse) Non-Hodgkin's lymphoma	258	0.3
Malignant neoplasm tonsil unspecified	254	0.3
Osteomyelofibrosis	247	0.3
Malignant neoplasm nasopharynx unspecified	233	0.3

Acute lymphoblastic leukaemia	228	0.3
Hodgkin's disease, unspecified	224	0.3

ICD: International Classification of Diseases

Supplemental Table 2: Receipt of potentially inappropriate interventions in the last 30 days of life

Intervention	Frequency in last 30 days	N (%) decedents
Blood transfusion	0	137,326 (90.6%)
	1	13,264 (8.7%)
	2	956 (0.6%)
	3+	72 (0.0%)
Major surgery	0	142,493 (94.0%)
	1	8,698 (5.7%)
	2	405 (0.3%)
	3+	22 (0.0%)
ICU admission	0	141,683 (93.4%)
	1	9,398 (6.2%)
	2	493 (0.3%)
	3+	44 (0.0%)
Mechanical ventilation	0	145,987 (96.3%)
	1	5,396 (3.6%)
	2	218 (0.1%)
	3+	17 (0.0%)
Chemotherapy	0	133,355 (88.0%)
	1+	18,263 (12.0%)
Feeding tube placement	0	149,971 (98.9%)
	1	1,603 (1.1%)
	2+	44 (0.0%)
Bronchoscopy	0	150,647 (99.4%)
	1	955 (0.6%)
	2+	16 (0.0%)
Dialysis	0	150,476 (99.2%)
	1	1,070 (0.7%)
	2	64 (0.0%)
	3+	8 (0.0%)
CPR	0	150,283 (99.1%)
	1+	1,335 (0.9%)
Defibrillation	0	151,227 (99.7%)
	1+	391 (0.3%)
Percutaneous coronary intervention	0	151,579 (100.0%)
	1	31 (0.0%)
	2	8 (0.0%)

Supplemental Table 3: Number and proportion of patients who received each potentially inappropriate intervention in last 30 days of life according to patient characteristics.

		Chemotherapy n=18,263	Surgery n=9,125	ICU admission n=9,935	Mechanical ventilation n=5,631	Feeding tube n=1,647	Blood transfusion n=14,292
Age at death	19-44	2,057 (59.7)	833 (24.2)	705 (20.5)	430 (12.5)	141 (4.1)	1,040 (30.2)
	45-54	4,836 (52.3)	1,807 (19.5)	1,420 (15.4)	765 (8.3)	355 (3.8)	2,106 (22.8)
	55-64	11,062 (44.4)	4,109 (16.5)	3,346 (13.4)	1,737 (7.0)	890 (3.6)	4,986 (20.0)
	65-74	14,376 (36.3)	6,029 (15.2)	4,949 (12.5)	2,461 (6.2)	1,136 (2.9)	7,632 (19.3)
	75-84	9,876 (22.6)	4,899 (11.2)	4,034 (9.2)	1,829 (4.2)	876 (2.0)	7,419 (17.0)
	85-94	2,302 (8.2)	1,710 (6.1)	1,388 (5.0)	567 (2.0)	287 (1.0)	3,596 (12.9)
	95-105	71 (2.5)	73 (2.6)	35 (1.3)	12 (0.4)	13 (0.5)	247 (8.8)
		p<0.001*	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Sex	Female	8,777 (12.0%)	4,064 (5.6%)	4,244 (5.8%)	2,397 (3.3%)	630 (0.9%)	6,247 (8.6%)
	Male	9,486 (12.1%)	5,061 (6.4%)	5,691 (7.2%)	3,234 (4.1%)	1,017 (1.3%)	8,045 (10.2%)
		p=0.93	p<.001	p<.001	p<.001	p<.001	p<.001
Rural status	Urban	15,672 (12.1%)	7,937 (6.1%)	8,474 (6.5%)	4,991 (3.8%)	1,468 (1.1%)	12,348 (9.5%)
	Rural	2,555 (12.0%)	1,171 (5.5%)	1,438 (6.8%)	626 (2.9%)	178 (0.8%)	1,922 (9.0%)
		p=0.88	p<0.001	p=0.18	p<0.001	p<0.001	p=0.03
Neighbourhood income quintile	1 (lowest)	3,502 (10.1%)	2,014 (5.8%)	2,307 (6.7%)	1,284 (3.7%)	378 (1.1%)	3,110 (9.0%)
	2	3,827 (11.5%)	2,004 (6.0%)	2,138 (6.4%)	1,203 (3.6%)	379 (1.1%)	3,139 (9.5%)
	3	3,672 (12.4%)	1,734 (5.8%)	1,937 (6.5%)	1,099 (3.7%)	324 (1.1%)	2,887 (9.7%)
	4	3,552 (13.1%)	1,705 (6.3%)	1,771 (6.6%)	1,012 (3.7%)	272 (1.0%)	2,576 (9.5%)
	5 (highest)	3,661 (13.8%)	1,639 (6.2%)	1,744 (6.6%)	1,010 (3.8%)	293 (1.1%)	2,543 (9.6%)
		p<0.001	p=0.04	p=0.85	p=0.81	p=0.62	p=0.01
Cancer site	Breast	2,206 (20.4%)	421 (3.9%)	438 (4.1%)	239 (2.2%)	46 (0.4%)	597 (5.5%)
	Colorectal	1,143 (10.6%)	947 (8.8%)	662 (6.1%)	454 (4.2%)	108 (1.0%)	873 (8.1%)
	Lung	3,864 (10.9%)	1,467 (4.1%)	2,377 (6.7%)	1,278 (3.6%)	200 (0.6%)	1,905 (5.4%)
	Other	9,154 (12.0%)	5,579 (7.3%)	5,828 (7.6%)	3,397 (4.4%)	1,192 (1.6%)	9,526 (12.4%)
	Pancreatic	1,116 (11.1%)	509 (5.1%)	398 (4.0%)	156 (1.6%)	76 (0.8%)	636 (6.3%)
	Prostate	780 (9.9%)	202 (2.6%)	232 (3.0%)	107 (1.4%)	25 (0.3%)	755 (9.6%)
		p<.001	p<.001	p<.001	p<.001	p<.001	p<.001

*All p-values from chi-square test

ICU: Intensive care unit

Supplemental Table 4: Number of potentially inappropriate interventions received in last 30 days of life according to patient characteristics

		0 interventions n=28,416	1 intervention n=51,338	2 interventions n=39,426	3+ interventions n=32,438	Unadjusted RR (95% CI)	Adjusted* RR (95% CI)
Age at death	19-44	1,447 (42.0%)	1,408 (40.9%)	464 (13.5%)	127 (3.7%)	1.00	1.00
	45-54	3,915 (42.3%)	3,842 (41.6%)	1,189 (12.9%)	300 (3.2%)	0.98 (0.94, 1.02)	0.97 (0.93, 1.01)
	55-64	10,850 (43.6%)	10,345 (41.5%)	2,950 (11.8%)	764 (3.1%)	0.94 (0.91, 0.98)	0.92 (0.88, 0.96)
	65-74	17,760 (44.8%)	16,325 (41.2%)	4,511 (11.4%)	1,021 (2.6%)	0.91 (0.87, 0.94)	0.88 (0.85, 0.92)
	75-84	21,081 (48.3%)	17,730 (40.6%)	4,044 (9.3%)	767 (1.8%)	0.82 (0.78, 0.85)	0.80 (0.77, 0.83)
	85-94	15,289 (54.6%)	10,846 (38.8%)	1,611 (5.8%)	233 (0.8%)	0.67 (0.64, 0.69)	0.67 (0.64, 0.70)
	95-105	1,787 (63.8%)	896 (32.0%)	106 (3.8%)	10 (0.4%)	0.51 (0.48, 0.55)	0.53 (0.49, 0.57)
Sex	Female	36,566 (50.1%)	28,652 (39.3%)	6,342 (8.7%)	1,355 (1.9%)	0.88 (0.87, 0.89)	0.89 (0.88, 0.90)
	Male	35,563 (45.2%)	32,740 (41.6%)	8,533 (10.8%)	1,867 (2.4%)	1.00	1.00
Rural status	Urban	62,764 (48.3%)	52,679 (40.5%)	12,147 (9.3%)	2,400 (1.8%)	1.00	1.00
	Rural	9,157 (43.1%)	8,584 (40.4%)	2,700 (12.7%)	815 (3.8%)	1.20 (1.18, 1.22)	1.19 (1.17, 1.21)
Neighbourhood income quintile	1 (lowest)	16,111 (46.5%)	14,410 (41.6%)	3,423 (9.9%)	729 (2.1%)	1.00	1.00
	2	15,544 (46.8%)	13,671 (41.2%)	3,305 (10.0%)	677 (2.0%)	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)
	3	14,125 (47.5%)	12,055 (40.6%)	2,885 (9.7%)	660 (2.2%)	0.99 (0.97, 1.00)	0.98 (0.96, 1.00)
	4	13,102 (48.5%)	10,625 (39.3%)	2,708 (10.0%)	582 (2.2%)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)
	5 (highest)	12,963 (48.9%)	10,442 (39.4%)	2,520 (9.5%)	567 (2.1%)	0.96 (0.94, 0.98)	0.96 (0.94, 0.98)
Cancer site	Breast	5,747 (53.2%)	4,096 (37.9%)	820 (7.6%)	145 (1.3%)	0.96 (0.93, 1.00)	0.99 (0.95, 1.03)
	Colorectal	5,570 (51.7%)	4,164 (38.6%)	898 (8.3%)	142 (1.3%)	1.00	1.00
	Lung	16,171 (45.5%)	14,901 (41.9%)	3,697 (10.4%)	783 (2.2%)	1.17 (1.14, 1.20)	1.13 (1.10, 1.16)
	Other	35,572 (46.5%)	31,399 (41.0%)	7,797 (10.2%)	1,805 (2.4%)	1.16 (1.13, 1.19)	1.13 (1.10, 1.16)
	Pancreatic	4,667 (46.4%)	4,007 (39.9%)	1,112 (11.1%)	266 (2.6%)	1.18 (1.14, 1.22)	1.15 (1.12, 1.19)
	Prostate	4,402 (56.0%)	2,825 (35.9%)	551 (7.0%)	81 (1.0%)	0.90 (0.86, 0.93)	0.88 (0.85, 0.92)

RR: relative risk; CI: confidence interval