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NEW PERSISTENT AND CHRONIC OPIOID USE IN CANCER SURVIVORS AFTER CURATIVE INTENT RADIATION

Elena V. Fernández
Virginia Commonwealth University

NEW PERSISTENT AND CHRONIC OPIOID USE IN CANCER SURVIVORS AFTER CURATIVE INTENT RADIATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Pharmacoeconomics and Health Outcomes at Virginia Commonwealth University

by

Elena Valerie Fernández, PharmD
Bachelor of Science in Biochemistry, University of Mary Washington, Fredericksburg, VA, 2012
Doctor of Pharmacy, Virginia Commonwealth University School of Pharmacy, Richmond VA, 2018

Advisor:

Norman V. Carroll, PhD, RPh
Professor of Pharmacoeconomics and Health Outcomes
Department of Pharmacotherapy and Outcomes Science

Committee Members:

Darcy P. Mays, PhD
Associate Professor and Chair
Department of Statistical Sciences and Operations Research

Pramit A. Nadpara, PhD, MS, BPharm
Assistant Professor
Department of Pharmacotherapy and Outcomes Science

Julie A. Patterson, PharmD, PhD
Assistant Professor
Department of Pharmacotherapy and Outcomes Science

Alexander N. Slade, MD, PhD
Radiation Oncology Chief Resident
Department of Radiation Oncology

Virginia Commonwealth University
Richmond, VA
August 2020

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"Greatness is not measured by what a man or woman accomplishes, but by the opposition he or she has overcome to reach his goals."

– Dorothy Height

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List of Abbreviations

AMA	American Medical Association
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CIR	Curative Intent Radiation
COU	Chronic Opioid Use
DEA	Drug Enforcement Administration
DTOU	During Treatment Only Use
EMR	Electronic Medical Record
FDA	Food and Drug Administration
HR	Hour
IMRT	Intensity Modulated Radiation Therapy
IQR	Interquartile Range
JAMA	Journal of the American Medical Association
MMWR	Morbidity and Mortality Weekly Report
MCG	Microgram
MLM	Mixed Linear Model
MRN	Medical Record Number
NPOU	New Persistent Opioid Use
NOU	Never Opioid Use
OME	Oral Morphine Equivalent
OE	Opioid Exposed
ON	Opioid Naïve
OR	Odds Ratio
PDM	Panel Data Model
PMP	Prescription Monitoring Program
POU	Previous Opioid Use
STD	Standard Deviation
TTD	Time to Discontinuation
UDT	Urine Drug Test
UTOE	Unknown Timing of Opioid Exposure
VCC	Virginia Coordinated Care
VCU	Virginia Commonwealth University
1CS	1 Year Cancer Survivors
3CS	3 Year Cancer Survivors
5CS	5 Year Cancer Survivors

ABSTRACT

NEW PERSISTENT AND CHRONIC OPIOID USE IN CANCER SURVIVORS AFTER CURATIVE INTENT RADIATION

By Elena Valerie Fernández, BS, PharmD, PhD Candidate

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University, 2020

Advisor: Norman V. Carroll, PhD, RPh, Professor of Pharmacoeconomics and Health Outcomes, Department of Pharmacotherapy & Outcomes Science

Background: Emerging evidence suggests that as more patients are surviving cancer, new persistent opioid use (no prior exposure to opioids before cancer therapy but requiring opioid prescriptions after curative intent treatment; NPOU) is of greater concern. In patients receiving curative intent radiation (definitive radiation therapy and as treatment for cure; CIR), the extent to which patients develop NPOU or continue opioid use (COU) following CIR is not known. Neither are factors associated with NPOU or COU, opioid doses, or time to discontinuation (TTD) of opioids in 5CS known. **Objectives:** Describe longitudinal trends opioid use in cancer survivors who received CIR, examine the association of NPOU and COU to patient specific factors as well as opioid dose levels and TTD of opioids. **Methods:** Electronic medical record data from individuals receiving CIR for any indication at Virginia Commonwealth University's Massey Cancer Center in the last 11 years was used to create a longitudinal record of the oral morphine equivalent (OME) of prescriptions to determine NPOU and COU. Descriptive statistics as well as incidence, binomial logistic regressions, panel data models, mixed linear models, Kaplan Meyer survival curves and Cox proportional hazard models were used. **Results:** Based on our analysis, 5CS at this institution were prescribed high 30-day average daily OME doses (mean: 94, SD: 131) which increased from late 2009 to 2012, then decreased after 2012. Men, those of white compared to black race, those with public insurance, and patients with additional chemotherapy or no additional surgery appeared to be

prescribed higher 30-day average daily OME doses between 2008 and 2018. Of 5CS who received CIR, 19.7% developed NPOU and 54.8% COU. Head and neck cancer, stage 3 disease, additional chemotherapy, African American race, certain insurance types, and comorbid conditions conferred increased odds of NPOU. Indigent insurance, anxiety, back pain, hypertension, and nicotine use were associated with increased odds of COU. Most 5CS do not utilize opioids long-term before or after CIR. 5CS with opioid prescriptions prior to radiation had sustained daily doses of 68.2 - 68.3 OMEs higher than those without opioid prescriptions. 5CS with public insurance, anxiety, depression, and other drug use were associated with higher average daily OMEs while diabetes and hypertension were associated with lower average daily OMEs. We predict that 5CS that undergo CIR will use at least some level of opioids, on average 4.1 daily OMEs one year after end of radiation. 5CS continue receiving opioid prescriptions for a median of 16.8 months after completion of CIR. Median TTD of opioids was shorter for patients without opioid exposure prior to therapy (NPOU; 13.0 months) compared to patients with opioid exposure prior to therapy (COU; 21.4 months). Factors associated with shorter TTD included NPOU and head and neck cancers. Conversely, additional surgery, death more than five years after diagnosis, as well as alcohol and nicotine use were associated with longer TTD of opioids. **Discussion:** Presence of comorbidities, substance use, and indigent or public insurance were associated with greater opioid burden, use, dose and length of time of opioid use. . Socioeconomic and health differences (African American race, indigent charity insurance, Medicaid, chronic conditions and substance use) in patients receiving CIR also result in increased opioid use, odds of NPOU and COU, opioid dose, and longer TTD of opioids. **Conclusions**: Our results have demonstrated substantial opioid use in cancer survivors. There are currently no evidence-based guidelines for opioid prescribing in cancer survivors. Guidelines to prevent misuse and opioid related deaths are warranted to prevent potential misuse due to high numbers of patients that continue to use opioids long after CIR, risk of NPOU, COU, and high OMEs utilized.

CHAPTER 1: INTRODUCTION

Background and Significance

Five-year survival from cancer diagnosis has increased from less than 50% to a mean of 67% (with a large range based on cancer site) over the last several decades.[1,2] This increase in survival, in part due to improvements in antineoplastic therapy, has led to an increase in both the aggregate number of cancer survivors, but also the duration of time patients spend in the survivorship period. These patients have either experienced cancer-free survival or have managed chronic or intermittent illness without recurrence.[1–3] There are more than 100 types of cancers each with its own treatment options and evidence based guidelines to direct therapy depending on disease severity, location, and provider and patient therapeutic goals.[4]

Approximately 50% of cancer patients will receive radiation therapy as a component of their treatment.[5] Radiation therapy can be used alone and in combination with surgery or chemotherapy. Radiation can be used neoadjuvantly (before surgery to reduce the size of the tumor) or adjuvantly (after surgery). Radiation therapy is widely used in many cancer types including eye, bladder, brain, breast, esophageal, gynecologic, lung, liver, prostate, and skin. Undergoing radiation therapy can subject patients to significant morbidity that can vary by treatment site, with patients treated for head and neck cancer tending to have a significant burden of radiation-related acute and late toxicity.[3,6,7]

Pain management is an important consideration for patients undergoing cancer disease treatment. Opioids are a cornerstone of pain management in patients with cancers, as malignancies themselves can lead to significant pain in addition to pain resulting from invasive surgery, chemotherapy, and radiation.[3,8,9] Additionally, pain management guidelines are lacking for patients nearing the end of life, or for cancers treated with palliative intent.[10–12]

For these reasons, there is a distinct divide in pain management for patients that have cancer versus those who do not. The former are often excluded from most pain studies. Cancer and non-cancer pain is treated differently in the literature and the focus of opioid prescribing guidelines, overuse, misuse, abuse, and adverse consequences leading to death has mostly focused on non-cancer pain.[8,10] In studies that have investigated pain in patients with cancer, it has been documented that pain has been significantly undertreated.[8,13–16] Specifically from 1994 to 2007, a systematic review found 43% of patients with cancer were potentially undertreated for pain.[8,17] Later studies from 2007-2013 suggest lower, but still significant prevalence of undertreatment of pain in 32% of patients.[8,14,17–21]

However, there is growing awareness of opioid use and misuse in patients with cancer.[8,22–26] It has been suggested that opioid utilization patterns (chronic opioid use by total daily dose, dose escalations, and dose reductions) are similar between patients with cancer pain and patients with non-cancer pain although patients were not matched.[27,28] Additionally, in Canada, trends in opioid prescribing in noncancer and cancer patients remained relatively stable between 2004 and 2013.[25] A propensity score matched study published in 2019 reported that respondents with cancer were significantly more likely to use prescription opioids than matched controls (OR: 2.43, 95% CI: 1.68-3.57).[24] One study utilizing validated self-report instruments (the Screener and Opioid Assessment for Patients With Pain (SOAPP), and the Cut Down-Annoyed-Guilty-Eye Opener (CAGE) questionnaire adapted to include drug use (CAGE-AID)) conducted at a single supportive care clinic for patients with cancer found that "men and patients who have anxiety, financial distress, and a prior history of alcoholism/illicit drug use are at increased risk of aberrant opioid and drug use behaviors" and suggests that roughly 20% of patients with cancer are at elevated risk for aberrant opioid and drug use behaviors.[23]

Cancer survivors are an important demographic to consider as opioid use and abuse have reached epidemic proportions in the United States. There are over 200 million opioid prescriptions utilized in the United States annually, but it is not known how many of those are for patients with cancer pain.[29] Per Substance Abuse and Mental Health Services Administration (SAMHSA) in 2015, 11.5 million Americans reported misusing prescription opioids and 1.9 million met diagnostic criteria for prescription opioid abuse.[30] There has also been a surge of opioid deaths from 4,200 in 1999 to 15,300 in 2013 and over 64,000 in 2016.[8,31] Further, three times the number of opioids were prescribed 2015 compared to 1999.[8,31]

For patients with cancer, pain is often managed by the patient's surgical, radiation, or medical oncologist, who may not have optimal training in pain management and palliative care.[32] There is emerging evidence of high rates of opioid misuse (use of opioids contrary to the directed or prescribed pattern of use, regardless of presence or absence of harm) in patients with cancer.[33–38] One study found that 58% of patients with cancer were noncompliant with their prescribed opioid therapy and were more likely to have higher morphine equivalent daily doses.[34] Another study found that more than 50% of urine drug tests (UDT) were abnormal in patients with cancer and the most common opioid findings were absent prescribed opioids (27%) and present unprescribed opioids (25%).[38] A study of 209 emergency department patients with cancer showed depression and illicit substance use were significantly associated with high risk of opioid misuse.[37] Ultimately, an estimated 29% of patients with cancer are at high-risk for misuse.[8,39]

Historically, there are five groups of pain types for patients with cancer: acute cancer-related pain, chronic cancer-related pain, preexisting chronic pain and cancer-related pain, history of drug addiction and cancer-related pain, and end-stage cancer-related pain.[40]

However, there is emerging evidence of a new group of patients with new persistent opioid use, defined as those who were opioid naïve (not exposed to opioids before cancer therapy) and who continue to fill opioid prescriptions beyond six months of curative intent treatment.[41,42] As more patients are surviving cancer, new persistent and continued chronic opioid use are of greater concern, especially as pain in this population is poorly characterized and there is little to no consensus on the therapeutic framework of treating pain for these patients.[21] Recent evidence suggests that cancer-directed therapies (especially surgery and radiation directed to the head and neck) may promote opioid use long after the cancer therapy is concluded.[7,42–44]

Additionally, there is anecdotal evidence that patients having certain cancers may be at higher risk for high opioid use after curative intent radiation (CIR, treatment with intent to cure, which is generally the case for all non-palliative cancer) due to differences in cancer site or demographics.[42] However, it has been suggested that radiation treatment alone is least likely to be associated with opioid use during treatment compared to other treatment modalities (surgery, chemotherapy, combinations).[45] Neither the extent to which cancer survivors who receive CIR develop new persistent opioid use nor what factors may put them at risk for developing new persistent and continued chronic opioid use is known. Understanding the factors associated with developing new persistent and continued chronic opioid use after radiotherapy may help identify patients that may have difficulty weaning off opioid regimens.

Specific Aims

1. In cancer survivors who received curative intent radiation (definitive radiation therapy as treatment for cure; CIR) for their malignancy, describe longitudinal trends in continued opioid use by 30-day average daily oral morphine equivalent (OME) opioid dose
    a. Describe variations over time in 30-day average daily OME dose overall and by cancer type
    b. Describe opioid-related public health initiatives that may have influenced trends in 30-day average daily OME dose over time
2. In cancer survivors who received CIR for their malignancy, examine incidence and characteristics associated with the risk of new persistent and continued chronic opioid use
    a. Identify the rate of new persistent and continued chronic opioid use
    b. Examine the association of new persistent and continued chronic opioid use with radiation specific factors such as modality
    c. Examine the association of new persistent and continued chronic opioid use with radiation specific clinical factors such as disease site, stage, and other treatment modalities (including surgery, chemotherapy, and immune therapy)
    d. Examine the association of new persistent and continued chronic opioid use with other non-radiation specific clinical factors such as disease stage and comorbidities
    e. Examine the association of new persistent and continued chronic opioid use with sociodemographic characteristics such as age, gender, race, and insurance status
    f. Using the significant associations found in prior analyses (2b-e) estimate the risk of continued chronic opioid use and developing new persistent opioid use
3. In cancer survivors who received CIR, examine new persistent opioid use and 30-day average daily OME dose after radiation therapy
    a. Describe 30-day average daily OME dose over time and at one year after CIR
    b. Examine variations in average daily OME dose over time before and after CIR
    c. Predict average daily OME dose between new persistent and continued chronic opioid use in the year following CIR
    d. Describe opioid use by time to discontinuation between new persistent opioid use in the months following CIR
4. In cancer survivors who received CIR for their malignancy, examine health disparities that may exist in sex, race, and socioeconomic status in patients with new persistent opioid use

Systematic Literature Review: Opioid Utilization in Cancer Survivors

Abstract

Background: With advancement of cancer treatment, cancer survivors are an important demographic to consider as opioid use and abuse have reached epidemic proportions in the United States. There has also been an increase in both the aggregate number of cancer survivors and the duration of time patients spend in the survivorship period. Pain management is an important consideration for patients undergoing cancer treatment but patients with cancer are often excluded from most pain studies and guidelines. Therefore, literature about the opioid use landscape in patients with cancer is far less known than for patients without cancer. Objective: To describe opioid utilization within cancer survivors from the literature. Methods: A systematic literature review was conducted in Pubmed/MEDLINE. A total of 80 articles were assessed for inclusion based on cancer survivorship sample and exclusion of narrative articles or main topics of opioid safety, efficacy, outcomes, or dosing. Results: 13 articles were included in this review, all but one article were published in North America and in the last three years. The majority of articles used samples of a specific cancer type or treatment modality. Discussion: A significant number of cancer survivors utilize opioids before, during, and after cancer treatment. Opioid use within cancer survivors appears to vary based on clinical characteristics such as cancer type, comorbid conditions, and treatment modality. Conclusion: Patients with cancer are at risk of high opioid use and certain characteristics such as cancer type or treatment modality may carry increased risk, although literature on the subject is still new. Future studies are needed to identify underlying risk factors for new persistent and chronic opioid use in cancer survivors of all types of cancer.

Background

Pain management is an important consideration for patients undergoing cancer disease treatment. Opioids are a cornerstone of pain management in patients with cancers, as malignancies themselves can lead to significant pain in addition to pain resulting from invasive treatments (surgery), chemotherapy, and radiation.[3,8,9] Additionally, pain management guidelines are lacking for patients nearing the end of life, or for cancers treated with palliative intent.[10–12] There is a distinct divide in pain management for patients that have cancer versus those who do not. The former are often excluded from most pain studies. Cancer and non-cancer pain is treated differently in the literature and the focus of opioid prescribing guidelines, overuse, misuse, abuse, and adverse consequences leading to death has mostly focused on non-cancer pain.[8,10] In studies that have investigated pain in patients with cancer, it has been documented that pain has been significantly undertreated.[8,13–16] Later studies from 2007-2013 suggest lower, but still significant prevalence of undertreatment of pain in 32% (range 4% to 68%) of patients.[8,14,17–21]

There is growing awareness of opioid use and misuse in patients with cancer.[8,22–25] It has been suggested that opioid utilization patterns (chronic opioid use by total daily dose, dose escalations, and dose reductions) are similar between patients with cancer pain and patients with non-cancer pain although patients were not matched.[27,28] A propensity score matched study published in 2019 reported that respondents with cancer were significantly more likely to use prescription opioids than matched controls (OR: 2.43, 95% CI: 1.68-3.57).[24]

Five-year survival from cancer diagnosis has increased from less than 50% to a mean of 67% (with a large range based on cancer site) over the last several decades.[1,2] This increase in survival, in part due to improvements in antineoplastic therapy, has led to an increase in both the aggregate number of cancer survivors, but also the duration of time

patients spend in the survivorship period. Cancer survivors are an important demographic to consider as opioid use and abuse have reached epidemic proportions in the United States. There are over 200 million opioid prescriptions utilized in the United States (US) annually, but it is not known how many of those are for patients with cancer pain.[29] This literature review aims to describe opioid utilization within cancer survivors.

Methods

In order to assess the landscape of opioid use in cancer survivors, a systematic literature review was conducted. Pubmed/MEDLINE was used to extract literature data. A broad search strategy of relevant terms was used to find evidence of opioid use in cancer survivors. The search strategy was as follows: ("Cancer Survivors/classification"[Mesh] OR “cancer survivors” OR “patients with cancer”) AND ("Analgesics, Opioids/administration and dosage"[Mesh] OR "Analgesics, Opioids/adverse effects"[Mesh] OR "Analgesics, Opioids/classification"[Mesh] OR “Analgesics, Opioids/economics"[Mesh] OR "Analgesics, Opioids/organization and administration"[Mesh] OR "Analgesics, Opioids/poisoning"[Mesh] OR "Analgesics, Opioids/standards "[Mesh] OR "Analgesics, Opioids/therapeutic use"[Mesh] OR "Analgesics, Opioids/toxicity"[Mesh] OR “opioid use” OR “opioid prescribing”) AND Humans[Mesh] AND English[lang].

Following PRISMA guidelines for reporting systematic reviews, the search resulted in 62 articles. Articles were also pulled from the reference lists of resulting literature and independent searches of key words (n = 11). A total of 80 articles were then assessed for inclusion and exclusion criteria by examining titles and abstracts (Figure 1.1).[46] Articles were included if they assessed opioid utilization in cancer survivors. Articles were excluded if the

patient population did not have cancer or were in end-of-life care; main topics of excluded articles involved opioid safety, efficacy, outcomes, or dosing; or were narrative articles.

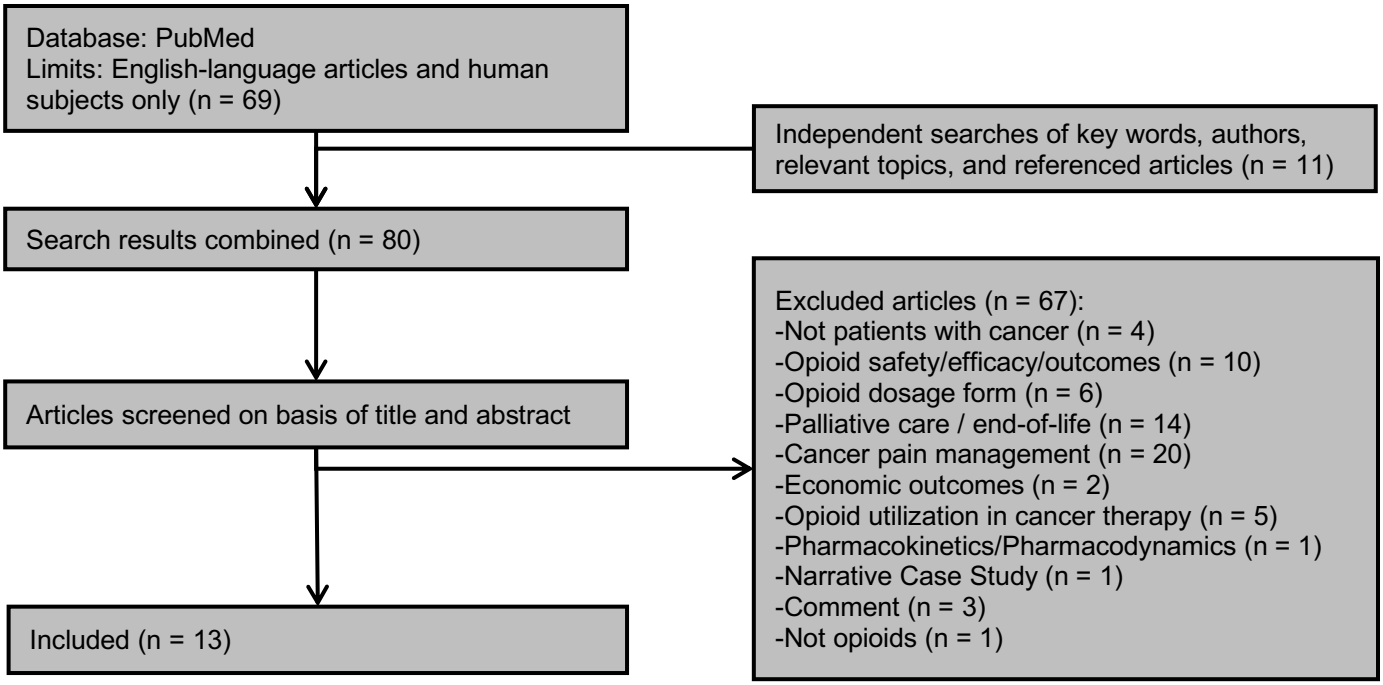

Figure 1.1: Prisma Flow Chart of Opioids in Cancer Survivors Literature Review

Results

The resulting studies with lead author and title are summarized in Table 1.1. Three studies identified in this literature review were conducted outside of the USA. A 2010 retrospective population-wide matched cohort study examined patients 18-64 years of age and more than 5 years after cancer diagnosis in the Ontario Health Insurance Plan and Drug Benefits Program. Results indicated that the opioid prescribing rate was 1.22 times higher among cancer survivors compared to matched controls without cancer.[47] These higher prescribing rates were associated with lower income, younger patients, living in more rural communities, and more comorbidities.[47] Additionally, over the course of the 36 month time frame of the study, the mean cumulative number of opioid prescriptions increased at a higher

rate for cancer survivors over matched controls. This study did not discuss the role of type of treatment.

Another study conducted in Canada utilized linked provincial administrative data from the government funded Pharmacare program from 2010-2015. Patients aged 24 to 70 years with cancer 5 years from diagnosis (index date) were examined to determine the opioid prescription rate.[48] This study found that continuous opioid use between diagnosis and index date was most strongly associated with higher rate of opioid use after index date. Other factors associated with higher rate of opioid use after index date included: opioid use before diagnosis, history of depression, comorbidity, and greater than two years of diabetes. Additionally, there were significant interactions between prior opioid use and opioid use between diagnosis and index date and most prescriptions from family physicians.[48] This study was limited to patients receiving surgery and did not discuss patients receiving radiation for their malignancy treatment.

The last article identified outside of the USA utilized a Norwegian prescription database to determine use of opioids 10 years after cancer diagnosis.[49] In this study, the one year periodic prevalence of any opioid use was higher in long-term cancer survivors than general population, as was the prevalence of persistent opioid use and prevalence of high-dose opioids.[49]

Ten studies were conducted inside the USA. Three of these articles would have been excluded from the review, due to the study population not being cancer survivors. However, these will be discussed due to their pertinence of comparing different treatment modalities. First, Silver et al. examined 198 patients with oropharyngeal cancer who underwent radiotherapy from 2012 to 2017 to assess risk factors for chronic opioid use and effect on overall survival.[43] It was determined that chronic opioid use was observed in 53% of patients

and associations with chronic use included pre-treatment opioid use and presence of a preexisting chronic pain condition at time of diagnosis. Multivariate analysis associations included tumor stage and anxiety/depression. Overall survival was worse for patients who had chronic opioid use, but was not significant when controlled for recurrence.[43] While this study investigated patients receiving radiation, it was limited to oropharyngeal cancer and patients with recurrence, which does not fit the definition of cancer survivors.

Secondly, a retrospective analysis at MD Anderson's supportive care clinic determined that half of patients who received definitive chemoradiotherapy for head and neck cancer were unable to discontinue their prescribed opioids.[6] While this study involved radiation as definitive cancer treatment, patients were limited to head and neck cancers and to those whose pain medications were managed by palliative care specialists, rather than their treating oncologists.

Third, electronic health records of 750 palliative care clinic patients at MD Anderson Cancer Center were reviewed between 2010 to 2015 for changes in type and dose of opioid prescriptions.[50] This study showed a decrease in median morphine equivalent daily dose from 78 mg per day (IQR: 30-150) in 2010 to 40 mg per day (IQR: 19-80) in 2015. However, morphine equivalent daily dose remained higher for males, those of white race, and a positive Cut-down, Annoyed, Guilty, Eye-opener (CAGE) questionnaire score for alcoholism. Additionally, this study identified hydrocodone as the most commonly prescribed opioid followed by oxycodone and transdermal fentanyl.[50]

The remaining seven articles were determined to be the most relevant articles for this research. Salz et al. conducted a Surveillance, Epidemiology and End Results (SEER) Medicare multilevel logistic regression analysis for chronic opioid use among opioid-naïve survivors of colorectal, lung, and breast cancers diagnosed from 2008 to 2013 with matched non-cancer controls.[51] In this study, one year after a survivor's diagnosis date, chronic opioid

use among lung and colorectal cancer survivors exceeded controls, but differences between survivors and controls declined each year for six years after diagnosis. Conversely, the rate of chronic opioid use among breast cancer survivors was lower than that of controls, suggesting that type of cancer was driving at least part of this relationship. On the whole, however, cancer survivors with chronic opioid use were more likely to have a higher daily dose of opioids than controls.[51] This study only examined opioid use of patients with colorectal, lung, and breast cancers and did not discriminate based on cancer treatment modality.

A cohort study from Kaiser Permanente Washington of 4,216 women greater or equal to 18 years, diagnosed with stage 1 or 2 breast cancer between January 1, 1990, and December 31, 2008 was conducted to estimate the association between chronic opioid use and risk of second breast cancer events.[52] Women in this study were considered chronic opioid users if, after 6 months from when they first accumulated 75 days of opioid possession in a 90-day window, they remained exposed to opioid therapy through follow up or the end of the study.[52] Cox proportional hazards models determined that the risk of second breast cancer events was not significantly higher among chronic opioid users versus non-chronic opioid users.[52] While the primary objective was to assess second breast cancer events, almost 10% of patients met the criteria for chronic use and almost a third of users were taking opioids for greater than 3 years.[52] This study was limited to patients with breast cancer before the surge of opioid deaths in 2016 and did not account for radiation.

Lee et al. conducted a Truven MarketScan database analysis in opioid naïve patients with cancer undergoing curative surgical treatment.[41] This study determined that 10% of these patients develop new persistent opioid use that required 30 mg or more of hydrocodone daily, which is similar to doses with chronic opioid use. Additionally, of those with new persistent opioid use, patients receiving adjuvant chemotherapy for any cancer investigated (breast,

melanoma, colorectal, gastric, thoracic) utilized higher doses of opioids than those that did not receive chemotherapy or those that received neoadjuvant chemotherapy.[41] Lee et al. did not investigate these effects in patients receiving radiation.

In a study of 311 opioid naive patients that received curative intent radiation (CIR) at the Icahn School of Medicine at Mount Sinai for head and neck cancers between January 1, 2011 and September 1, 2017, 12.9% continued to use opioids 6 months following radiation therapy.[42] In multivariable analysis, delivery of induction chemotherapy (OR 2.86, CI (95%) 1.32–6.21) and alcohol abuse (OR 3.75, CI (95%) 1.66–8.47) were statistically significant risk factors for prolonged opioid use.[42] Univariate analysis found various other positive associations with prolonged opioid use including current smoking, radiation therapy dose, concurrent chemotherapy, and daily milligram morphine equivalents, whereas prior surgery was negatively associated.[42] While this article most closely attempts to answer our research question, patients were only included if they were opioid naïve and received radiation for head and neck cancer.

A study published in 2019 of 976 Medicare patients from the Surveillance, Epidemiology and End Results (SEER)- Medicare database with non-distant metastatic head and neck cancer were evaluated for risk of acute and chronic opioid use. This study determined that patients were least likely to use opioids during therapy with radiation alone in comparison to other treatment modalities. Additionally, multivariable logistic analyses determined that tobacco use (OR 3.84, CI (95%) 1.44-10.24) and opioids prescribed prior to treatment (OR 3.56, CI (95%) 1.95-6.50) resulted in increased risk of opioid use six months following treatment.[45] This study suggests that patients with head and neck cancer are at high risk for opioid use, however the study did not evaluate other cancers and did not find statistical

differences in opioid use at 3 or 6 months based on treatment type (chemotherapy, surgery, radiation).[45]

Schumacher et al. did investigate long term use of opioids from electronic medical record data between 2013 and 2017 at a single institution in 276 head/neck cancer patients one year after CIR and found that 7.2% of patients developed long-term opioid use.[53] However, this study only evaluated opioid use status at one year of follow-up, which may not constitute cancer survivorship and the authors did not evaluate prior to therapy opioid use and thus could not differentiate between chronic and new persistent use of opioids post CIR.[53]

Another study at a single institution investigated continued use of opioids in 199 patients diagnosed with any cancer after curative intent therapy over a 3 year period.[54] Cass et al. reported that 38% of patients continued to receive opioid prescriptions with an average of 4.8 prescriptions per patient of mean milli morphine equivalents per prescription of 319 mg over an average of 9.5 months following curative intent therapy.[54] Additionally, from logistic regression, patients who received chemotherapy (OR: 7.25; 95% CI: 2.09-25.17), used pain-modifying medications (OR, 4.61; 95% CI, 2.25-9.44), and had lower stages of cancers (compared to stage 3) (Stage 0 - OR: 13.5; 95% CI: 2.07- 88.07) (stage 1- OR: 4.01; 95% CI: 1.26-12.79) (stage 2 - OR, 4.05; 95% CI: 1.26-13.06) were significantly more likely to continue to receive prescriptions for opioids and continue opioid use long-term.[54]

Table 1.1: Summary of Literature Review Articles

	Authors	Title
1	Sutradhar et al. (2017)[47]	Cancer survivorship and opioid prescribing rates: A population-based matched cohort study among individuals with and without a history of cancer
2	Barbera et al. (2019)[48]	Factors associated with opioid use in long-term cancer survivors
3	Fredheim et al. (2019)[49]	A complete national cohort study of prescriptions of analgesics and benzodiazepines to cancer survivors in Norway
4	Silver et al. (2019)[43]	Chronic opioid use in patients undergoing treatment for oropharyngeal cancer
5	Kwon et al. (2013)[6]	Predictors of long-term opioid treatment among patients who receive chemoradiation for head and neck cancer

6	Haider et al. (2017)[50]	Opioid prescription trends among patients with cancer referred to outpatient palliative care over a 6-year period
7	Salz et al. (2019) [51]	Trends in opioid use among older survivors of colorectal, lung, and breast cancers
8	Boudreau et al. (2019)[52]	Risk of second breast cancer events with chronic opioid use in breast cancer survivors
9	Lee et al. (2017)[41]	New persistent opioid use among patients with cancer after curative-intent surgery
10	Smith et al. (2019)[42]	Risk of prolonged opioid use among cancer patients undergoing curative intent radiation therapy for head and neck malignancies
11	McDermott et al. (2019)[45]	Short- and long-term opioid use in patients with oral and oropharynx cancer
12	Schumacher et al. (2019)[53]	Long-term opioid use in curative-intent radiotherapy: One-year outcomes in head/neck cancer patients
13	Cass et al. (2018)[54]	Analysis of opioid use following curative cancer treatment at a large urban safety-net hospital

Discussion

This systematic literature review reports that there are a significant number of cancer survivors that heavily utilize opioids, even long after cancer therapy, compared to the general population.[6,41–43,45,47–49,51,53,54] Additionally, it is suggested that half of patients that use opioids during cancer treatment have difficulty or do not stop opioid use.[50]

Opioid use in cancer survivors seems to vary based on cancer type or location. This may be due to variations in how caustic various cancer are, or that a majority of the studies presented focus on one or few cancer types (breast, head and neck, colorectal, lung, melanoma, gastric, thoracic). Studies that utilized samples with varied cancer types suggest that type of cancer may play a role in the relationship of opioid use in cancer survivorship.[41,45,47,51] From the presented studies, five focused solely on head and neck cancers, which may have the highest observed pain burden and ultimately greatest risk for continued opioid use, but this was not conclusive from the articles presented.

Articles presented in this review suggest that various patient clinical characteristics increase risk of opioid use. Comorbid conditions such as pre-existing chronic pain conditions, anxiety, depression, alcohol and tobacco use as well as status cancer/tumor stage and pre-

treatment of opioids were reported to increase risk of chronic opioid utilization. Additionally, treatment modality may be associated with increased opioid utilization in cancer survivors post treatment, but several of the studies reported in this review did not differentiate by treatment modality, or isolated their patient sample by specific treatment modality (i.e. only surgery patients).[41,47,48,51,53]

In this review, we described three articles that compared opioid use in patients with cancer receiving palliative treatment and varying cancer treatment modalities.[6,43,50] Palliative care patients may experience more pain than those without advanced disease, and may receive higher doses of opioids to manage their pain.[21] The purpose of this review was to address opioid use within cancer survivors, however these studies shed light on differences in opioid use with different treatment modalities.

Lastly, while this study was not limited to patient samples from the United States, the majority of studies presented were conducted in North America with only one article from Europe. This may be due to higher attention to this topic in the United States.[55] However, there was some evidence that as attention to opioid use has increased, opioid dosage may be decreasing over time.[50]

A major limitation of this review is that any research conducted in this area is recent, as all of the articles cited in this review were published in the last six years, and all but one in the last three years. Several of the studies presented focused on one type of cancer treatment or one treatment modality. To date, there is not a study that establishes risk of new persistent opioid use in cancer survivors of different treatment modalities and cancer types. Another limitation of this review is that several articles were conducted at single institutions that may not be representative of cancer treatment in the general population.[6,42,50,54] Lastly, several

studies reported utilizing medical record prescription data rather than pharmacy claims data. This could result in an overestimation of opioid use in cancer survivors.[48,53]

Conclusion

Patients with cancer are at risk of developing new persistent and continued chronic opioid use behaviors, although has not been studied well and literature on the topic is only 3 years old. Opioid use in several cancer types such as head and neck are better studied than others. Even less studied is the potential for patients with cancer to develop new-persistent opioid use. Future studies are needed to identify underlying risk factors for new persistent and chronic opioid use in cancer survivors of any type of cancer.

Human Subjects Research

This research was approved under the VCU IRB: HM20014385. In order to ensure the protection of human subjects as well as data safety, the following steps were taken. First, results were, or will be, only disseminated in aggregate; no identifiable information was or will be disseminated. In order to de-identify the data, medical record number (MRN) and treatment data were extracted from the VCU ARIA database, cancer registry, relevant data from the Cerner database (clinical and demographic information), and merged. After pharmacy data, clinical data from radiation treatment records, and clinical data from the registry were extracted, combined, and merged by the researchers, a randomly generated key code was used in lieu of the patient's medical record number to identify individuals in the data. A key file linking the randomly generated key code to the MRNs was stored in a different computer than the primary database, and the key file was kept in a password protected file. Original identifying information was stripped from the primary database. Only those conducting the analysis had access to the data after de-identification.

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CHAPTER 2: LONGITUDINAL OPIOID PRESCRIPTION USE IN PATIENTS WITH CANCER RECEIVING RADIOTHERAPY FROM 2008 TO 2018 AT A SINGLE CANCER CENTER

Abstract

Background: Cancer survivors receiving potentially caustic radiation for their malignancies are an important demographic to consider as opioid use and abuse have reached epidemic proportions in the United States. Objective: This study described opioid prescriptions overall, and by various subgroups, from 2008-2018 prescribed at a single cancer center. Methods: A retrospective longitudinal analysis of opioid prescriptions by oral morphine equivalent (OME) doses in cancer survivors overall, and by subgroups of cancer type, additional cancer therapy (chemotherapy or surgery), opioid medication, and basic demographic information (sex, race, insurance type) was conducted. Results: Overall, there was an increase in 30-day average daily OME dose prescribing from late 2009 to 2012, which decreased after 2012. Men, those of white compared to black race, and patients with additional chemotherapy or no additional surgery appeared to be prescribed higher 30-day average daily OME doses between 2008 and 2018. Discussion: This study suggests that patients with cancer at this institution received higher rates of opioid prescriptions per patient and 30-day average daily OME doses than in the general American, non-cancer public. Changes in opioid prescribing over the course of the study could be due to addressing under treatment of cancer pain (until 2012) or from various public health or institution-specific initiatives to decrease opioid use (after 2012). This was the first study to describe patient characteristics that result in differences in the 30-day average daily OME doses in patients with cancer receiving radiation in the last decade. Conclusion: Opioid prescription use for patients with cancer receiving radiation followed similar trends, but showed higher per patient prescriptions and 30-day average daily OME dose quantities,

compared to other previously reported trends in patients without cancer and outside of the United States.

Background

Five-year survival from cancer diagnosis has increased from less than 50% to a mean of 67% (with a large range based on cancer site) over the last several decades.[1,2] This improvement in survival has led to an increase in both the aggregate number of cancer survivors and the duration of time patients spend in the survivorship period. Consequently, long-term management of this population is of increasing concern.

Approximately 50% of patients with cancer will receive radiation therapy as a component of their treatment.[3] Undergoing radiation therapy can subject patients to significant morbidity that can vary by treatment site, with patients treated for head and neck cancer tending to have a significant burden of radiation-related acute and late toxicity.[4,5] Therefore, opioid use for pain management is a mainstay of cancer treatment regimens. It has been suggested that curative intent radiation (CIR) treatment alone is least likely to be associated with opioid use compared to other treatment modalities (surgery, chemotherapy, combinations), but, certain cancers may be at higher risk for high opioid use after CIR.[6,7] Notably, pain is generally managed by the patient's surgical, radiation, or medical oncologist, who may not have optimal training in pain management and palliative care.[8]

Cancer and non-cancer pain are treated differently in the literature. Opioid prescribing guidelines and discussions of overuse, misuse, abuse, and adverse consequences leading to death have been focused on patients treated for non-cancer pain.[9,10] Pain has been significantly under treated in studies that have investigated treatment patterns in patients with cancer.[9,11–14] Specifically, from 1994 to 2007, a systematic review found that 43% of patients

with cancer were potentially under treated for pain.[9,15] Later studies from 2007-2013 suggest a lower, but still significant prevalence of under treatment of pain in 32% of patients.[9,12,15–19] At the same time, opioid use and misuse has been increasingly characterized in patients with cancer.[9,20–23]

There are over 200 million opioid prescriptions utilized in the United States annually, but it is not known how many of those are for patients with cancer pain.[24] Further, three times the number of opioids were prescribed 2015 compared to 1999.[9,25] Two studies have suggested that opioid utilization patterns are similar between patients with cancer pain and patients with non-cancer pain, although patients were not matched.[26,27] In Canada, trends in opioid prescribing in non-cancer and cancer patients remained relatively stable between 2004 and 2013, although opioid prescription rates were consistently higher for patients with cancer.[23] A propensity score matched study published in 2019 reported that respondents with cancer were significantly more likely to use prescription opioids than matched controls (OR: 2.43, 95% CI: 1.68-3.57).[22] There is also emerging evidence of high rates of opioid misuse in patients with cancer.[28–33] Ultimately, an estimated 29% of patients with cancer are at high-risk for misuse.[9,34]

Cancer survivors are an important demographic to consider given substantial opioid use and the increase in survivorship that has transformed many cancers into chronic diseases. The objective of this study is to describe opioid prescription use overall and by various demographics including cancer type, gender, race, ethnicity, and primary insurance payer from 2008-2018 at a single cancer center. The objectives of this study are to address Specific Aim 1 (Table 2.1), which includes describing longitudinal trends and public health initiatives that may have influenced trends in continued opioid use in cancer survivors who received CIR.

Table 2.1: Methods for Specific Aim 1

Specific Aim 1		
In cancer survivors who received curative intent radiation therapy (treatment for cure) for their malignancy, describe longitudinal trends in continued opioid use by 30-day average daily oral morphine equivalent (OME) opioid dose		Method
1a	Describe variations over time in 30-day average daily OME dose overall and by cancer type	Descriptive time series
1b	Describe opioid-related public health initiatives that may have influenced trends in 30-day average daily OME dose over time	Descriptive time series

Methods

A retrospective longitudinal analysis of chronic opioid prescription use in individuals classified as cancer survivors (no death within 5 years, no recurrence of disease within 5 years, or no presence of metastatic disease; 5CS) who received first-line radiation treatment at Virginia Commonwealth University Massey Cancer Center for a cancer diagnosis between January 1, 2008 and December 31, 2018 was conducted. Electronic medical record data from patients 18 years of age or older with any cancer type and stage receiving radiation with or without additional treatment modalities (surgery, chemotherapy) and at least a 14-day supply of opioids were included. Prisoners were excluded. Additionally, patients receiving radioisotopes or radium as their primary radiation therapy were excluded. Data on cancer type, medications, and basic demographic information (e.g. sex, race, ethnicity and insurance status) were used. Descriptive statistics and graphical analysis were conducted using Stata v15.1 and Microsoft Excel.

Opioid Prescription Equivalencies

Medication prescribing data was coded to create a monthly longitudinal record of the average daily oral morphine equivalent (OME) dose for each opioid prescription and then average OME dose of prescriptions per month by the following equation to create comparable OME dose based on established conversion factors (Table 2.2):

$$Daily\ OME = Medication\ Milligram\ (Mg)\ Strength \times Number\ of\ Doses \times Daily\ Frequency \times OME\ Conversion\ Factor\ (Table\ 2.2)$$

Daily OME dose was averaged for all prescriptions written in the same month overall for 30-day average daily OME dose, as well as monthly by various subgroups. Due to the differing approach to pain treatment acutely, inpatient opioids were excluded. Additionally, this study's objective was to investigate long-term opioid use, therefore, only prescriptions written for greater than a 14-day supply were included. Prescriptions from five patients were removed from the analysis for presumption of outliers due to their calculated OME dosages being far greater than upper quartile plus 1.5 the interquartile range.[35]

Table 2.2: Opioid Dose Oral Morphine Equivalencies[36]

Opioid (strength in mg except where noted)	OME Conversion Factor
Buprenorphine, transdermal patch (MCG/HR)	N/A
Buprenorphine, tablet and film	N/A
Buprenorphine, film (MCG)	N/A
Butorphanol	7
Codeine	0.15
Dihydrocodeine	0.25
Fentanyl, buccal/SL tablet or lozenge/troche (MCG)	0.13
Fentanyl, film or oral spray (MCG)	0.18
Fentanyl, nasal spray (MCG)	0.16
Fentanyl, transdermal patch (MCG/HR)	7.2
Hydrocodone	1
Hydromorphone	4
Levomethadyl acetate	8
Levorphanol tartrate	11
Meperidine	0.1
Methadone	3
Morphine	1
Opium	1
Oxycodone	1.5
Oxymorphone	3
Pentazocine	0.37
Tapentadol	0.4
Tramadol	0.1

Patient Subgroups

Patients were sub-grouped based on cancer type, additional cancer therapy (chemotherapy or surgery), type of opioid medication, and basic demographic information (sex, insurance type). It was expected that patients would have different 30-day average daily OME doses for different cancer types due to varying cancer treatment algorithms and evidence-based guidelines (i.e. surgery or chemotherapy). Once OME dose was averaged monthly and by patient subgroups, 30-day average daily OME dose was plotted over time. Trends were described and were compared to opioid-related public health initiatives that may have provided external influences on longitudinal trends.

Results

Summary statistics for all opioid prescriptions each year after exclusion criteria were applied are presented in Table 2.3. Summary statistics for individual prescription daily OME doses are presented in Table 2.4. Of the opioid prescriptions in the sample, there were 3,791 unique patients who received radiation and outpatient opioid prescriptions with a greater than 14-day supply. An average of 2.7 prescriptions per patient (standard deviation: 6.7 prescriptions, median: 1 prescription, range 1-79 prescriptions, interquartile range: 0) were written for these patients. There were 10,352 unique outpatient opioid prescriptions, of which 4,186 had sufficient data to calculate a daily OME dose.

Table 2.3: Summary Statistics of Opioid Prescriptions by Year

Year	Number of Newly Diagnosed Patients	Total Rx Prescribed	Mean Rxs per Patient	Standard Deviation of Rxs per Patient	Median Rxs per Patient	IQR	Range
2008	352	42	2.1	1.8	1	1.3	1-7
2009	414	354	3.5	3.8	2	3	1-18
2010	415	595	5.3	6.2	2	6	1-29
2011	377	748	4.3	5.6	2	3	1-27
2012	378	829	3.5	4.3	2	3	1-30
2013	383	732	3.4	5.0	1	2	1-35

2014	379	715	3.0	3.4	1	2	1-17
2015	383	892	3.6	4.4	2	3	1-27
2016	485	947	3.6	4.5	2	3	1-34
2017	483	1073	3.7	4.5	2	3	1-25
2018	74	802	4.6	5.4	2	5	1-29

Rxs: Prescriptions; IQR: Interquartile Range

Table 2.4: Summary Statistics of Opioid Prescription Daily OME Dose

N	Range	Mean	Standard Deviation	Median	Interquartile Range
4,186	2-1440	94	131	60	60

Overall 30-Day Average Daily OME Dose Over Time

Figure 2.1 presents 30-day average daily OME doses per month that were plotted over 11 years from 2008-2018. Overall, 30-day average daily OME dose increased from 2008 to 2011, at which point 30-day average daily OME dose peaked in 2012 and then decreased gradually over the remaining course of the study. In addition to 30-day average daily OME dose decreasing after 2012, the variation in 30-day average daily OME dose also gradually decreased.

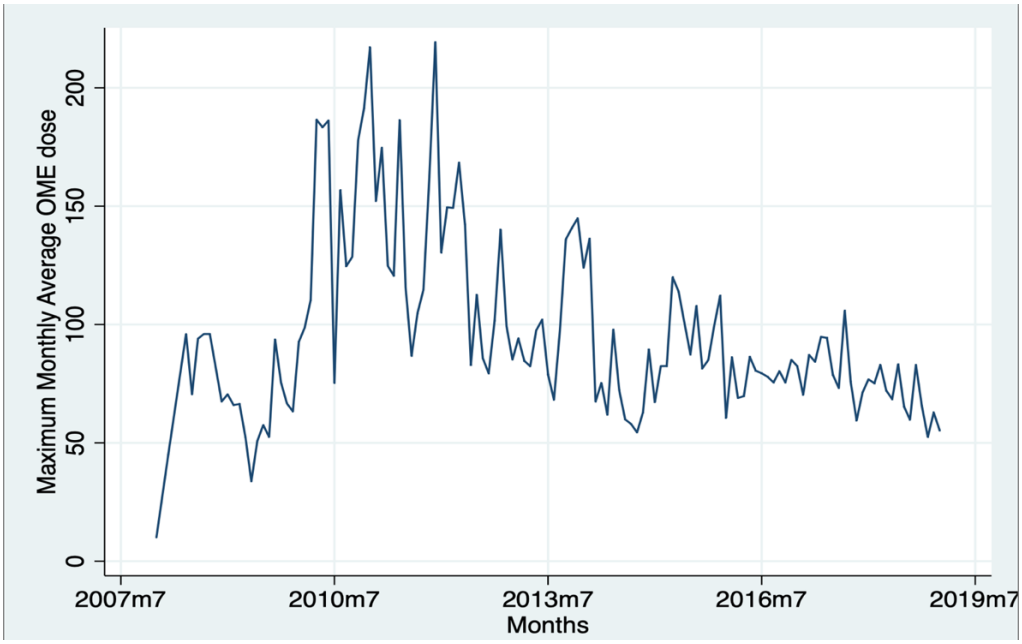

Figure 2.1: 30-Day Average Daily OME Dose for 5CS from 2008-2018. Months on x-axis are in chronological order (i.e. m7 = July).

Subgroup Analyses

The first subgroup analysis indicates that (Figure 2.2a: gender) males and females generally follow similar trends for the overall 30-day average daily OME dose prescriptions. For both males and females, 30-day average daily OME doses initially increase and then decrease or plateau with decreasing variability. However, it appears that males were prescribed much higher overall 30-day average daily OME doses with greater variation in overall 30-day average daily OME dose than for females until around 2016. Female 30-day average daily OME dose peaked between 2009 and 2010, and after 2011, the OME dose remained relatively stable.

The sample included 1,329 African American patients with a total of 4,369 prescriptions, of which 1,814 had a calculated OME dose. There were 2,389 white patients with a total of 5,530 prescriptions, of which 2,204 had a calculated OME dose. These two groups made up the majority of the sample (Figure 2.2b.). There were only 168 patients of other races/ethnicities with 453 total prescriptions and 168 calculated OME doses (Figure 2.2bi). Over the 10 years of data, white patients were generally prescribed higher 30-day average daily OME doses compared to African American patients, but the 30-day average daily OME doses for white and African American patients converge over time as the variation in dose decreases.

Notably, and upon further review, there was one patient that identified as multiracial that caused the “other” patient group to have extremely high 30-day average daily OME dose between 2010 and 2012 (Figure 2.2b). Also, in mid 2012, there may have been a change in the electronic medical record documentation options for race to include ethnicity. Figure 2.2b shows that patient inclusion in the “Other” group ends in mid 2012, while patient inclusion in a group of “Other of Hispanic or Latino or Spanish Origin” begins around that time.

Figure 2.2c shows that, unsurprisingly, laryngeal cancer resulted in the highest 30-day average daily OME doses over time as head and neck cancers are notoriously caustic. Of the 4,186 prescriptions with calculated daily OME dose, almost 25% were written for patients with breast cancer (n = 1,037). For these prescriptions, Figure 2.2c shows that 30-day average daily OME dose was high and highly variable before 2012, then subsequently leveled off after 2012. Lung and bronchial cancers (n = 359 prescriptions with calculated daily OME dose) followed the trend seen in breast cancer 30-day average daily OME doses, with a high 30-day average daily OME dose in the first half of the study followed by a leveling off at lower 30-day average daily OME doses.

A majority of opioid prescriptions were written for patients receiving additional treatment modalities. Of the opioid prescriptions written, 72% were for patients that received additional chemotherapy and 51% that received additional definitive surgery. Unsurprisingly, over the course of this study, patients receiving additional chemotherapy were prescribed higher 30-day average daily OME doses than those that did not receive chemotherapy (Figure 2.2d). This is most likely due to the caustic nature of multiple rounds of chemotherapy. Notably, at the end of 2013, there was a spike in 30-day average daily OME dose for patients that did not receive chemotherapy. Upon further review, two individual patients contributed to excessively high daily OME dose at this time. On the other hand, patients who received additional definitive surgery were prescribed consistently lower 30-day average daily OME doses (Figure 2.2e). Additionally, the trend in 30-day average daily OME dose for patients that received additional definitive surgery follows very closely to what is seen in the 30-day average daily OME dose overall.

Of the prescribed medications, oxycodone was by far the most commonly prescribed in patients with complete information (n = 2,600 prescriptions with calculated daily OME doses).

In general, 30-day average daily OME doses for oxycodone had less variation than other medications in the 11 years studied, although 30-day average daily OME doses were higher towards the beginning of the study (Figure 2.2f). For the next most commonly prescribed medication with complete information, morphine (n = 571 prescriptions with calculated daily OME doses), 30-day average daily OME doses were high and highly variable throughout the course of the study. Tramadol (n = 451 prescriptions with calculated daily OME doses), a less potent opioid, had consistently low 30-day average daily OME doses throughout the course of the study. For ease of visualization, these three medications (oxycodone, morphine, and tramadol) were plotted separately in Figure 2.2fi. Interestingly, hydromorphone 30-day average daily OME doses were high before 2013, and after 2013 dramatically decreased and remained stable. On the other hand, methadone 30-day average daily OME doses dramatically increased after 2013. For ease of visualization, hydromorphone and methadone were plotted separately in Figure 2.2fii. Unfortunately, while widely prescribed, fentanyl and hydrocodone prescriptions were almost all missing at least one essential variable to accurately calculate a daily OME dose (98.3% and 99.7%, respectively) and we were thus not able to describe 30-day average daily OME doses over time for these medications.

Lastly, prescriptions were sub-grouped by primary payer to observe variations of 30-day average daily OME doses by insurance. Before 2014, there were large 30-day average daily OME doses with large variations for all insurance types, except commercial and Medicare (Figure 2.2g). Commercial and Medicare 30-day average daily OME doses were relatively stable across the study time, except for a single peak in late 2013 and early 2014 in the Medicare subgroup. The remaining insurance types (indigent, Medicaid, insurance that was not specified, and self-paid) were relatively stable despite having moderate variations after 2014. Of all of the insurance types, commercial insurance and patients who paid out of pocket

(self-pay) consistently had lower prescribed 30-day average daily OME doses. Because the results from individual insurance types were complex, groups were divided into Public (Indigent, Military, Medicaid, and Medicare) or Private (commercial and self-pay) options based on the payer (Figure 2.2gi). Patients with public insurance were generally prescribed higher 30-day average daily OME doses. However, a similar trend was seen in public versus private insurance as for white and African American patients, where 30-day average daily OME doses converge over time as the variation decreases.

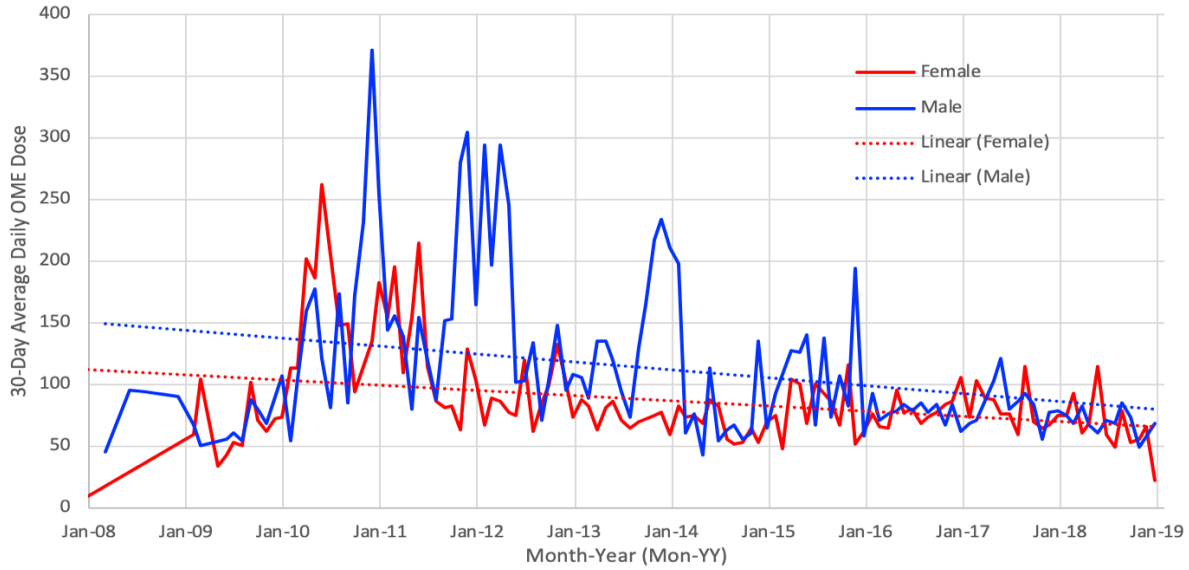

Figure 2.2a: 30-Day Average Daily OME Dose by Gender from 2008-2018

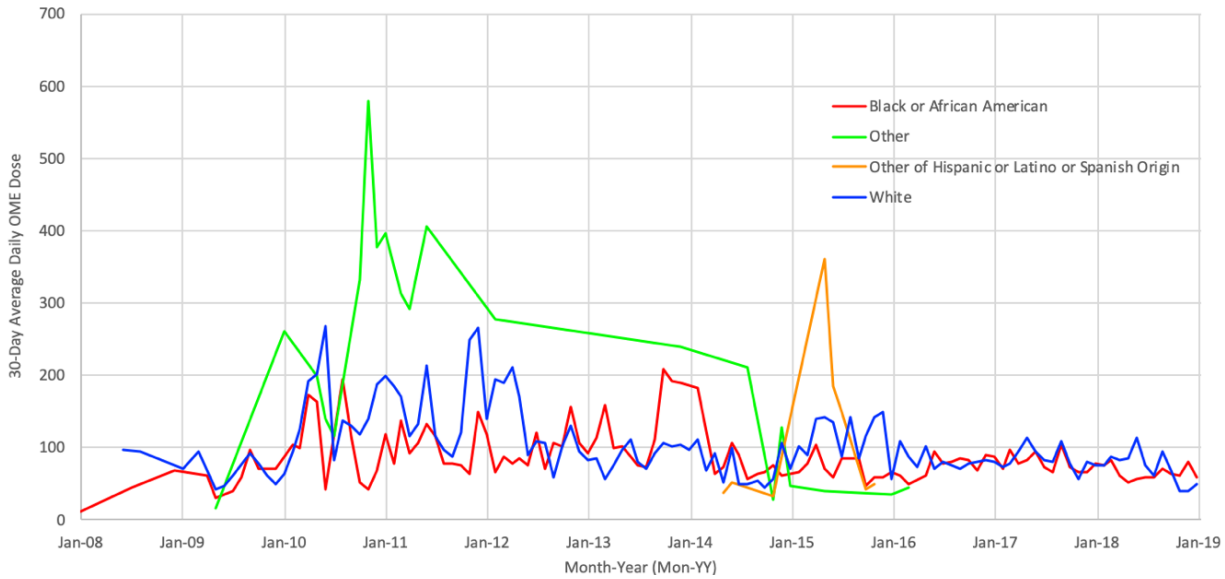

Figure 2.2b: 30-Day Average Daily OME Dose by Race from 2008-2018

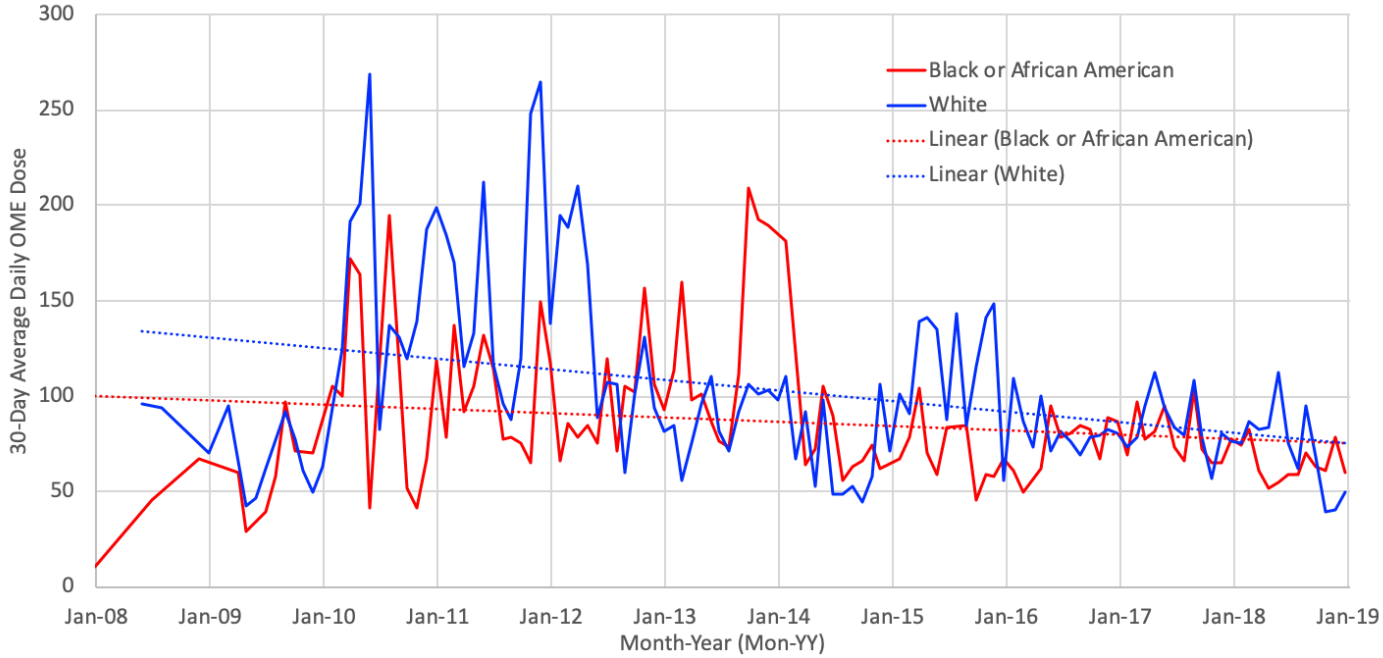

Figure 2.2bi: 30-Day Average Daily OME Dose by Race from 2008-2018 (Black or African American and White only)

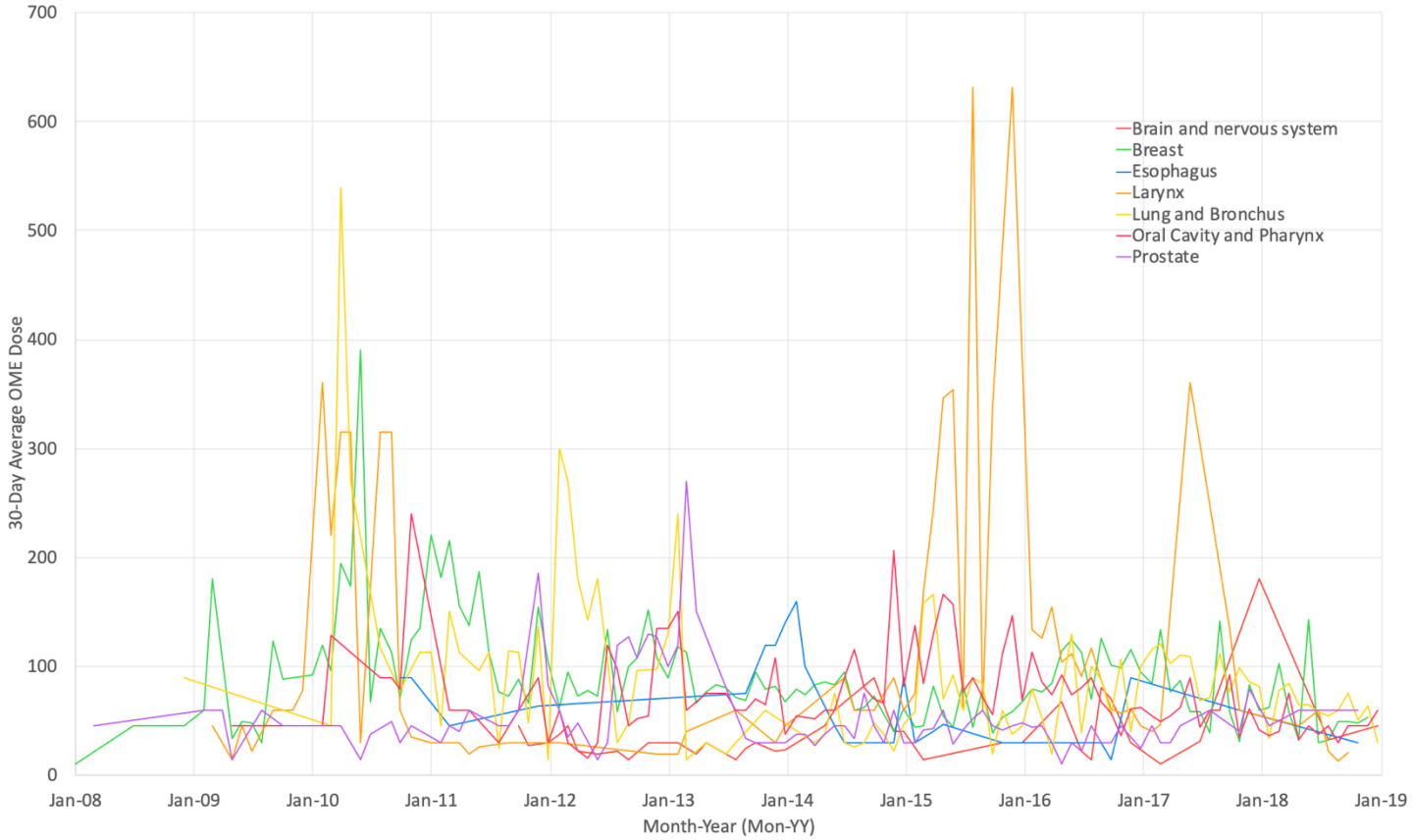

Figure 2.2c: 30-Day Average Daily OME Dose by Cancer Type from 2008-2018

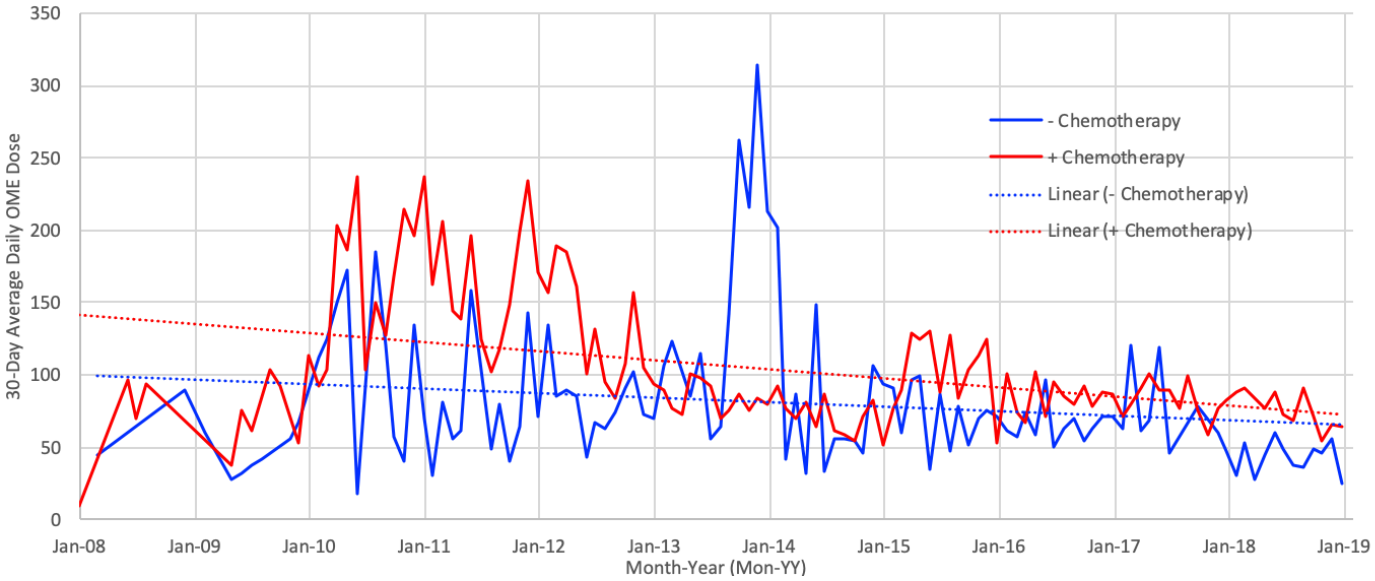

Figure 2.2d: 30-Day Average Daily OME Dose by Additional Chemotherapy from 2008-2018

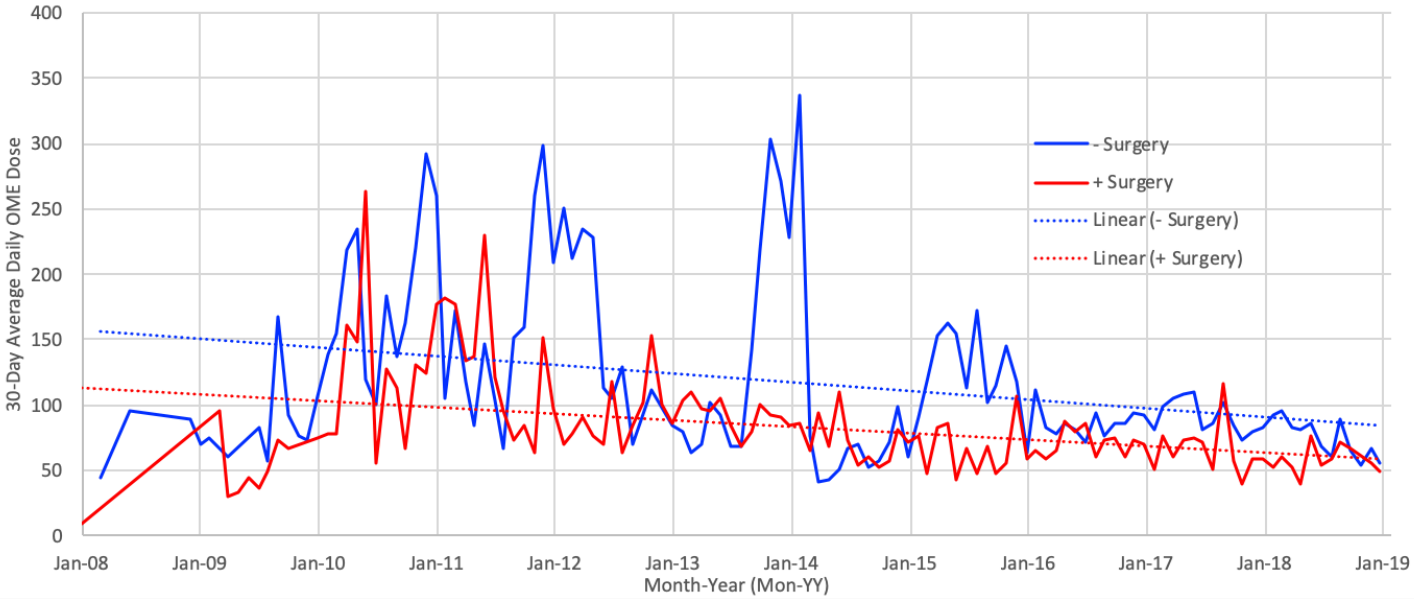

Figure 2.2e: 30-Day Average Daily OME Dose by Additional Definitive Surgery from 2008-2018

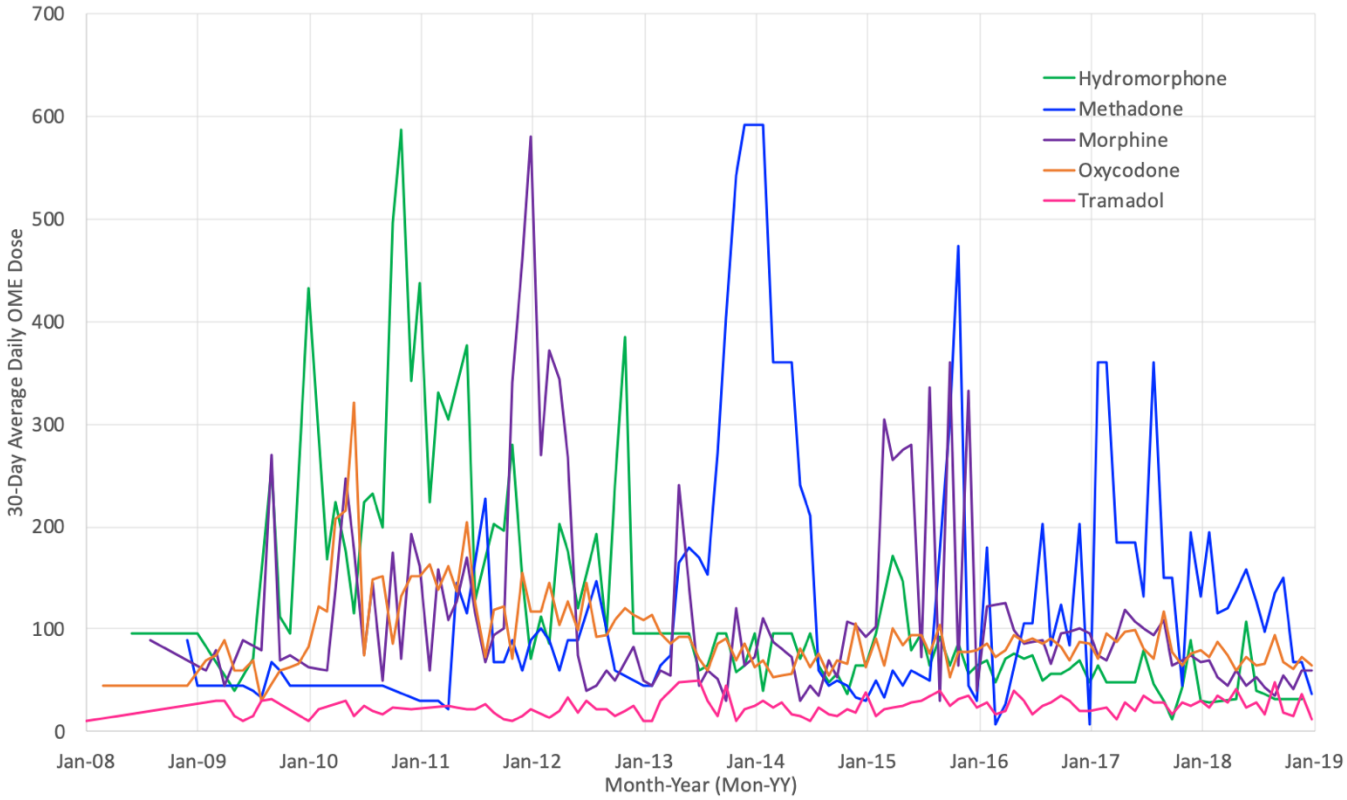

Figure 2.2f: 30-Day Average Daily OME Dose by Opioid Medication from 2008-2018

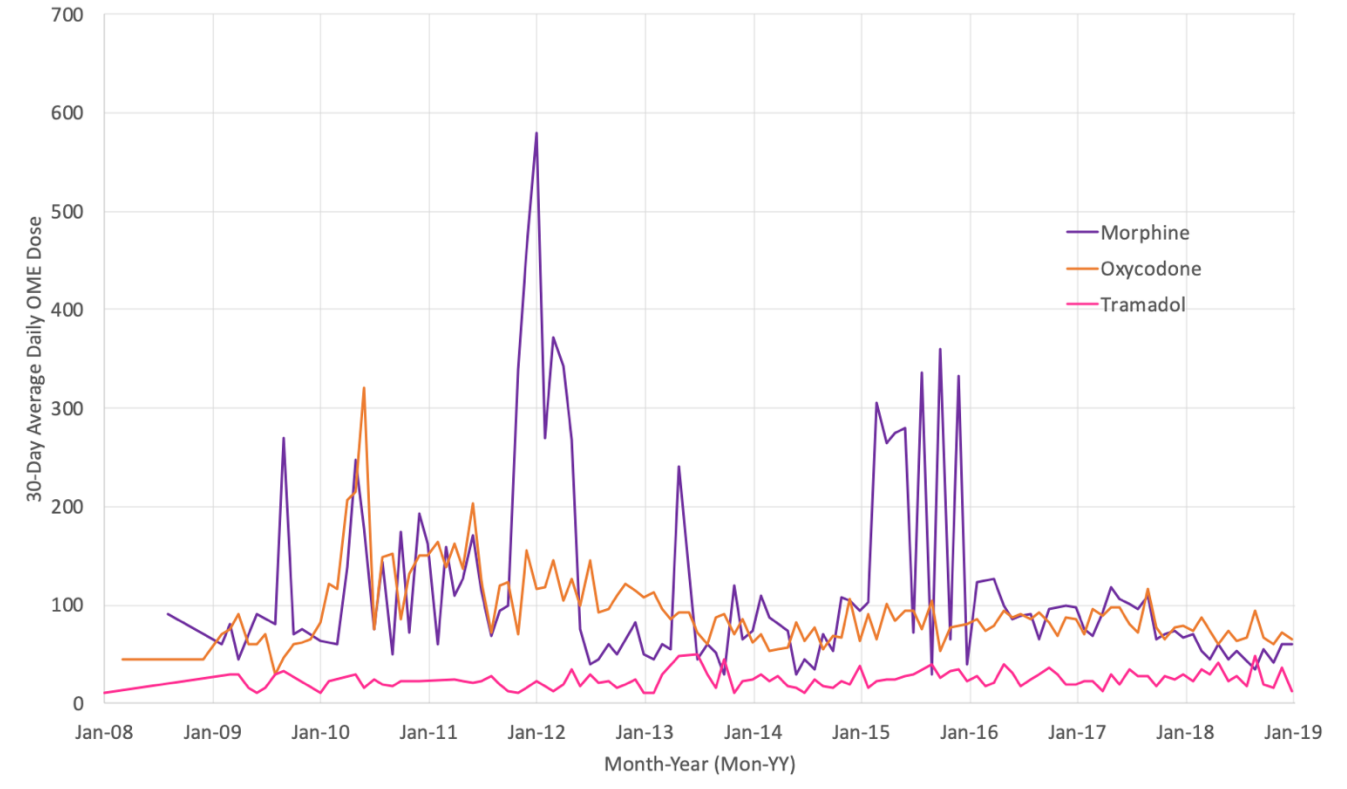

Figure 2.2fi: 30-Day Average Daily OME Dose by Opioid Medications (Morphine, Oxycodone, and Tramadol) from 2008-2018

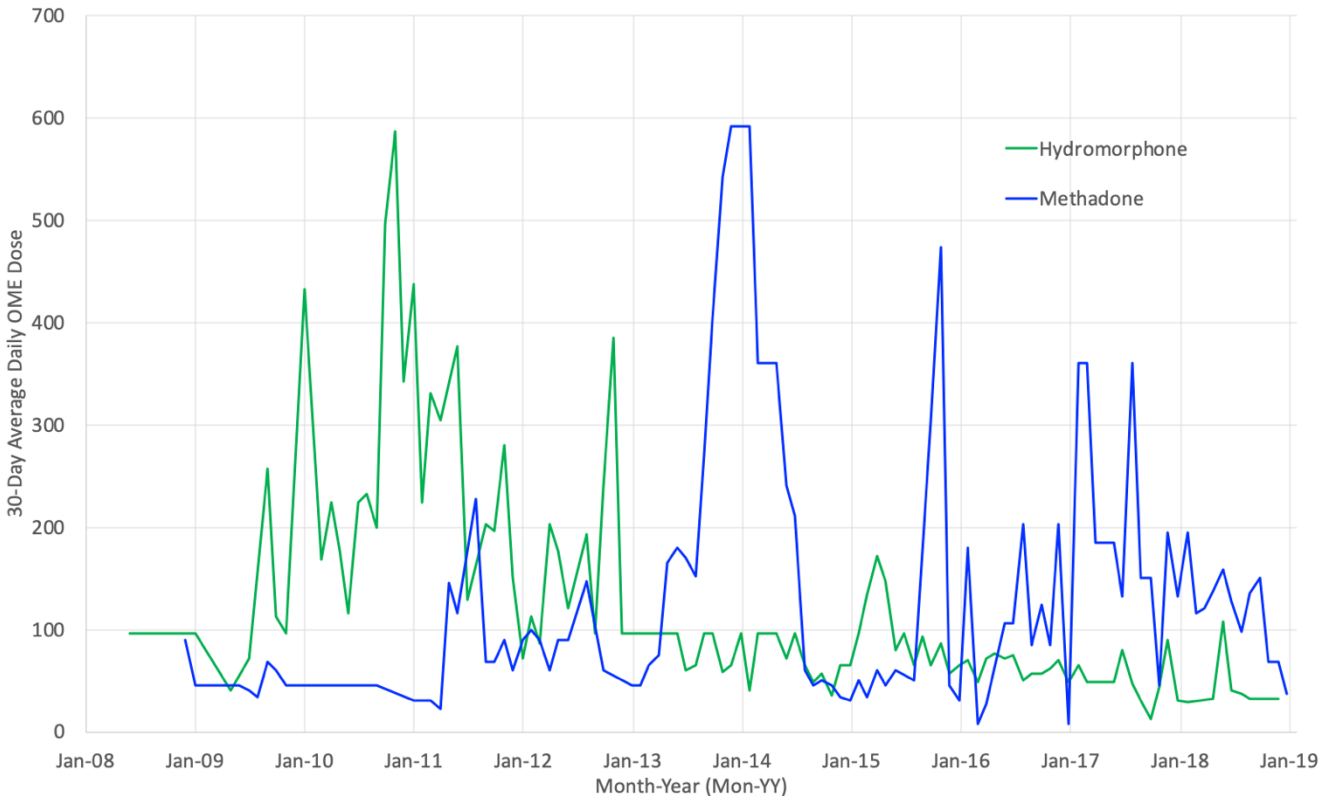

Figure 2.2fii: 30-Day Average Daily OME Dose by Opioid Medications (Hydromorphone and Methadone) from 2008-2018

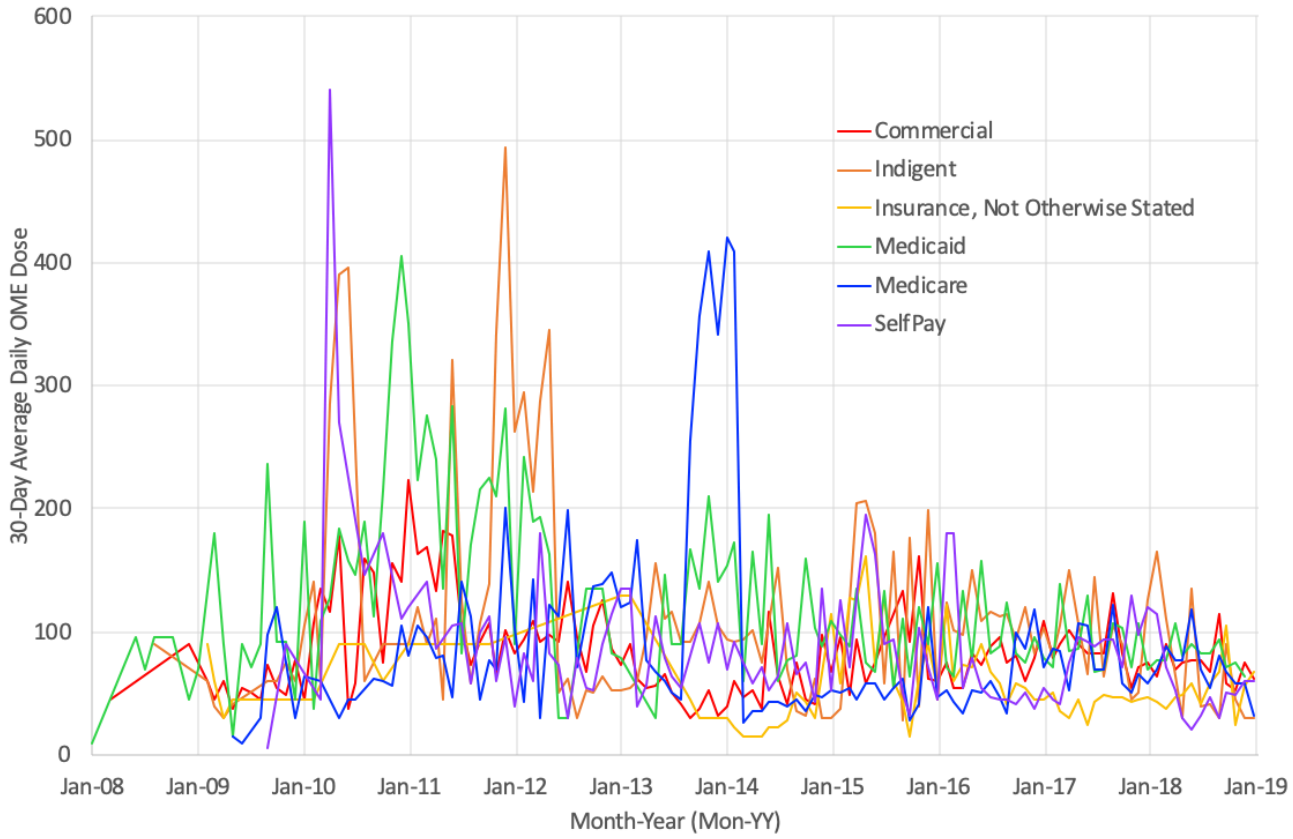

Figure 2.2g: 30-Day Average Daily OME Dose by Payer from 2008-2018

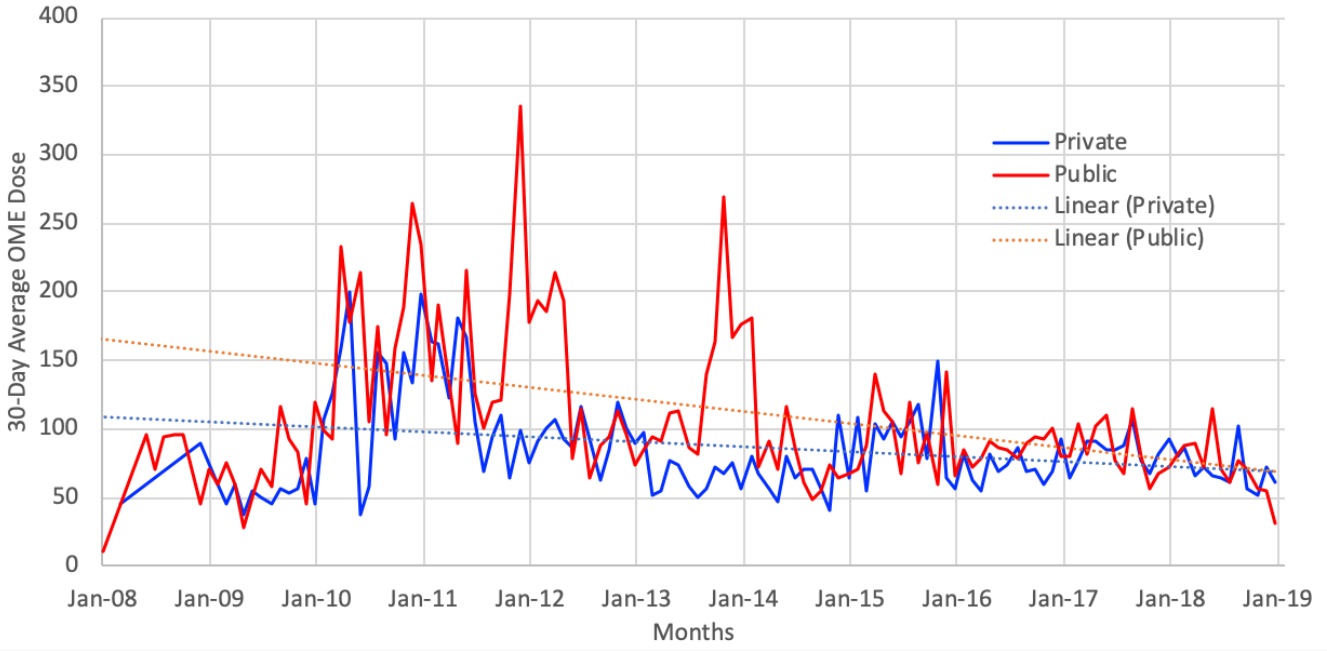

Figure 2.2gi: 30-Day Average Daily OME Dose by Public or Private Payer from 2008-2018

Discussion

Patients with cancer receiving radiation in the sample studied received an average of 2 - 5 opioid prescriptions over the time period analyzed. In comparison, a study from the CDC reported 11 years of overall (not limited to outpatient medications of at least 14-day supply) opioid prescribing trends in non-cancer patients. The CDC study indicated that there was almost one prescription per American before 2012, declining to less than 6 prescriptions per 10 Americans in 2014 (Figure 2.3).[37] Our study suggests that patients with cancer at this academic institution received higher rates of opioid prescriptions per patient than in the general American, non-cancer public. It has been reported that patients with cancer utilize significantly higher amounts of opioids compared to non-cancer patients due to the caustic nature of the disease, treatment, and regular management. A 2019 propensity score matched study reported 2.4 increased odds of opioid prescription use for patients with cancer compared with

matched controls.[22] Additionally, a Canadian time series analysis reported patients with cancer greater than five years had statistically significant 1.44 more opioid prescriptions compared with patients without cancer from 2004-2013.[38]

In this study, we observed an increase in prescriptions per patient at this institution over the time period of the study. It is possible the increase arose because the number of patients with high opioid prescription burden increased as more patients were accepted to the institution for treatment or from increases in patient survival due to advances in cancer management. It is also possible that opioid prescribing became increasingly part of patient disease management. It has been well documented that pain in patients with cancer has historically been significantly under treated.[9,11–14] As reported previously, 43% of patients with cancer from 1994-2007 and 32% of patients with cancer from 2007-2013 were potentially under treated for pain.[9,12,15–19] These studies may have influenced prescribers managing patients with cancer to increase opioid prescribing. The Canadian study previously referenced also saw an increase in patients and opioid prescriptions for patients with cancer greater than 5 years, however, even larger increases in opioid prescriptions were noticed from evaluating specific medication subclasses.[38]

From the CDC prescribing trends in the general, non-cancer American public, opioid prescribing rate trends suggest that an external influence or event occurred between 2010 and 2012 to change the behavior of providers prescribing opioids.[37] Guy Jr et al. note that decreases during this time followed the "publication of two national guidelines defining high-dose opioid prescribing as >200 MME/day […, and] coincided with studies demonstrating progressively increasing overdose risk at prescribed opioid dosages exceeding 20, 50, and 100 [OME] per day and publications highlighting associations of prescribed opioids with overdose deaths."[39] Notably, these guidelines excluded patients with cancer.[10] Additionally,

there has been significant attention dedicated in recent years to opioid utilization, as there has been a surge of opioid deaths from 4,200 in 1999, to 15,300 in 2013, and over 64,000 in 2016.[9,25] In response, many public health initiatives were enacted in the health care community by agencies like the U.S. Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), Drug Enforcement Administration (DEA), and various medical organizations to highlight and address issues related to the opioid epidemic (Table 2.5). While this study did not investigate if a single event contributed to changes in opioid prescribing practices, it can be seen from the trends that initiatives not specifically targeted to patients with cancer may have influenced providers of cancer patients to closely monitor and decrease overall daily OME doses when possible. Future evaluation of this data with interrupted time series analysis could determine if specific public health initiatives (or potential institutional policy or protocol changes) may have resulted in opioid prescribing changes at this institution.

This study identified very high 30-day average daily OME doses prescribed for patients with cancer receiving radiation over the course of the study. While there are evidence based recommendations for opioid formulations to use for patients with cancer undergoing therapy, there are no daily OME dose recommendations for patients with cancer.[40] The 2016 chronic opioid prescribing guidelines for non-cancer pain (cancer pain explicitly excluded) recommends avoiding daily OME doses greater than 90 and for prescribers to use caution with daily OME doses greater than 50.[10] In this study, we regularly saw 30-day average daily OME doses over 100 (although doses decreased over time after 2010-2011), and after 2009, all 30-day average daily OME doses were over 50. These 30-day average daily OME prescribed doses are notably higher than what is recommended in non-cancer pain guidelines, but are not outside the norm of general practice. A HealthCore Integrated Research Environment (HIRE) database study from 2006 to 2014 of a commercially insured population in the United States

reported quartiles of daily OME in which the "fourth quartile mean ± SD doses were 162.9 ± 168.4 and 100.7 ± 91.5 in the cancer pain and non-cancer pain cohorts, respectively."[26]

This is the first descriptive study to investigate patient characteristics that result in differences in the 30-day average daily OME doses in patients with cancer receiving radiation in the last decade. Over the course of this study of patients with cancer receiving radiation, males, those of white race, those that received additional chemotherapy or did not receive additional definitive surgery, and those with public insurance had higher 30-day average daily OME doses. The difference observed with gender could be real, or it could be attributed to weight-based dosing that is clinically indicated for some opioid medications (namely long acting opioid medications). However, the trends of 30-day average daily OME doses for males and females converging over time suggests that the observed difference, at least in earlier years of the study, was likely due to more than differences in weights between males and females.

Surgery is a painful component of many cancer treatment regimens. Our study found that patients that receive surgery in addition to radiation generally have lower 30-day average daily OME doses than those that do not. This is likely due to the fact that additional definitive surgery, while painful in the short term, resulted in pain source control. Further, this suggests that additional surgery, when indicated, may allow for lower daily OME doses to be prescribed.

Future time series analysis is needed to determine if changes in prescribing practices were significant over time or if differences in prescribing practices were significant between subgroup characteristics. Additional studies from medication subgroups are also warranted. A Canadian study published in 2017 reported differences in opioid prescribing trends based on medication type, but focused mainly on long acting versus short acting opioid medications.[38] The electronic medical record from which this data was pulled only captured the medication

active ingredient, not formulation. While methadone is not generally used for pain management alone, it can be used for pain management in the context of opioid use disorder. Future investigations should identify if patients were switched from other high dose opioids to methadone in the context of opioid use disorder management, which may coincide with an increase in awareness of the opioid epidemic and opioid dependence. Additionally, determination of formulation based on dosing frequency should be explored to determine use of long acting versus short acting opioids. Lastly, further studies could be done to determine if insurance pressures exist on prescribers, including formulary restrictions and dose quantity or day supply limits.

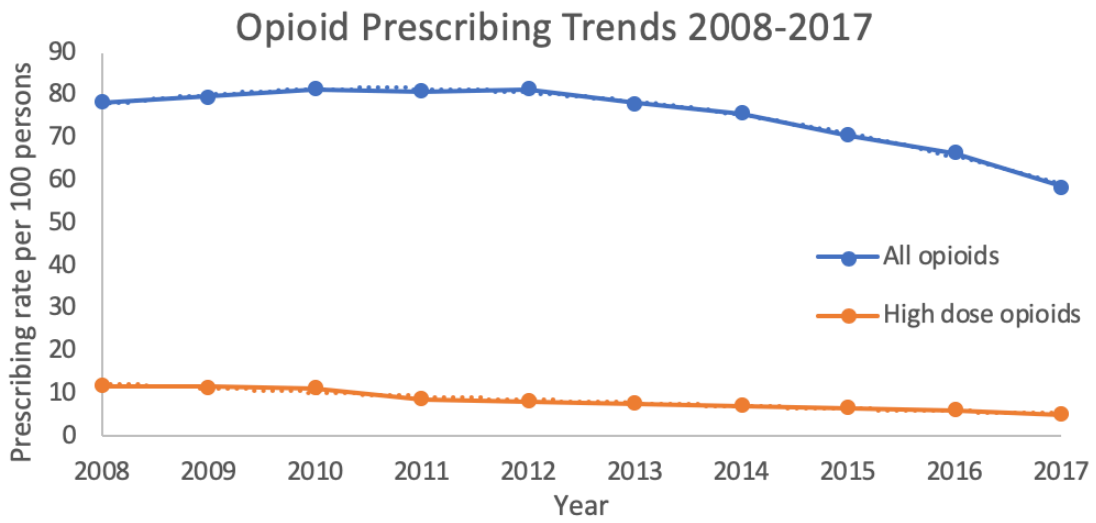

Figure 2.3: Trends in Annual Opioid Prescribing Rates from the CDC by Overall and High-Dosage Prescriptions Adapted for 2008-2017[37]

Table 2.5: Selected Events Related to the Opioid Epidemic between June 2008 and May 2018, adapted from the Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse[41]

Date	Event
5/2010	FDA approved new formulation of OxyContin
4/2011	White House Office of National Drug Control Policy report: Responding to America's Prescription Drug Abuse Crisis, comprehensive action plan to address national prescription drug abuse released
3/2012	The single-shared TIRF REMS went live
2/2013	February 20, JAMA Article "Pharmaceutical Overdose Deaths, Unites States, 2010" published[42]

3/2013	March 1, FDA and health professional organizations asked prescribers of opioids to ensure knowledge of FDA-approved product labeling for opioids, adequate training in opioid therapy, and encouraged all prescribers to help curb nation's opioid epidemic
4/2013	April 16, FDA took multiple actions related to OxyContin
4/2014	April 3, FDA approved Evzio (naloxone hydrochloride injection) for emergency treatment of opioid overdose as the 1st auto-injector designed to deliver naloxone outside of a healthcare setting
7/2014	CDC published "Opioid Painkiller Prescribing" citing 46 people die per day from prescription opioid overdose[43]
10/2014	October 6, DEA reschedules hydrocodone combination products from schedule III to schedule II
1/2015	AMA starts Opioid Task Force
10/2015	October 13, JAMA article "Nonmedical Prescription Opioid Use and Use Disorders Among Adults Aged 18 Through 64 Years in the United States, 2003-2013" published[25]
11/2015	November 18, FDA approved Narcan nasal spray, the 1st approved nasal spray version of naloxone
3/2016	March 22, FDA required class-wide safety labeling changes for IR opioid pain medications including new boxed warning about serious risks of misuse and abuse, leading to addiction, overdose and death
4/2016	April 19, CDC Guidelines for Chronic Pain Released[10]
8/2016	August 16, US Surgeon General Vivek H. Murthy calls on physicians to raise awareness and further efforts to end opioid overdose epidemic August 31, FDA required class-wide changes to drug labeling to help inform health care providers and patients of serious risks associated with combined use of opioid medications and benzodiazepines
12/2016	December 7, Senate passed "21st Century Cures Act" with $1 billion to curb opioid epidemic
3/2017	March 14, Virginia Board of Medicine provides Regulations on Opioid Prescribing and Buprenorphine
7/2017	July 6, the JAMA article by Scott Gottlieb and Janet Woodcock, "Marshaling FDA Benefit-Risk Expertise to Address the Current Opioid Abuse Epidemic," published July 6, following FDA's request, Endo announced voluntarily removal of Opana ER from the market
8/2017	AMA provides guidance to physicians to co-prescribe naloxone
10/2017	October 23, The New Yorker article "The Family that Build an Empire of Pain" published[44] October 26, Trump declares opioid epidemic a public health emergency
11/2017	November 1, President's commission on combating drug addiction and the opioid crisis report released[45]
1/2018	January 4, MMWR article "Drug and Opioid Involved Deaths – Unites States, 2013-2017" published[46]

AMA: American Medical Association; CDC: Centers for Disease Control and Prevention; DEA: Drug Enforcement Administration; FDA: Food and Drug Administration; JAMA: Journal of the American Medical Association; MMWR: Morbidity and Mortality Weekly Report

Limitations

The major limitation of this study was from the descriptive nature of the objectives that resulted in a lack of definitive statistical analysis. Future analyses should determine if statistical differences existed in 30-day average daily OME doses prescribing overall and if there were significant statistical differences between subgroup characteristics.

Another limitation was from a large amount of missing prescription data information to calculate accurate daily OME doses. In order to accurately calculate a daily OME dose, a

medication name, medication strength, tablet or quantity amount (number of dose), daily frequency, and the OME conversion factor were needed. Due to the inherent limitations of documentation of the prescriptions from the electronic medical record, 59.6% of prescriptions were missing at least one component of the OME dose calculation. This may have led to bias in the calculated 30-day average daily OME dose, especially since some medications seemed to have more missing data than others (i.e. data were not missing at random). The authors considered imputing missing data to address this issue, however, it was ultimately decided that imputation was not necessarily due the large sample size of available prescriptions for which all data was available to calculate 30-day average daily OME dose.

Another limitation was due to the inherent flexibility that prescribers often use when writing prescriptions for patients, particularly for “as needed” (i.e. PRN) dosing. Ranges were often provided in prescriptions for dose and frequency (i.e. 1-2 tablets every 4-6 hours per day). Therefore, daily OME doses were calculated based on patients using the highest possible dose at the greatest frequency for the ranges given in a prescription. Therefore, it is possible that 30-day average daily OME doses may be overestimated. However, minimum daily OME doses were also calculated for all prescriptions and differences in results were negligible.

Lastly, due to the nature of electronic medical record documentation, only one race was recorded for each patient. It is possible that a transition of documentation within the electronic medical record occurred to allow for addition of ethnicity to be included at some point in the study. Patients initially reporting “Multiple” for race could have changed their responses fall into a different group.

Conclusion

Cancer survivors are an important demographic to consider for opioid utilization, as opioids are the mainstay to manage disease- and treatment-related pain. This longitudinal study described opioid prescriptions for patients with cancer receiving radiation overall, as well as variations in demographics including cancer type, gender, race, ethnicity, and primary insurance payer from 2008-2018 at a single academic cancer center. Opioid prescription trends followed similar trends, but higher 30-day average daily OME dose quantities compared to other previously reported trends in patients without cancer and outside of the United States.

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CHAPTER 3: INCIDENCE AND ASSOCIATED RISKS OF NEW PERSISTENT AND CONTINUED OPIOID USE IN PATIENTS WITH CANCER RECEIVING RADIOTHERAPY

Abstract

Background: Improvements in cancer therapy have led to an increase in the aggregate number of cancer survivors and the duration of time spent in the survivorship period. There is growing awareness of opioid use in cancer survivors as this population increases. Pain management is an important consideration for patients with cancer, as malignancies, invasive surgery, chemotherapy, and radiation can all lead to significant pain. Approximately 50% of cancer patients will receive radiation therapy as a component of their treatment. For these patients, new persistent opioid use (NPOU; opioid naïve before cancer therapy, but fill opioid prescriptions beyond curative intent treatment) as well as continued chronic opioid use (COU; filled opioid prescriptions before cancer therapy and continued to be prescribed opioids beyond curative intent treatment) is of increasing concern. Neither the extent to which cancer survivors who receive curative intent radiation (CIR) develop NPOU or COU, nor factors that put them at risk for developing NPOU or COU, are known. Objective: Calculate incidence of and examine characteristics associated with COU and NPOU. Methods: Electronic medical record clinical and prescribing data from cancer survivors receiving radiotherapy for any indication from a single academic cancer center from January 1, 2008 through December 31, 2018 was utilized to determine NPOU and COU incidence. Associations of radiation-related, non-radiation related clinical, and sociodemographic variables on NPOU development and COU were assessed by bivariate analysis and multivariable binary logistic regression. Subgroup and sensitivity analyses were then conducted. Results: Of patients with cancer receiving radiation,19.7% of opioid naïve patients developed NPOU and 54.8% patients with opioid exposure prior to radiation continued opioid use. Certain cancer types, including head and

neck cancer (OR 3.90, 95% CI, 2.59-5.86), stage 3 disease (OR 1.75, 95% CI, 1.01-3.05), and additional chemotherapy (OR 1.58, 95% CI, 1.21-1.98) conferred increased odds of NPOU. Sociodemographic factors that conferred increased risk of NPOU included African American race (OR 1.38, 95% CI, 1.11-1.71), certain insurance types, and comorbid conditions including anxiety (OR 1.52, 95% CI, 1.11-2.08), arthritis (OR 1.58, 95% CI, 1.16-2.15), back pain (OR 1.94, 95% CI, 1.46-2.58), depression (OR 1.56, 95% CI, 1.08-2.25), lung disease (OR 1.84, 95% CI, 1.39-2.43), other opioid use (OR 3.05, 95% CI, 1.02-9.13), and nicotine use (OR 1.51, 95% CI, 1.21-2.08). Indigent provided health insurance (OR 2.39, 95% CI, 1.00-5.73), anxiety (OR 2.00, 95% CI, 1.11-3.60), back pain (OR 2.86, 95% CI, 1.65-4.86), hypertension (OR 1.77, 95% CI, 1.06-2.96), and nicotine use (OR 2.60, 95% CI, 1.46-4.64) were significantly associated with increased odds of COU after radiation. Discussion: Roughly one in five patients with cancer receiving CIR without prior exposure to opioids developed NPOU and more than half of patients with prior opioid exposure were COU. Patients with head and neck cancers may be at highest risk of NPOU, but other cancers such as colorectal, gastrointestinal, female genital, and respiratory also carry significant risk. This study identified socioeconomic and health differences in patients receiving radiation that result in increased odds of NPOU and COU. Conclusion: This study demonstrated substantial NPOU and COU in cancer survivors receiving radiation therapy with health disparities. Opioid use in these patients warrants evidence-based recommendations and guidelines to prevent misuse and opioid related deaths.

Background

Five-year survival from cancer diagnosis has increased from less than 50% to a mean of 67% (with a large range based on cancer site) over the last several decades.[1,2] This

increase in survival, in part due to improvements in antineoplastic therapy, has led to an increase in both the aggregate number of cancer survivors and the duration of time patients spend in the survivorship period. Approximately 50% of cancer patients will receive radiation therapy as a component of their treatment.[3] Undergoing radiation therapy can subject patients to significant morbidity that can vary by treatment site, with patients treated for head and neck cancer tending to have a significant burden of radiation-related toxicity.[4–6]

Opioids are a cornerstone of pain management in patients with cancer, as malignancies themselves can lead to significant pain, in addition to pain resulting from invasive surgery, chemotherapy, and radiation.[6–8] Cancer and non-cancer pain is treated differently in the literature and opioid prescribing guidelines have mostly focused on non-cancer pain.[7,9] In studies that have investigated pain in patients with cancer, it has been documented that pain has been significantly undertreated.[7,10–13] For patients with cancer, pain is often managed by the patient's surgical, radiation, or medical oncologist, who may not have optimal training in pain management and palliative care. Specifically, radiation oncologist prescribing patterns have been explicitly described.[14] Factors associated with increased written opioid prescriptions by radiation oncologists were: male sex, ≥25 years since graduation, group practice greater than ten, participation in the Physician Quality Reporting System, and southern location.[14]

Historically, there have been five groups of pain types for patients with cancer: acute cancer-related pain, chronic cancer-related pain, preexisting chronic pain and cancer-related pain, history of drug addiction and cancer-related pain, and end-stage cancer-related pain.[15] However, there is emerging evidence of a new group of patients with new persistent opioid use (NPOU), defined as those who were opioid naïve (not exposed to opioids before cancer therapy) and who continue to fill opioid prescriptions after curative intent treatment.[16,17] As more patients are surviving cancer, NPOU is of greater concern, especially as pain in this

population is poorly characterized and there is little-to-no consensus on the therapeutic framework of treating pain in patients with cancer.[18]

Two studies have suggested that opioid use in patients with cancer is associated with worse survival.[19,20] Hence, there is growing awareness of opioid use and misuse in patients with cancer.[7,21–25] A propensity score matched study published in 2019 reported that respondents with cancer were significantly more likely to use prescription opioids than matched controls (OR: 2.43, 95% CI: 1.68-3.57).[23] There is also emerging evidence of high rates of opioid misuse (use of opioids contrary to the directed or prescribed pattern of use, regardless of presence or absence of harm) in patients with cancer.[26–31] One study found that 58% of patients with cancer were non-compliant with their prescribed opioid therapy and were more likely to have higher morphine equivalent daily doses.[27] Another study found that more than 50% of urine drug tests (UDT) were abnormal in patients with cancer and the most common opioid findings were absence of prescribed opioids (27%) and presence of unprescribed opioids (25%).[31] A study of 209 emergency department patients with cancer showed depression and illicit substance use were significantly associated with a high risk of opioid misuse.[30] Ultimately, an estimated 29% of patients with cancer are at high-risk for misuse.[7,32]

Neither the extent to which cancer survivors who receive curative intent radiation (CIR) develop NPOU and COU, nor the factors that put them at risk are known. Understanding the factors associated with COU or developing NPOU after radiotherapy may help identify patients receiving radiation that may have difficulty weaning off opioid regimens. The objective of this study was to calculate the incidence of and examine characteristics associated with NPOU and COU.

Methods

Data Source, Patient Identification, and Patient Covariates

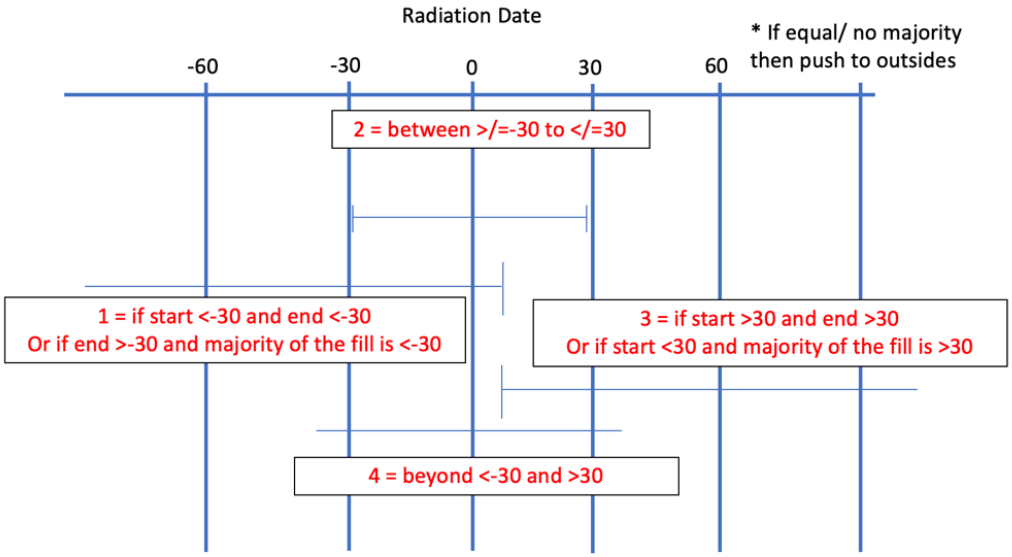
We utilized electronic medical record data from cancer survivors who received radiotherapy for any indication at Virginia Commonwealth University Massey Cancer Center between January 1, 2008 and December 31, 2018. Patients 18 years of age or older with any cancer type and stage receiving radiation with or without additional treatment modalities (i.e. surgery, chemotherapy) were included. We only included patients that classified as cancer survivors (5CS), defined as the absence of metastatic disease or recurrence within 5 years of diagnosis. Prisoners were excluded. Covariate information on the date of cancer diagnosis, cancer type, stage, treatment type, treatment details, comorbid conditions, germane social history (including alcohol, tobacco, or illicit drug use), and demographic information (e.g., age, race, ethnicity and insurance status and type - including Virginia Coordinated Care [VCC], the institution sponsored health insurance for which all medical records should be available for these patients) was used. Prescribed opioid medications were included if written for the outpatient setting for at least a 14-day supply.

Patient Grouping and Categorization

Patients were grouped based on variations in treatment and by cancer type. As cancer treatment algorithms and evidence-based guidelines vary for different cancer types, it was expected that patients that fall in different subgroups (i.e. receive surgery versus those that do not), have different pain levels and overall potential risk of COU or developing NPOU. In order to classify patients by COU and NPOU criteria, patients were grouped by previously published methods and as follows.[16,33] Patients and written prescriptions were first indexed by days since radiation, where 0 was start of radiation, -30 was 30 days before start of radiation, and 30 was 30 days after start of radiation. Because prescriptions were written with varying day-supply

greater than 14 days with or without ongoing refills, prescription rules were established to classify prescriptions based on day-prescribed and day-supply in comparison to start of radiation therapy as follows: (1) before radiation (2) during radiation (3) after radiation (4) continuous (Figure 3.1). Based on prescription classifications, patients were initially stratified by opioid exposure as opioid naïve (ON) or opioid exposed (OE) to determine final categorizations of: NPOU, Never Opioid User (NOU), and Chronic Opioid User (COU) (Table 3.1).[16,17] Due to the inherent limitations of documentation of the prescriptions from the electronic medical record, 5.2% of prescriptions were missing components required to determine when the prescriptions were ordered in relation to radiation treatment and thus were classified as UTOE: "Unknown Timing of Opioid Exposure"

Figure 3.1: Prescription Index Rules



1: Prescription used before radiation
2: Prescription used during radiation
3: Prescription used after radiation
4: Prescription used continuously
>/= : greater than or equal to; </= : less than or equal to
* Note: If the prescription fill overlapped more than one category, the prescription was assigned to whichever category in which majority of the prescription was contained

Table 3.1: Summary of Patient Groups by Opioid Exposure

	Group	Abbreviation	Definition
Pre-Radiation Treatment			
	Opioid Naïve	ON	No known prescribed opioids ≥30 days before treatment
	Opioid Exposed	OE	Known opioids prescribed ≥30 days before treatment
Pre- and Post-Radiation Treatment			
	Chronic Opioid User	COU	Prescribed at least one opioid prescription 30 days before treatment (OE) and at least one opioid prescription 30 days after treatment
	Never Opioid User	NOU	Had no known opioid prescription history before (ON) or after treatment
	New Persistent Opioid User	NPOU	Previously ON who was prescribed at least one opioid prescription 30 after treatment
	Previous Opioid User	POU	Prescribed at least one opioid prescription 30 days before treatment (OE) and no known opioid prescription history after treatment
	During Treatment Only User	DTOU	Prescribed opioids only between 30 days before treatment and 30 days after treatment

Statistical Analyses: Incidence and Binomial Logistic Regression

The percent of ON patients who received CIR that develop new persistent opioid use was determined by incidence (Specific Aim 2a, Table 3.2) as follows:

$$\frac{number\ of\ NPOU}{total\ number\ of\ ON}$$

The percent of OE patients who received CIR that continued chronic opioid use was determined by incidence (Specific Aim 2a, Table 9) as follows:

$$\frac{number\ of\ COU}{total\ number\ of\ OE}$$

In order to examine characteristics associated with COU and NPOU, associations of radiation-related, non-radiation related clinical, and sociodemographic variables with opioid exposure were assessed by bivariate analysis. Descriptive statistics including means, medians, standard deviations, and interquartile ranges were calculated for patient clinical, radiation, and sociodemographic characteristics, as well as opioid prescriptions. One-way ANOVA was conducted for continuous variables against opioid exposure status. Chi-squared tests were used on categorical variables with Fisher's exact test used when expected cell

counts were less than 5. P-values of <0.05 were considered statistically significant. Statistical analyses were conducted using Stata v15.1 and SAS v9.4 (SAS Institute, Cary, NC).

Table 3.2: Methods for Specific Aim 2

Specific Aim 2		
In cancer survivors who received curative intent radiation therapy for their malignancy, examine incidence and characteristics associated with the risk of new persistent and continued chronic opioid use		Method
2a	Identify the rate of new persistent and continued chronic opioid use	Incidence
2b	Examine the association of new persistent and continued chronic opioid use with radiation modality	Binary logistic regression
2c	Examine the association of new persistent and continued chronic opioid use with radiation specific clinical factors such as disease site, stage, and other treatment modalities (including surgery, chemotherapy, and immune therapy)	Binary logistic regression
2d	Examine the association of new persistent and continued chronic opioid use with other non-radiation specific clinical factors such as disease stage and comorbidities	Binary logistic regression
2e	Examine the association of new persistent and continued chronic opioid use with sociodemographic characteristics such as age, gender, race, and insurance status	Binary logistic regression
2f	Using significant associations found in prior analyses (2b-e) estimate the risk of developing new persistent and continued chronic opioid use	Binary logistic regression

Binomial logistic regression for patient groups by opioid exposure against the radiation-related, non-radiation related clinical, and sociodemographic variables was conducted. Binomial logistic regression was chosen over multinomial logistic regression to provide odds of developing NPOU compared to NOU and COU compared to POU for 5CS. Odds ratios (OR) and 95% confidence intervals (95% CI) were reported (Specific Aims 2b-2e, Table 3.2). Table 3.3 lists the models used for multivariable binary logistic regression. A stepwise binary logistic model was run to determine the best fitting model. The SAS automated input of p-value less than 0.05 to be included in the stepwise model was utilized. A final binary logistic regression model was then built with significant associations from the stepwise model and important theoretical characteristics (Specific aims 2b-2e, Table 3.2) to determine the risk of developing COU and NPOU (Specific Aim 2f, Table 3.2). As an extension of Specific Aim 2f, Specific Aim 4 determined explicit health disparities in risk of NPOU, including gender and race. Type 3 analysis of effects for significance of variables in each model overall was reported in

Supplemental Table 3.1. Supplemental multinomial logistic regressions for each model type were also conducted.

Table 3.3: Logit Transformed Multivariable Binomial Logistic Regression Models for each COU (POU reference group) and NPOU (NOU reference group)

Regression	Model
Radiation Specific	$\log\left\{\frac{p}{1-p}\right\}=\beta_0+\beta_1(\text{Radiation Modality})+\varepsilon^a$
Radiation Specific, Clinical	$\log\left\{\frac{p}{1-p}\right\}=\beta_0$ + β_1(Cancer Type) + β_2(Clinical Stage) + β_3(Additional Chemotherapy) +β_4 (Additional Surgery) + β_5 (Additional Hormonal Therapy) + β_6 (Additional Immunotherapy) + β_7 (Additional Other Therapy) + ε^a
Non-Radiation Specific, Clinical	$\log\left\{\frac{p}{1-p}\right\}=\beta_0$ + β_1(Cancer Type) + β_2(Clinical Stage) + β_3(Comorbid Anxiety) +β_4 (Comorbid Arthritis) + β_5 (Comorbid Back Pain) + β_6 (Comorbid Depression) + β_7 (Comorbid Diabetes) + β_8 (Comorbid Heart Disease) + β_9 (Comorbid Hypertension) + β_{10} (Comorbid Lung Disease) + β_{11} (Comorbid Psychosis) + β_{12} (Comorbid Stroke) + β_{13} (Death After More Than 5 years of Diagnosis) + β_{12} (Recurrence After More Than 5 years of Diagnosis) + ε^a
Socio-demographic	$\log\left\{\frac{p}{1-p}\right\}=\beta_0$ + β_1(Age) + β_2(Race) + β_3(Gender) + β_4 (Insurance Type) + β_5 (Alcohol Use) + β_6 (Nicotine Use) + β_7 (Opioid Use) + β_8 (Other Drug Use) + ε^a
Opioid Medication Specific	$\log\left\{\frac{p}{1-p}\right\}=\beta_0$ + β_1(Number of Opioid Prescriptions) + β_2(Buprenorphine Prescription) + β_3(Codeine Prescription) + β_4(Dihydrocodeine Prescription) + β_5 (Fentanyl Prescription) + β_6 (Hydrocodone Prescription) + β_7 (Hydromorphone Prescription) + β_8 (Meperidine Prescription) + β_9 (Methadone Prescription) + β_{10} (Morphine Prescription) + β_{11} (Oxycodone Prescription) + β_{12} (Oxymorphone Prescription) + β_{13} (Tapentadol Prescription) + β_{14} (Tramadol Prescription)+ ε^a
Stepwise Model	$\log\left\{\frac{p}{1-p}\right\}=\beta_0$ + $\beta_{1\text{-}4}$(Radiation Specific Significant Factors) +$\beta_{5\text{-}11}$ (Radiation Specific, Clinical Significant Factors)+ $\beta_{12\text{-}23}$ (Non-Radiation Specific, Clinical Significant Factors)+ $\beta_{24\text{-}31}$ (Sociodemographic Significant Factors)+ ε^a
Final Model (Stepwise + Theoretical)	$\log\left\{\frac{p}{1-p}\right\}=\beta_0$ + $\beta_{1\text{-}4}$(Radiation Specific Significant Factors) +$\beta_{5\text{-}11}$ (Radiation Specific, Clinical Significant Factors)+ $\beta_{12\text{-}23}$ (Non-Radiation Specific, Clinical Significant Factors)+ $\beta_{24\text{-}31}$ (Sociodemographic Significant Factors)+ $\beta_{32\text{-}n}$(Theoretical Factors) + ε^a

NPOU: New Persistent Opioid User; NOU: Never Opioid User; COU: Chronic Opioid User; POU: Previous Opioid User

Subgroup and Sensitivity Analyses

In order to assess the rigor of our results, we conducted a subgroup analysis and two sensitivity analyses. First, a subgroup analysis for patients with VCC was conducted to compare to patients without VCC to determine if differences existed due to potentially missed pre- or post- radiation opioid prescriptions in patients without VCC. Then, we conducted sensitivity analysis with patients with cancer that received radiation that lived without recurrence, metastatic disease, or death for at least 3 years (3-year cancer survivors; 3CS) and for at least 1 year (1-year cancer survivors; 1CS) after diagnosis.

Results

Between January 1, 2008 and December 31, 2018, 7,767 patients over the age of 18 underwent radiation therapy for their malignancies at a single institution (Figure 3.2). Of these patients, 3,887 survived without metastasis or recurrence of their disease beyond 5 years (5-year cancer survivors; 5CS). The majority of patients (84.1%) were opioid naïve prior to start of radiation therapy. Only 10.7% (n = 414) of patients had known opioid prescriptions with at least a 14 day-supply written 30 days or more prior to radiation therapy.

Table 3.4 describes sample sizes, patient demographics, and clinical factors grouped by opioid exposure status. After grouping patients by opioid exposure before and after radiation, the majority of 5CSs (67.5%) were classified into the NOU group. Of all opioid naïve 5CSs (n = 3,269), 19.7% developed NPOU. However, of 5CSs prescribed opioids prior to radiation therapy (n = 414), 54.8% continued opioid use after radiation. Only 5.2% (n =204) of 5CSs had documented opioid prescriptions for which timing in relation to radiation therapy could not be determined.

From bivariate analysis, all clinical and sociodemographic factors were associated with statistically significant differences in opioid exposure groups, except for death 5 or more years after diagnosis. NPOU and COU 5CSs were slightly younger than NOU and POU 5CSs and had higher numbers of opioids prescribed. In any opioid exposure group, 5CSs were more likely to be female, have breast cancer, have commercial insurance or Medicare, and be white (except in COU for which there were more African American 5CSs). In addition to radiation therapy, almost half of 5CSs (44.9%) had additional chemotherapy, 70.4% had additional surgery, and 40.3% had additional hormonal therapy. Lastly, more than 85% of 5CSs reported no substance use.

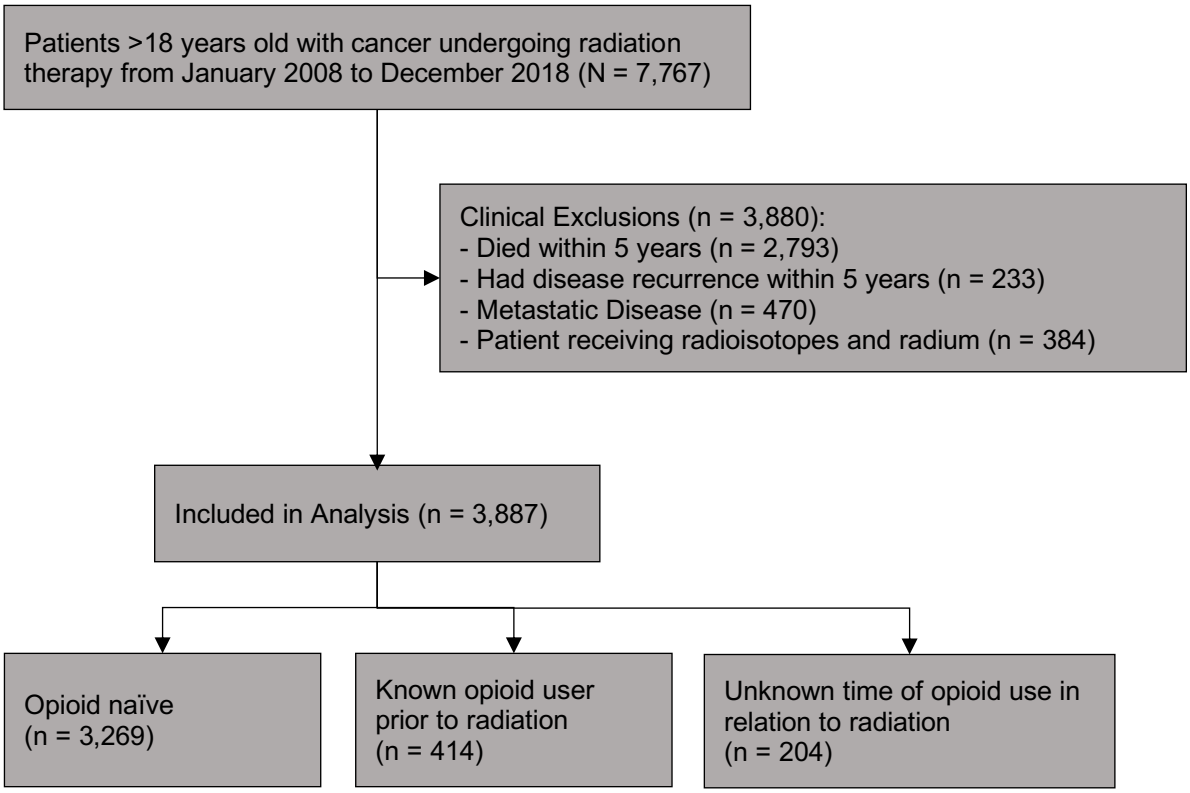


Figure 3.2: Consort Diagram

Table 3.4: 5CS Demographics Overall and by Opioid Exposure

	Overall (n = 3,887)		COU (n = 227, 5.8%)	NPOU (n = 645, 16.6%)	POU (n = 187, 4.8%)	NOU (n = 2,624, 67.5%)	P-value
Covariates	Mean (Std)	Median (IQR)	Mean (Std)	Mean (Std)	Mean (Std)	Mean (Std)	
Age	58.8 (12)	59 (16)	55.5 (11.8)	56.7 (12.4)	57.7 (12.9)	59.6 (11.9)	<0.0001
Number of Opioid Prescriptions**	7.5 (13.9)	2 (5)	18.6 (20.6)	7.6 (12.8)	1.4 (0.9)	0.0 (<0.1)	<0.0001
	N	%	N (%)	N (%)	N (%)	N (%)	
Died After 5 or more years of Diagnosis							
Yes	145	3.7	11 (4.9)	27 (4.0)	6 (3.2)	97 (3.7)	0.7305
No	3742	96.3	216 (95.2)	619 (96.0)	181 (96.8)	2527 (96.3)	
Recurrence of Disease After 5 or more years of Diagnosis							
Yes	25	0.6	0 (0)	3 (0.5)	0 (0)	22 (0.8)	0.0018†
No	3862	99.4	227 (100)	642 (99.5)	187 (100)	2,602 (99.2)	
Gender							
Female	2,796	72.0	156 (68.7)	390 (60.5)	154 (82.4)	1,948 (74.3)	<0.0001
Male	1,090	28.0	71 (31.3)	255 (39.5)	33 (17.7)	675 (25.7)	
Race							
White	2,368	60.9	101 (44.5)	354 (54.88)	103 (55.1)	1,675 (63.9)	<0.0001
Black or African American	1,326	34.1	111 (48.9)	267 (41.4)	76 (40.6)	817 (31.2)	
Other	192	4.9	15 (6.6)	24 (3.7)	8 (4.3)	131 (5.0)	
Insurance							
Commercial	1,603	41.3	64 (28.2)	201 (31.2)	79 (42.3)	1,186 (45.2)	<0.0001†
VCC	223	5.7	34 (15.0)	55 (8.5)	11 (5.9)	119 (4.5)	
Insurance, Not Specified	297	7.6	18 (7.9)	61 (9.5)	15 (8.0)	185 (7.1)	
Medicaid	203	5.2	28 (12.3)	58 (9.0)	12 (6.4)	93 (3.6)	
Medicare	1,286	33.1	57 (25.1)	193 (30.0)	60 (32.1)	892 (34.0)	
Military	51	1.3	2 (0.9)	5 (0.8)	3 (1.6)	40 (1.5)	
Self-Pay	202	5.2	22 (9.7)	65 (10.1)	5 (2.7)	99 (3.8)	
Unknown	21	0.5	2 (0.9)	7 (1.1)	2 (1.1)	9 (0.3)	
Cancer Type							<0.0001†
Breast	2,053	52.8	103 (45.4)	180 (27.9)	122 (65.2)	1,535 (59.4)	
Colorectal	204	5.3	11 (4.8)	67 (10.4)	3 (1.6)	111 (4.3)	
Female Genital	158	4.1	4 (1.8)	47 (7.3)	6 (3.2)	94 (3.6)	
Gastrointestinal	95	2.4	12 (5.3)	22 (3.4)	4 (2.1)	45 (1.7)	
Head and Neck	386	9.9	25 (11.0)	121 (18.8)	9 (4.8)	191 (7.4)	
Leukemia, Lymphoma, Other Hematopoietic	147	3.8	8 (3.5)	24 (3.7)	13 (7.0)	98 (3.8)	
Lung and Bronchus	259	6.7	18 (7.9)	78 (12.1)	10 (5.4)	127 (4.9)	
Other	272	7.0	28 (12.3)	80 (12.4)	12 (6.4)	132 (5.1)	
Prostate	312	8.0	18 (7.9)	26 (4.0)	8 (4.3)	252 (9.7)	

Clinical Stage							
0	327	8.5	9 (4.0)	24 (3.8)	5 (2.7)	265 (10.1)	<0.0001
1	1,083	28.0	52 (23.0)	137 (21.5)	58 (31.0)	772 (29.9)	
2	989	25.6	80 (35.4)	142 (22.3)	62 (33.2)	642 (24.9)	
3	500	12.9	38 (16.8)	160 (25.1)	18 (9.6)	239 (9.2)	
Unknown	969	25.1	47 (20.8)	174 (27.3)	44 (23.9)	660 (25.6)	
Radiation Modality							
Brachytherapy	455	11.7	12 (5.3)	42 (6.5)	12 (6.4)	367 (14.2)	<0.0001†
Conformal or 3-D	403	10.4	33 (14.5)	56 (8.7)	29 (15.5)	250 (9.7)	
External Beam	567	14.6	25 (11.0)	93 (14.4)	18 (9.6)	399 (15.4)	
IMRT	641	16.5	46 (20.3)	175 (47.1)	22 (11.8)	350 (13.5)	
Photons	1,588	40.9	92 (40.5)	240 (37.2)	90 (48.1)	1,082 (41.9)	
Photons and Electrons	73	1.9	5 (2.2)	6 (0.9)	7 (3.7)	47 (1.8)	
Stereotactic Radiosurgery	114	3.0	12 (5.3)	26 (4.0)	8 (4.3)	58 (2.2)	
Other	45	1.2	2 (0.9)	7 (1.1)	1 (0.5)	32 (1.2)	
Additional Chemotherapy							
Yes	1,744	44.9	129 (56.8)	390 (60.5)	119 (63.6)	1,010 (38.5)	<0.0001
No	2,143	55.1	98 (43.2)	255 (39.5)	68 (36.4)	1,614 (61.5)	
Additional Surgery							
Yes	2,735	70.4	149 (65.6)	356 (55.2)	147 (78.6)	1,936 (73.8)	<0.0001
No	1,152	29.6	78 (34.4)	289 (44.8)	40 (21.4)	688 (26.2)	
Additional Hormonal Therapy							
Yes	1,566	40.3	70 (30.8)	153 (23.7)	89 (47.6)	1,174 (44.7)	<0.0001
No	2,321	59.7	157 (69.2)	492 (76.3)	98 (52.4)	1,450 (55.3)	
Additional Immunotherapy							
Yes	182	4.7	13 (5.7)	30 (4.7)	23 (12.3)	107 (4.1)	<0.0001
No	3,705	95.3	214 (94.3)	615 (95.4)	164 (87.7)	2,517 (95.9)	
Additional Other Therapy							
Yes	33	0.9	3 (1.3)	5 (0.8)	1 (0.5)	21 (0.8)	0.0018†
No	3854	99.2	224 (98.7)	640 (99.2)	186 (99.5)	2,603 (99.2)	
Comorbid Conditions							
Anxiety +	442	11.4	74 (32.6)	118 (18.3)	29 (15.5)	205 (7.8)	<0.0001
Anxiety -	3,444	88.6	153 (67.4)	527 (81.7)	158 (84.5)	2,418 (92.2)	
Arthritis +	466	12.0	83 (36.6)	97 (15.0)	40 (21.4)	232 (8.8)	<0.0001
Arthritis -	3,420	88.0	144 (63.4)	548 (85.0)	147 (78.6)	2,391 (91.2)	
Back Pain +	486	12.5	96 (42.3)	140 (21.7)	33 (17.7)	204 (7.8)	<0.0001
Back Pain -	3,400	87.5	131 (57.7)	505 (78.3)	154 (82.4)	2,419 (92.2)	
Depression +	321	8.3	63 (27.8)	84 (13.0)	28 (15.0)	138 (5.3)	<0.0001
Depression -	3,565	91.7	164 (72.3)	561 (87.0)	159 (85.0)	2,485 (94.7)	
Diabetes +	463	11.9	52 (22.9)	97 (15.0)	34 (18.2)	266 (10.1)	<0.0001
Diabetes -	3,423	88.1	175 (77.1)	548 (85.0)	153 (81.8)	2,357 (89.9)	
Heart Disease +	769	19.8	94 (41.4)	185 (28.7)	48 (25.7)	427 (16.3)	<0.0001

Heart Disease -	3,117	80.2	133 (58.6)	460 (71.3)	139 (74.3)	2,196 (83.7)	
Hypertension +	1,313	33.8	138 (60.8)	285 (44.2)	78 (41.7)	781 (29.8)	<0.0001
Hypertension -	2,573	66.2	89 (39.2)	360 (55.8)	109 (58.3)	1,842 (70.2)	
Lung Disease +	513	13.2	76 (33.5)	165 (25.6)	30 (16.0)	227 (8.7)	<0.0001
Lung Disease -	3,373	86.8	151 (66.5)	480 (74.4)	157 (84.0)	23,96 (91.4)	
Substance Use							
Alcohol +	121	3.1	31 (13.7)	33 (5.1)	9 (4.8)	44 (1.7)	<0.0001
Alcohol -	37,65	96.9	196 (86.3)	612 (94.9)	178 (95.2)	2,579 (98.3)	
Nicotine +	594	15.3	109 (48.0)	186 (28.8)	35 (18.7)	249 (9.5)	<0.0001
Nicotine -	3,292	84.7	118 (52.0)	459 (71.2)	152 (81.3)	2,374 (90.5)	
Other Opioid +	30	0.8	5 (2.2)	18 (2.8)	2 (1.1)	5 (0.2)	<0.0001†
Other Opioid -	3,856	99.2	222 (97.8)	627 (97.2)	185 (98.9)	2,618 (99.8)	
Other Drug +	103	2.7	26 (11.5)	38 (5.9)	7 (3.7)	31 (1.2)	<0.0001
Other Drug -	3,783	97.4	201 (88.6)	607 (94.1)	180 (96.3)	2,592 (98.8)	

n = 3,886, missing clinical data for 1 patient; 204 patients had unknown opioid exposure timing (UTOE); Chi Squared test used unless stated; ** Number of prescriptions includes prescriptions written during radiation therapy that were not included in this analysis; †: Fisher's Exact Test; 5CS: 5-year Cancer Survivors; Std: Standard Deviation; IQR: Interquartile Range; COU: Chronic Opioid User; NPOU: New Persistent Opioid User; POU: Previous Opioid User; NOU: Never Opioid User; IMRT: Intensity Modulated Radiation Therapy; VCC: Virginia Coordinated Care

Characteristics Associated with NPOU and COU

Six multivariable binary logistic models were built to examine the associations of NPOU and COU with: radiation modality (Specific Aim 2b), radiation specific clinical factors (Specific Aim 2c), non-radiation specific clinical factors (Specific Aim 2d), sociodemographic characteristics (Specific Aim 2e), a stepwise model estimating the risk of NPOU and COU, and lastly, a theoretical model from significant associations of the stepwise regression with other significant and relevant characteristics identified in previous models (Specific Aim 2f).

In the final theoretical model for likelihood of development of NPOU (Table 3.5), patients of African American race, certain insurance types, certain cancer types, stage 3 disease (meaning more advanced disease spreading beyond the primary tumor, but not to distant sites), additional chemotherapy, certain comorbid conditions, and nicotine and other opioid use were significantly more likely to develop NPOU controlling for other factors, compared to

patients that had no known opioid prescriptions. Conversely, there was a significant decrease in risk of NPOU with increase in age controlling for other factors.

From individual binary logistic models addressing specific groups of characteristics, other covariates were additionally found be associated with increased risk of NPOU development. When examining only sociodemographic factors, men were found to carry increased risk of NPOU when controlling for other factors. Radiation specific factors resulted in decreased risk of NPOU based on certain radiation modalities, but were not found to be significant in the stepwise model. Gender and additional surgery did not meet the p-value of significance to be included in the stepwise model, but were included in the final theoretical model, as they are important clinical factors.

In the final model for 5CSs exposed to opioids prior to radiation (Table 3.6), use of VCC insurance, comorbid anxiety, back pain, hypertension, and nicotine use were significantly associated with increased odds of continuing opioid use after radiation. Some covariates were found to be significant in individual binary logistic models addressing specific groups of characteristics (including colorectal, gastrointestinal, and head and neck cancers), but these were not found to be significant in the final model.

Table 3.5: NPOU Binary Logistic Regressions for 5CS Not Exposed to Opioids Prior to Radiation

NPOU, NOU = reference (n = 3,215)	Sociodemographic	Radiation Specific	Radiation Specific, Clinical	Non-Radiation Specific, Clinical	Stepwise	Stepwise + Theoretical
Covariates	OR (95% CI)					
Age	0.98 (0.97, 0.99)				**0.98 (0.97, 0.99)**	**0.98 (0.97, 0.99)**
Race						
African American	**1.23 (1.01, 1.49)**				**1.38 (1.11, 1.71)**	**1.38 (1.11, 1.71)**
Other	0.80 (0.50, 1.28)				0.75 (0.46, 1.23)	0.75 (0.46, 1.22)
White	Reference					
Gender						
Male	**1.64 (1.35, 2.00)**					1.01 (0.76, 1.34)
Female	Reference					
Insurance Type						
Commercial	Reference					

VCC	**1.99 (1.36, 2.90)**				**1.61 (1.07, 2.44)**	**1.60 (1.06, 2.42)**
Insurance, Not Specified	**1.68 (1.20, 2.36)**				**1.47 (1.02, 2.12)**	**1.47 (1.02, 2.12)**
Medicaid	**2.53 (1.70, 3.75)**				**2.08 (1.35, 3.23)**	**2.08 (1.34, 3.21)**
Medicare	**1.83 (1.39, 2.41)**				**1.53 (1.14, 2.04)**	**1.52 (1.14, 2.03)**
Military	0.69 (0.26, 1.80)				0.92 (0.34, 2.49)	0.93 (0.34, 2.52)
Self-Pay	**2.57 (1.75, 3.77)**				**1.97 (1.30, 2.98)**	**1.96 (1.30, 2.97)**
Cancer Type						
Breast	Reference					
Colorectal			**3.25 (2.14, 4.94)**	**3.99 (2.74, 5.80)**	**3.26 (2.21, 4.81)**	**3.09 (2.03, 4.69)**
Female Genital			**4.13 (2.62, 6.52)**	**3.29 (2.16, 5.02)**	**2.72 (1.74, 4.26)**	**2.57 (1.62, 4.08)**
Gastrointestinal			**2.80 (1.52, 5.14)**	**3.06 (1.71, 5.48)**	**3.48 (1.90, 6.37)**	**3.24 (1.70, 6.19)**
Head and Neck			**4.61 (3.14, 6.77)**	**4.49 (3.31, 6.10)**	**4.27 (3.10, 5.89)**	**3.90 (2.59, 5.86)**
Leukemia, Lymphoma, Other Hematopoietic			1.58 (0.92, 2.70)	**1.93 (1.16, 3.19)**	**1.69 (1.01, 2.84)**	1.48 (0.82, 2.66)
Lung and Bronchus			**3.53 (2.21, 5.64)**	**3.07 (2.12, 4.46)**	**2.91 (1.96, 4.31)**	**2.52 (1.55, 4.10)**
Other			**5.09 (3.41, 7.61)**	**4.49 (3.14, 6.42)**	**4.84 (3.33, 7.02)**	**4.48 (2.93, 6.85)**
Prostate			0.91 (0.52, 1.57)	0.66 (0.42, 1.06)	0.85 (0.51, 1.40)	0.72 (0.38, 1.37)
Clinical Stage						
0	Reference					
1			1.10 (0.68, 1.77)	1.12 (0.70, 1.81)	1.06 (0.65, 1.74)	1.07 (0.66, 1.75)
2			1.18 (0.71, 1.96)	1.60 (0.98, 2.61)	1.16 (0.69, 1.96)	1.18 (0.70, 1.98)
3			**1.77 (1.04, 3.02)**	**2.69 (1.61, 4.48)**	**1.74 (1.00, 3.03)**	**1.75 (1.01, 3.05)**
Additional Chemotherapy			**1.75 (1.39, 2.21)**		**1.58 (1.23, 2.02)**	**1.55 (1.21, 1.98)**
Additional Surgery			0.82 (0.63, 1.07)			0.86 (0.65, 1.14)
Additional Hormonal Therapy			1.11 (0.84, 1.47)			
Additional Immunotherapy			1.05 (0.66, 1.66)			
Additional Other Therapy			1.24 (0.45, 3.48)			
Death After 5 or more years of Diagnosis				1.05 (0.65, 1.70)		
Recurrence After 5 or more years of Diagnosis				0.43 (0.11, 1.66)		
Comorbid conditions						
Anxiety				**1.59 (1.17, 2.15)**	**1.52 (1.11, 2.08)**	**1.52 (1.11, 2.08)**
Arthritis				**1.36 (1.00, 1.84)**	**1.56 (1.15, 2.13)**	**1.58 (1.16, 2.15)**
Back Pain				**2.06 (1.56, 2.72)**	**1.94 (1.46, 2.58)**	**1.94 (1.46, 2.58)**
Depression				**1.68 (1.17, 2.40)**	**1.55 (1.08, 2.23)**	**1.56 (1.08, 2.25)**
Diabetes				0.89 (0.65, 1.21)		
Heart Disease				1.18 (0.92, 1.51)		
Hypertension				**1.29 (1.03, 1.62)**		
Lung Disease				**2.23 (1.70, 2.92)**	**1.84 (1.39, 2.43)**	**1.84 (1.39, 2.43)**
Substance Use						
Alcohol Use	1.18 (0.69, 2.01)					
Nicotine Use	**2.65 (2.07, 3.38)**				**1.59 (1.21, 2.08)**	**1.58 (1.21, 2.08)**
Other Opioid Use	**4.81 (1.67, 13.85)**				**3.14 (1.05, 9.38)**	**3.05 (1.02, 9.13)**
Other Drug Use	1.05 (0.59, 1.86)					
Radiation Modality						
Brachytherapy		**0.29 (0.15, 0.57)**				
Conformal or 3-D		**0.46 (0.32, 0.64)**				
External Beam		**0.46 (0.34, 0.62)**				
IMRT		Reference				

Other		0.46 (0.20, 1.05)				
Photons		**0.45 (0.36, 0.57)**				
Photons and Electrons		**0.26 (0.11, 0.61)**				
Stereotactic Radiosurgery		0.91 (0.56, 1.50)				

Bold denotes statistical significance; 5CS: 5-year Cancer Survivors; NPOU: New Persistent Opioid User; NOU: Never Opioid User; OR: Odds Ratio; 95% CI: 95% Confidence Interval; IMRT: Intensity Modulated Radiation Therapy; VCC: Virginia Coordinated Care

Table 3.6: COU Binary Logistic Regressions for 5CS Exposed to Opioids Prior to Radiation

COU, POU = reference (n = 413)	Sociodemographic	Radiation Specific	Radiation Specific, Clinical	Non-Radiation Specific, Clinical	Stepwise	Stepwise + Theoretical
Covariates	OR (95% CI)					
Age	0.99 (0.97, 1.02)					0.98 (0.96, 1.01)
Race						
African American	1.36 (0.87, 2.13)					1.29 (0.76, 2.18)
Other	1.78 (0.67, 4.72)					1.88 (0.64, 5.50)
White	Reference					
Gender						
Male	1.52 (0.89, 2.61)					1.16 (0.51, 2.64)
Female	Reference					
Insurance Type						
Commercial	Reference					
VCC	**2.53 (1.12, 5.72)**					**2.39 (1.00, 5.73)**
Insurance, Not Specified	1.14 (0.50, 2.57)					1.28 (0.53, 3.11)
Medicaid	1.55 (0.69, 3.50)					1.62 (0.65, 4.04)
Medicare	1.22 (0.67, 2.25)					1.25 (0.63, 2.48)
Military	0.81 (0.12, 5.47)					0.93 (0.12, 7.29)
Self-Pay	**3.49 (1.19, 10.23)**					2.89 (0.87, 9.62)
Cancer Type						
Breast	Reference					
Colorectal			2.59 (0.61, 10.97)	**5.29 (1.24, 22.58)**	**4.67 (1.07, 20.49)**	4.23 (0.83, 21.53)
Female Genital			0.81 (0.20, 3.26)	1.12 (0.25, 5.06)	1.33 (0.31, 5.71)	0.71 (0.15, 3.40)
Gastrointestinal			3.26 (0.93, 11.45)	**6.77 (1.92, 23.85)**	**5.15 (1.47, 18.07)**	**4.03 (1.02, 15.98)**
Head and Neck			2.32 (0.85, 6.33)	**3.96 (1.59, 9.89)**	2.34 (0.90, 6.03)	1.76 (0.53, 5.89)
Leukemia, Lymphoma, other Hematopoietic			0.59 (0.18, 1.93)	1.03 (0.37, 2.82)	1.06 (0.39, 2.84)	0.59 (0.14, 2.50)
Lung and Bronchus			1.16 (0.34, 3.99)	1.12 (0.43, 2.96)	1.19 (0.46, 3.07)	0.99 (0.25, 3.98)
Other			**2.76 (1.06, 7.19)**	**5.56 (2.26, 13.66)**	**5.19 (2.07, 13.00)**	**4.49 (1.53, 13.22)**
Prostate			1.52 (0.47, 4.89)	**2.95 (1.12, 7.72)**	**2.72 (1.02, 7.26)**	1.54 (0.32, 7.44)
Clinical Stage						
0	Reference					
1			0.52 (0.16, 1.75)	0.59 (0.17, 2.11)	0.47 (0.14, 1.64)	0.46 (0.12, 1.76)
2			0.77 (0.22, 2.65)	0.85 (0.24, 2.99)	0.67 (0.20, 2.30)	0.46 (0.16, 2.55)
3			0.97 (0.25, 3.76)	1.12 (0.29, 4.41)	0.89 (0.23, 3.40)	0.79 (0.17, 3.66)

Additional Chemotherapy			0.85 (0.49, 1.46)			0.85 (0.46, 1.57)
Additional Surgery			0.71 (0.33, 1.53)			0.70 (0.29, 1.66)
Additional Hormonal Therapy			0.77 (0.46, 1.28)			
Additional Immunotherapy			0.58 (0.27, 1.25)			
Additional Other Therapy			2.52 (0.24, 26.63)			
Death After 5 or more years of Diagnosis				1.37 (0.44, 4.25)		
Comorbid conditions						
Anxiety				1.64 (0.91, 2.95)	**1.91 (1.10, 3.31)**	**2.00 (1.11, 3.60)**
Arthritis				1.37 (0.80, 2.33)		
Back Pain				**3.04 (1.80, 5.15)**	**3.17 (1.88, 5.35)**	**2.83 (1.65, 4.86)**
Depression				1.57 (0.86, 2.87)		
Diabetes				0.92 (0.51, 1.67)		
Heart Disease				1.39 (0.84, 2.29)		
Hypertension				1.35 (0.81, 2.24)	**1.85 (1.16, 2.93)**	**1.77 (1.06, 2.96)**
Lung Disease				**1.93 (1.10, 3.37)**		
Substance Use						
Alcohol Use	1.11 (0.43, 2.85)					
Nicotine Use	**3.13 (1.83, 5.35)**				**3.27 (1.96, 5.47)**	**2.60 (1.46, 4.64)**
Other Opioid Use	0.61 (0.10, 3.66)					
Other Drug Use	1.22 (0.42, 3.50)					
Radiation Modality						
Brachytherapy		0.69 (0.10, 4.77)				
Conformal or 3-D		0.54 (0.26, 1.10)				
External Beam		0.67 (0.30, 1.47)				
IMRT	Reference					
Other		0.93 (0.08, 10.80)				
Photons		**0.48 (0.27, 0.87)**				
Photons and Electrons		0.33 (0.10, 1.17)				
Stereotactic Radiosurgery		0.72 (0.26, 2.04)				

Bold denotes statistical significance; 5CS: 5-year Cancer Survivors; COU: Chronic Opioid User; POU: Previous Opioid User; OR: Odds Ratio; 95% CI: 95% Confidence Interval; UTOE: Unknown Timing of Opioid Exposure; IMRT: Intensity Modulated Radiation Therapy; VCC: Virginia Coordinated Care

Subgroup Analysis: Patients with VCC

A major concern of the initial analysis was that there were potential opioid prescriptions missed because they were written outside of the institution and therefore not captured from the electronic health record. In order to assess the robustness of our initial results, a subgroup analysis of patients utilizing the institution-provided indigent care (VCC), which requires patients to get all of their care at the institution, was conducted. It is expected that these patients have complete records. Demographics for 5CS with VCC are described in Table 3.7.

In comparison to the entire sample, patients with VCC had increased incidence of opioid prescription use after radiation. Of opioid naïve patients utilizing VCC (n = 175), 31.4% developed NPOU. For patients prescribed opioids prior to radiation therapy (n = 45), 75.6% continued opioid use after radiation. Compared to the entire sample, 5CS with VCC were slightly younger and generally had a higher number of opioid prescriptions written. While the VCC cohort had a similar gender spread (mostly female, 74.9%) to the entire sample, the race distribution was quite different. Instead of white patients (60.9%) as in the entire sample, the VCC patient subgroup was made up of mostly African American patients (57.9%). Additionally, the patients in the VCC subgroup may be sicker than the 5CS group, as the proportion of all types of comorbid diseases, advanced clinical stage of disease burden, and substance use in this subgroup were higher. However, differences in disease burden for these patients may be due to inherent health disparities between non-indigent and indigent populations.

In the final logistic regression model for likelihood of developing NPOU for patients with VCC (Table 3.8), female genital cancers, arthritis, and nicotine use were associated with significantly greater odds of NPOU when controlling for other factors. In comparison to the entire sample, there were less significant factor associations with NPOU, but factors that were

significant in this group were also significant in the entire sample. Also, the factors of association in this subgroup of VCC patients had higher odds of NPOU. There were no significant associations to COU (data not shown) in this subgroup, although this may be due to insufficient power to detect differences from the smaller sample size (n =45).

Table 3.7: Demographics of 5CS with VCC

	Overall (n = 224)		COU (n = 34)	NPOU (n = 55)	POU (n = 11)	NOU (n = 120)	P-value
Covariates	Mean (Std)	Median (IQR)	Mean (Std)	Mean (Std)	Mean (Std)	Mean (Std)	
Age	53.5 (10.2)	55 (13)	55.1 (9.3)	50.5 (12.2)	51.3 (9.1)	54.6 (9.4)	0.0993
Number of Opioid Prescriptions**	12.6 (18.4)	4 (15)	16.7 (18.4)	13.3 (19.9)	1.9 (1.6)	0 (0)	<0.0001
Died After 5 or more years of Diagnosis							
Yes	8	3.6	3 (8.8)	2 (3.6)	0 (0)	3(2.5)	0.0180†
No	216	96.4	31 (91.2)	53 (96.4)	11 (100)	117 (97.5)	
Recurrence of Disease After 5 or more years of Diagnosis							
Yes	1	0.5	0 (0)	0 (0)	0 (0)	1 (0.8)	0.5357†
No	223	99.6	34 (100)	55 (100)	11 (100)	119 (99.2)	
Gender							
Female	167	74.9	25 (73.5)	39 (70.9)	9 (81.8)	91 (76.5)	0.0020†
Male	56	25.1	9 (26.5)	16 (29.1)	2 (18.2)	28 (23.5)	
Race							
White	73	32.7	7 (20.6)	24 (43.6)	2 (18.2)	39 (32.8)	<0.0001
Black or African American	129	57.9	22 (64.7)	28 (50.9)	8 (72.7)	71 (59.7)	
Other	21	9.4	5 (14.7)	3 (5.5)	1 (9.1)	9 (7.6)	
Insurance							
VCC	223	100.0	34 (100)	55 (100)	11 (100)	119 (100)	N/A
Cancer Type							
Breast	112	50.2	22 (64.7)	17 (30.9)	7 (63.6)	65 (54.5)	0.0001Ψ
Female Genital	43	19.3	1 (2.9)	15 (27.3)	2 (18.2)	23 (19.3)	
Head and Neck	12	5.4	0 (0)	4 (7.3)	0 (0)	8 (6.7)	
Other	33	14.7	5 (14.7)	18 (32.7)	2 (18.2)	8 (6.7)	
Prostate	23	10.3	6 (17.7)	1 (1.8)	0 (0)	15 (12.6)	
Clinical Stage							
0	17	7.6	1 (2.9)	2 (3.6)	0 (0)	14 (11.8)	0.1950Ψ
1	49	22.0	8 (23.5)	13 (23.6)	2 (18.2)	26 (21.9)	
2	74	33.2	14 (41.2)	13 (23.6)	3 (27.3)	42 (35.3)	
3	30	13.5	7 (20.6)	11 (20.0)	1 (9.1)	10 (8.4)	
Unknown	53	23.8	4 (11.8)	16 (29.1)	5 (45.5)	27 (22.7)	
Radiation Modality							
Brachytherapy	33	14.8	4 (11.8)	5 (9.1)	4 (36.4)	19 (16.0)	0.3802Ψ

Conformal or 3-D	36	16.1	7 (20.6)	9 (16.4)	2 (18.2)	18 (15.1)	
External beam	23	10.3	3 (8.8)	6 (10.9)	1 (9.1)	13 (10.9)	
IMRT	25	11.2	3 (8.8)	10 (18.2)	1 (9.1)	11 (9.2)	
Photons	103	50.0	16 (47.0)	24 (43.6)	3 (2.7)	57 (47.5)	
Stereotactic radiosurgery	3	1.3	1 (2.9)	1 (1.8)	0 (0)	1 (0.8)	
Additional Chemotherapy							
Yes	107	47.8	19 (55.9)	33 (60.0)	4 (36.4)	49 (40.8)	<0.0001†
No	117	52.2	15 (44.1)	22 (40.0)	7 (63.6)	71 (59.2)	
Additional Surgery							
Yes	163	72.8	27 (79.4)	36 (65.5)	9 (81.8)	88 (73.3)	0.0008†
No	61	27.2	7 (20.6)	19 (34.6)	2 (18.2)	32 (26.7)	
Additional Hormonal Therapy							
Yes	93	41.5	15 (6.7)	14 (25.5)	6 (54.6)	58 (48.3)	<0.0001†
No	131	58.5	19 (55.9)	41 (74.6)	5 (45.5)	62 (51.7)	
Additional Immunotherapy							
Immune +	14	6.3	4 (11.8)	3 (5.5)	0 (0)	7 (3.1)	0.0119†
Immune -	210	93.8	30 (88.2)	52 (94.6)	11 (100)	113 (94.2)	
Additional Other Therapy							
Yes	4	1.8	1 (2.9)	1 (1.8)	0 (0)	2 (1.7)	0.1308†
No	220	98.2	33 (97.1)	54 (98.2)	11 (100)	118 (98.3)	
Comorbid Conditions							
Anxiety +	49	22.0	8 (23.5)	15 (27.3)	2 (18.2)	24 (20.2)	0.0016†
Anxiety -	174	78.0	26 (76.5)	40 (72.7)	9 (81.8)	95 (79.8)	
Arthritis +	42	18.8	13 (38.2)	9 (16.4)	3 (27.3)	15 (12.6)	<0.0001†
Arthritis -	181	81.2	21 (61.8)	46 (83.6)	8 (72.7)	104 (87.4)	
Back Pain +	65	29.2	16 (47.1)	17 (30.9)	4 (36.4)	27 (22.7)	<0.0001†
Back Pain -	158	70.9	18 (52.9)	38 (69.1)	7 (63.6)	92 (77.3)	
Depression +	27	12.1	5 (14.7)	5 (9.1)	1 (9.1)	16 (13.5)	0.0063†
Depression -	196	87.9	29 (85.3)	50 (90.9)	10 (90.9)	103 (86.6)	
Diabetes +	45	20.2	4 (11.8)	7 (12.7)	0 (0)	32 (26.9)	<0.0001†
Diabetes -	178	79.8	30 (88.2)	48 (87.3)	11 (100)	87 (73.1)	
Heart Disease +	65	29.2	13 (38.2)	16 (29.1)	3 (27.3)	33 (27.7)	0.0007†
Heart Disease -	158	70.9	21 (61.8)	39 (70.9)	8 (72.7)	86 (72.3)	
Hypertension +	141	63.3	22 (64.7)	30 (54.6)	9 (81.8)	77 (64.7)	0.0004†
Hypertension -	82	36.8	12 (35.3)	25 (45.5)	2 (18.2)	42 (35.3)	
Lung Disease +	47	21.1	11 (32.4)	15 (27.3)	3 (27.3)	18 (15.1)	0.0001†
Lung Disease -	176	78.9	23 (67.7)	40 (72.7)	8 (72.7)	101 (84.9)	
Substance Use							
Alcohol +	12	5.4	3 (8.8)	1 (1.8)	3 (27.3)	5 (4.2)	0.0004†
Alcohol -	211	94.6	31 (91.2)	54 (98.2)	8 (72.7)	114 (95.8)	
Nicotine +	80	35.9	18 (52.9)	26 (47.3)	6 (54.6)	29 (24.4)	<0.0001†
Nicotine -	143	64.1	16 (47.1)	29 (52.7)	5 (45.5)	90 (75.6)	
Other Opioid +	3	1.4	1 (2.9)	0 (0)	1 (9.1)	1 (0.8)	0.0244†
Other Opioid -	220	98.7	33 (97.1)	55 (100)	10 (90.9)	118 (99.2)	

Other Drug +	18	8.1	4 (11.8)	5 (9.1)	2 (18.2)	7 (5.9)	0.0035†
Other Drug -	205	91.9	30 (88.2)	50 (90.9)	9 (81.8)	112 (94.1)	

n = 223, missing clinical data for 1 patient; 4 patients had unknown opioid exposure timing (UTOE); Chi Squared test used unless stated; ** Number of prescriptions includes prescriptions written during radiation therapy that were not included in this analysis; †: Fisher's Exact Test; ψ: Unable to Calculate Fishers Exact Test; 5CS: 5-year Cancer Survivors; Std: Standard Deviation; IQR: Interquartile Range COU: Chronic Opioid User; NPOU: New Persistent Opioid User; POU: Previous Opioid User; NOU: Never Opioid User; IMRT: Intensity Modulated Radiation Therapy

Table 3.8: NPOU Binary Logistic Regressions of 5CS with VCC ON Prior to Radiation

	5 Year Cancer Survivors (n = 3,215)		**5 Year Cancer Survivors with VCC (n = 174)**	
NPOU, NOU = reference	Stepwise	Theoretical	Stepwise	Theoretical
Covariates				
Age	**0.98 (0.97, 0.99)**	**0.98 (0.97, 0.99)**		0.96 (0.91, 1.00)
Race				
African American	**1.38 (1.11, 1.71)**	**1.38 (1.11, 1.71)**		0.80 (0.34, 1.86)
White	Reference			
Other	0.75 (0.46, 1.23)	0.75 (0.46, 1.22)		2.39 (0.42, 13.70)
Gender				
Male		1.01 (0.76, 1.34)		0.65 (0.10, 4.08)
Female	Reference			
Insurance Type				
Commercial	Reference			
VCC	**1.61 (1.07, 2.44)**	**1.60 (1.06, 2.42)**		
Insurance, Not Specified	**1.47 (1.02, 2.12)**	**1.47 (1.02, 2.12)**		
Medicaid	**2.08 (1.35, 3.23)**	**2.08 (1.34, 3.21)**		
Medicare	**1.53 (1.14, 2.04)**	**1.52 (1.14, 2.03)**		
Military	0.92 (0.34, 2.49)	0.93 (0.34, 2.52)		
Self-Pay	**1.97 (1.30, 2.98)**	**1.96 (1.30, 2.97)**		
Cancer Type				
Breast	Reference			
Colorectal	**3.26 (2.21, 4.81)**	**3.09 (2.03, 4.69)**		
Female Genital	**2.72 (1.74, 4.26)**	**2.57 (1.62, 4.08)**	**2.60 (1.10, 6.15)**	**4.22 (1.19, 15.03)**
Gastrointestinal	**3.48 (1.90, 6.37)**	**3.24 (1.70, 6.19)**		
Head and Neck	**4.27 (3.10, 5.89)**	**3.90 (2.59, 5.86)**	1.52 (0.39, 5.89)	4.28 (0.42, 43.16)
Leukemia, Lymphoma, other Hematopoietic	**1.69 (1.01, 2.84)**	1.48 (0.82, 2.66)		
Lung and Bronchus	**2.91 (1.96, 4.31)**	**2.52 (1.55, 4.10)**		
Other	**4.84 (3.33, 7.02)**	**4.48 (2.93, 6.85)**	**7.13 (2.59, 19.66)**	**20.06 (2.79, 144.22)**
Prostate	0.85 (0.51, 1.40)	0.72 (0.38, 1.37)	0.22 (0.03, 1.79)	0.93 (0.04, 25.10)
Clinical Stage				
0	Reference			
1	1.06 (0.65, 1.74)	1.07 (0.66, 1.75)		3.25 (0.47, 22.67)
2	1.16 (0.69, 1.96)	1.18 (0.70, 1.98)		2.16 (0.29, 16.08)
3	**1.74 (1.00, 3.03)**	**1.75 (1.01, 3.05)**		4.38 (0.46, 41.67)
Additional Chemotherapy	**1.58 (1.23, 2.02)**	**1.55 (1.21, 1.98)**		1.43 (0.51, 4.04)
Additional Surgery		0.86 (0.65, 1.14)		3.24 (0.91, 11.49)
Comorbid conditions				
Anxiety	**1.52 (1.11, 2.08)**	**1.52 (1.11, 2.08)**		0.98 (0.35, 2.71)

Arthritis	**1.56 (1.15, 2.13)**	**1.58 (1.16, 2.15)**		**4.70 (1.42, 15.51)**
Back Pain	**1.94 (1.46, 2.58)**	**1.94 (1.46, 2.58)**		2.14 (0.84, 5.41)
Depression	**1.55 (1.08, 2.23)**	**1.56 (1.08, 2.25)**		0.40 (0.10, 1.59)
Lung Disease	**1.84 (1.39, 2.43)**	**1.84 (1.39, 2.43)**		1.00 (0.35, 2.84)
Substance Use				
Nicotine Use	**1.59 (1.21, 2.08)**	**1.58 (1.21, 2.08)**	**2.55 (1.20, 5.42)**	**2.69 (1.13, 6.43)**
Other Opioid Use	**3.14 (1.05, 9.38)**	**3.05 (1.02, 9.13)**		

Bold denotes statistical significance; 5CS: 5-year Cancer Survivors; ON: Opioid Naïve; NPOU: New Persistent Opioid User; NOU: Never Opioid User; OR: Odds Ratio; 95% CI: 95% Confidence Interval

Sensitivity Analyses

To assess the robustness of our results, we conducted two sensitivity analyses with patients that lived at least 3 years (3-year cancer survivors [3CS]) and 1 year (1-year cancer survivors [1CS]) without recurrence, metastasis, or death. This increased patient sample size from the original sample by 7.5% and 28.9%, respectively.

In comparison to 5CS, 3CS were only slightly older, had slightly more opioid prescriptions, but had more deaths and recurrence (Table 3.9 for ON prior to radiation; Table 3.10 for OE prior to radiation). Proportions of other clinical and demographic covariates were similar to that of the entire sample including: gender, insurance spread, cancer type and stage, additional therapies, comorbid conditions, and substance use. In comparison to 5CS, 3CS had increased incidence of opioid prescription use after radiation. Of opioid naïve cancer survivors (n = 3,456), 20.9% developed NPOU (compared to 19.7% in 5CS) and for patients prescribed opioids prior to radiation therapy (n = 462), 56.9% continued opioid use after radiation (compared to 54.8% in 5CS).

In comparison to 5CS, 1CS were generally sicker with more deaths, more recurrence, more diabetes, and later stage disease (Table 3.9 for ON prior to radiation; Table 3.10 for OE prior to radiation). Additionally, 1CS were slightly older, were higher proportion of males, had more opioid prescriptions, had less breast cancers, more lung cancers, more chemotherapy and less surgery, and less commercial insurance, but more Medicare. In comparison to 5CS,

1CS had increased incidence of opioid prescription use after radiation (and increased incidence from the three-year sensitivity analysis). Of opioid naïve 1CS (n = 4,135), 25.0% developed NPOU (compared to 19.7% in 5CS) and for patients prescribed opioids prior to radiation therapy (n = 574), 61.0% continued opioid use after radiation (compared to 54.8% in 5CS).

In the logistic regression assessing factors for associations of development of NPOU, 3CS and 1CS showed increased odds of developing NPOU with African American race, most insurance types compared to commercial insurance, certain cancer types, additional chemotherapy, and nicotine use, controlling for other factors. As survival decreased, other opioid use was no longer significantly associated with increased odds of NPOU. For 1CS, decreased odds of NPOU were found with surgery and most radiation modalities. While decreased odds of NPOU with surgery was only seen in 1CS, findings from Chapter 2 suggest that additional surgery, while acutely painful, may reduce opioid dose requirement and long-term use due to pain source control. Increased odds of NPOU were demonstrated with death or recurrence after more than one year of diagnosis for 1CS.

The logistic model assessing for patients with opioid assessing likelihood of continuing opioid use after radiation with opioid exposure prior to radiation for 5CS, 3CS, and 1CS (Table 3.12), use of VCC insurance, comorbid back pain, comorbid hypertension, and nicotine use conferred increased odds of COU across groups. Data from patients only surviving less time than the 5CS resulted in similar odds of NPOU and COU. However, the 1CS group had statistically significant association of increased odds of NPOU and COU with death after more than one year from diagnosis.

Table 3.9: Demographics for 5CS, 3CS, and 1CS that were ON prior to Radiation

	5-year Cancer Survivors		3-year Cancer Survivors		1-year Cancer Survivors	
	NOU (n = 2,624)	**NPOU (n = 645)**	**NOU (n = 2,732)**	**NPOU (n = 724)**	**NOU (n = 3,100)**	**NPOU (n = 1,035)**
Covariates	Mean (Std)	Mean (Std)	Mean (Std)	Mean (Std)	Mean (Std)	Mean (Std)
Age	59.6 (11.9)	56.7 (12.4)	59.9 (11.9)	57.3 (12.8)	60.7 (12.2)	58.3 (12.7)
Number of Opioid Prescriptions**	4.5 (13.5)	7.6 (12.8)	0.0 (<0.1)	7.8 (13.2)	0.0 (<0.1)	7.9 (12.7)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Died 5, 3,1 or more years After Diagnosis						
Yes	97 (3.7)	27 (4.0)	224 (8.2)	96 (13.3)	557 (18.0)	384 (37.1)
No	2527 (96.3)	619 (96.0)	2,508 (91.8)	628 (86.7)	2,543 (82.0)	651 (62.9)
Recurrence of Disease 5, 3, 1 or more years After Diagnosis						
Yes	22 (0.8)	3 (0.5)	58 (2.1)	22 (3.0)	147 (4.7)	125 (12.1)
No	2,602 (99.2)	642 (99.5)	2,674 (97.9)	702 (97.0)	2,953 (95.3)	910 (87.9)
Gender						
Female	1,948 (74.3)	390 (60.5)	2,016 (73.8)	440 (60.8)	2,215 (71.5)	590 (57.0)
Male	675 (25.7)	255 (39.5)	716 (26.2)	284 (39.2)	885 (28.5)	445 (43.0)
Race						
White	1,675 (63.9)	354 (54.9)	1,743 (63.8)	392 (54.1)	1,989 (64.2)	576 (55.7)
Black or African American	817 (31.2)	267 (41.4)	852 (31.2)	302 (41.7)	964 (31.1)	421 (40.7)
Other	131 (5.0)	24 (3.7)	137 (5.0)	30 (4.1)	147 (4.7)	38 (3.7)
Insurance						
Commercial	1,186 (45.2)	201 (31.2)	1,205 (44.1)	220 (30.4)	1,299 (41.9)	301 (29.1)
VCC	119 (4.5)	55 (8.5)	123 (4.5)	59 (8.2)	137 (4.4)	78 (7.5)
Insurance, Not Specified	185 (7.1)	61 (9.5)	185 (6.8)	65 (9.0)	197 (6.4)	83 (8.0)
Medicaid	93 (3.6)	58 (9.0)	92 (3.4)	66 (9.1)	108 (3.5)	101 (9.8)
Medicare	892 (34.0)	193 (30.0)	981 (35.9)	234 (32.3)	1,190 (38.4)	363 (35.1)
Military	40 (1.5)	5 (0.8)	41 (1.5)	5 (0.7)	44 (1.4)	8 (0.8)
Self-Pay	99 (3.8)	65 (10.1)	97 (3.6)	67 (9.3)	108 (3.5)	93 (9.0)
Unknown	9 (0.3)	7 (1.1)	8 (0.3)	8 (1.1)	117 (0.8)	8 (0.8)
Cancer Type						
Breast	1,535 (59.4)	180 (27.9)	1,584 (58.0)	200 (27.6)	1,637 (52.8)	232 (22.4)
Colorectal	111 (4.3)	67 (10.4)	124 (4.5)	73 (10.1)	143 (4.6)	97 (9.4)
Female Genital	94 (3.6)	47 (7.3)	117 (4.3)	59 (8.1)	136 (4.4)	72 (7.0)
Gastrointestinal	45 (1.7)	22 (3.4)	52 (1.9)	30 (4.1)	88 (2.8)	79 (7.6)
Head and Neck	191 (7.4)	121 (18.8)	208 (7.6)	128 (17.7)	265 (8.5)	174 (16.8)
Leukemia, Lymphoma, Other Hematopoietic	98 (3.8)	24 (3.7)	100 (3.7)	27 (3.7)	109 (3.5)	38 (3.7)
Lung and Bronchus	127 (4.9)	78 (12.1)	159 (5.8)	97 (13.4)	294 (9.5)	195 (18.8)
Other	132 (5.1)	80 (12.4)	123 (.5)	82 (11.3)	153 (4.9)	117 (11.3)
Prostate	252 (9.7)	26 (4.0)	265 (9.7)	28 (3.9)	275 (8.9)	31 (3.0)
Clinical Stage						
0	265 (10.1)	24 (3.8)	270 (9.9)	24 (3.4)	276 (8.8)	27 (2.6)
1	772 (29.9)	137 (21.5)	803 (29.5)	154 (21.5)	877 (28.0)	182 (17.8)
2	642 (24.9)	142 (22.3)	675 (24.8)	161 (22.5)	755 (24.1)	227 (22.2)
3	239 (9.2)	160 (25.1)	274 (10.1)	181 (25.3)	389 (12.4)	317 (30.9)
Unknown	660 (25.6)	174 (27.3)	703 (25.8)	195 (27.3)	823 (26.6)	272 (26.5)
Radiation Modality						
Brachytherapy	367 (14.2)	42 (6.5)	377 (13.8)	49 (6.8)	395 (12.7)	59 (8.7)

Conformal or 3-D	250 (9.7)	56 (8.7)	264 (9.7)	61 (8.4)	297 (9.6)	92 (8.9)
External Beam	399 (15.4)	93 (14.4)	433 (15.8)	108 (14.9)	564 (18.2)	166 (16.0)
IMRT	350 (13.5)	175 (47.1)	379 (13.9)	188 (26.0)	430 (13.9)	271 (26.2)
Photons	1,082 (41.9)	240 (37.2)	1,123 (41.1)	261 (36.0)	1,209 (39.0)	359 (34.7)
Stereotactic Radiosurgery	58 (2.2)	26 (4.0)	70 (2.6)	34 (4.7)	109 (3.5)	53 (5.1)
Other	79 (3.0)	13 (2.0)	86 (3.2)	23 (3.2)	101 (3.3)	35 (3.4)
Additional Chemotherapy						
Yes	1,010 (38.5)	390 (60.5)	1,064 (38.9)	440 (60.8)	1,277 (41.2)	654 (63.2)
No	1,614 (61.5)	255 (39.5)	1,668 (61.1)	284 (39.2)	1,823 (58.8)	381 (36.8)
Additional Surgery						
Yes	1,936 (73.8)	356 (55.2)	2,000 (73.2)	388 (53.6)	2,161 (79.7)	500 (48.3)
No	688 (26.2)	289 (44.8)	732 (26.8)	336 (46.4)	939 (30.3)	535 (51.7)
Additional Hormonal Therapy						
Yes	1,174 (44.7)	153 (23.7)	1,210 (44.3)	173 (23.9)	1,244 (40.1)	190 (18.4)
No	1,450 (55.3)	492 (76.3)	1,522 (55.7)	551 (76.1)	1,856 (59.9)	845 (81.6)
Additional Immunotherapy						
Yes	107 (4.1)	30 (4.7)	108 (3.9)	34 (4.7)	114 (3.7)	40 (3.9)
No	2,517 (95.9)	615 (95.4)	2,624 (96.0)	690 (95.3)	2,986 (96.3)	995 (96.1)
Additional Other Therapy						
Yes	21 (0.8)	5 (0.8)	21 (0.8)	5 (0.7)	23 (0.7)	8 (0.8)
No	2,603 (99.2)	640 (99.2)	2,711 (99.2)	719 (99.3)	3,077 (99.3)	1027 (99.2)
Comorbid Conditions						
Anxiety +	205 (7.8)	74 (32.6)	209 (7.7)	127 (17.5)	228 (7.4)	165 (15.9)
Anxiety -	2,418 (92.2)	153 (67.4)	2,523 (92.3)	597 (82.5)	2,872 (92.6)	870 (84.1)
Arthritis +	232 (8.8)	83 (36.6)	241 (8.8)	107 (14.8)	272 (8.8)	150 (14.5)
Arthritis -	2,391 (91.2)	144 (63.4)	2,491 (91.2)	617 (85.2)	2,828 (91.2)	885 (85.5)
Back Pain +	204 (7.8)	96 (42.3)	213 (7.8)	152 (21.0)	228 (7.4)	196 (18.9)
Back Pain -	2,419 (92.2)	131 (57.7)	2,519 (92.2)	572 (79.0)	2,872 (92.6)	839 (81.1)
Depression +	138 (5.3)	63 (27.8)	140 (5.1)	96 (13.3)	153 (4.9)	121 (11.7)
Depression -	2,485 (94.7)	164 (72.3)	2,592 (94.9)	628 (86.7)	2,947 (95.1)	914 (88.3)
Diabetes +	266 (10.1)	52 (22.9)	284 (10.4)	110 (15.2)	322 (10.4)	177 (17.1)
Diabetes -	2,357 (89.9)	175 (77.1)	2,448 (89.6)	614 (84.8)	2,778 (89.6)	858 (82.9)
Heart Disease +	427 (16.3)	94 (41.4)	53 (16.6)	200 (27.6)	522 (16.8)	277 (26.8)
Heart Disease -	2,196 (83.7)	133 (58.6)	2,279 (83.4)	524 (72.4)	2,578 (83.1)	758 (73.2)
Hypertension +	781 (29.8)	138 (60.8)	818 (30.0)	315 (43.5)	917 (29.6)	445 (43.0)
Hypertension -	1,842 (70.2)	89 (39.2)	1,914 (70.0)	409 (56.5)	2,183 (70.4)	590 (57.0)
Lung Disease +	227 (8.7)	76 (33.5)	243 (8.9)	187 (25.8)	290 (9.4)	273 (26.4)
Lung Disease -	23,96 (91.4)	151 (66.5)	2,489 (91.1)	537 (74.2)	2,810 (90.6)	762 (73.6)
Substance Use						
Alcohol +	44 (1.7)	33 (5.1)	45 (1.6)	37 (5.1)	52 (1.8)	60 (5.8)
Alcohol -	2,579 (98.3)	612 (94.9)	2,687 (98.4)	687 (94.9)	3,084 (98.3)	975 (94.2)
Nicotine +	249 (9.5)	186 (28.8)	254 (9.3)	202 (27.9)	288 (9.3)	283 (27.3)
Nicotine -	2,374 (90.5)	459 (71.2)	2,478 (90.7)	522 (72.1)	2,812 (90.7)	752 (72.7)
Other Opioid +	5 (0.2)	18 (2.8)	5 (0.2)	18 (2.5)	7 (0.2)	18 (1.7)
Other Opioid -	2,618 (99.8)	627 (97.2)	2,727 (99.8)	706 (97.5)	3,093 (99.8)	1017 (98.3)

Other Drug +	31 (1.2)	38 (5.9)	35 (1.3)	40 (5.5)	44 (1.4)	56 (5.4)
Other Drug -	2,592 (98.8)	607 (94.1)	2,697 (98.7)	684 (94.5)	3,056 (98.6)	979 (94.6)

** Number of prescriptions includes prescriptions written during radiation therapy that were not included in this analysis; Std: Standard Deviation; IQR: Interquartile Range; ON: Opioid Naïve; 5CS: 5-Year Cancer Survivors; 3CS: 3-Year Cancer Survivors; 1CS: 1-Year Cancer Survivors; NPOU: New Persistent Opioid User; NOU: Never Opioid User; IMRT: Intensity Modulated Radiation Therapy; VCC: Virginia Coordinated Care

Table 3.10: Demographics for 5CS, 3CS, and 1CS that were OE Prior to Radiation

	5-year Cancer Survivors		3-year Cancer Survivors		1-year Cancer Survivors	
	POU (n = 187)	**COU (n = 227)**	**POU (n = 199)**	**COU (n = 263)**	**POU (n = 224)**	**COU (n = 350)**
Covariates	Mean (Std)	Mean (Std)	Mean (Std)	Mean (Std)	Mean (Std)	Mean (Std)
Age	57.7 (12.9)	55.5 (11.8)	57.5 (12.9)	55.8 (11.4)	57.9 (13.1)	56.8 (12.0)
Number of Opioid Prescriptions**	1.4 (0.9)	18.6 (20.6)	1.5 (1.2)	20.1 (22.2)	1.6 (1.3)	19.1 (21.5)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Died 5, 3, 1 or more years After Diagnosis						
Yes	6 (3.2)	11 (4.9)	16 (8.0)	44 (16.7)	36 (16.1)	128 (36.6)
No	181 (96.8)	216 (95.2)	183 (92.0)	219 (83.3)	188 (83.9)	222 (63.4)
Recurrence of Disease 5, 3, 1 or more years After Diagnosis						
Yes	0 (0)	0 (0)	4 (2.0)	10 (3.8)	12 (5.4)	39 (11.1)
No	187 (100)	227 (100)	195 (98.0)	253 (96.2)	212 (94.6)	311 (88.9)
Gender						
Female	154 (82.4)	156 (68.7)	165 (82.9)	180 (68.4)	184 (82.1)	229 (65.4)
Male	33 (17.7)	71 (31.3)	34 (17.1)	83 (31.6)	40 (17.9)	121 (34.6)
Race						
White	103 (55.1)	101 (44.5)	106 (53.3)	123 (46.8)	123 (54.9)	161 (46.0)
Black or African American	76 (40.6)	111 (48.9)	85 (42.7)	125 (47.5)	93 (47.5)	171 (48.9)
Other	8 (4.3)	15 (6.6)	8 (4.0)	15 (5.7)	8 (3.6)	18 (5.1)
Insurance						
Commercial	79 (42.3)	64 (28.2)	83 (41.7)	69 (26.2)	91 (40.6)	86 (24.6)
VCC	11 (5.9)	34 (15.0)	11 (5.5)	37 (14.1)	13 (5.8)	45 (12.9)
Insurance, Not Specified	15 (8.0)	18 (7.9)	16 (8.0)	18 (6.8)	18 (8.0)	26 (7.4)
Medicaid	12 (6.4)	28 (12.3)	13 (6.5)	34 (12.9)	14 (6.3)	44 (12.6)
Medicare	60 (32.1)	57 (25.1)	64 (32.2)	77 (29.3)	75 (33.5)	113 (32.3)
Military	3 (1.6)	2 (0.9)	3 (1.5)	2 (0.8)	3 (1.3)	3 (0.9)
Self-Pay	5 (2.7)	22 (9.7)	7 (3.5)	24 (9.1)	8 (3.6)	31 (8.9)
Unknown	2 (1.1)	2 (0.9)	2 (1.0)	2 (0.8)	2 (0.9)	2 (0.6)
Cancer Type						
Breast	122 (65.2)	103 (45.4)	132 (66.3)	117 (44.4)	141 (62.9)	140 (40.0)
Colorectal	3 (1.6)	11 (4.8)	3 (1.5)	14 (5.3)	3 (1.33)	19 (5.4)
Female Genital	6 (3.2)	4 (1.8)	7 (3.5)	6 (2.3)	8 (3.6)	10 (2.9)
Gastrointestinal	4 (2.1)	12 (5.3)	4 (0.2)	13 (4.9)	9 (4.0)	31 (8.9)
Head and Neck	9 (4.8)	25 (11.0)	9 (0.5)	32 (12.2)	9 (4.0)	44 (12.6)
Leukemia, Lymphoma, Other Hematopoietic	13 (7.0)	8 (3.5)	13 (6.5)	8 (3.0)	15 (6.7)	12 (3.4)
Lung and Bronchus	10 (5.4)	18 (7.9)	10 (5.0)	24 (9.1)	14 (6.3)	39 (11.1)

Other	12 (6.4)	28 (12.3)	13 (6.5)	31 (11.8)	16 (4.1)	36 (10.3)
Prostate	8 (4.3)	18 (7.9)	8 (4.0)	18 (6.8)	9 (4.0)	19 (5.4)
Clinical Stage						
0	5 (2.7)	9 (4.0)	6 (3.0)	12 (4.6)	8 (3.6)	13 (3.7)
1	58 (31.0)	52 (23.0)	61 (30.7)	62 (23.7)	65 (29.0)	78 (22.4)
2	62 (33.2)	80 (35.4)	68 (34.2)	86 (32.8	74 (33.0)	109 (31.2)
3	18 (9.6)	38 (16.8)	20 (10.1)	44 (16.8)	25 (11.2)	74 (21.2)
Unknown	44 (23.9)	47 (20.8)	44 (22.1)	58 (22.1)		
Additional Chemotherapy						
Yes	119 (63.6)	129 (56.8)	127 (63.8)	147 (55.9)	144 (64.3)	206 (58.9)
No	68 (36.4)	98 (43.2)	72 (36.2)	116 (44.1)	80 (35.7)	144 (41.1)
Additional Surgery						
Yes	147 (78.6)	149 (65.6)	159 (79.9)	173 (65.8)	174 (77.7)	220 (62.9)
No	40 (21.4)	78 (34.4)	40 (20.1)	90 (34.2)	50 (22.3)	130 (37.1)
Additional Hormonal Therapy						
Yes	89 (47.6)	70 (30.8)	94 (47.2)	78 (29.7)	99 (44.2)	90 (25.7)
No	98 (52.4)	157 (69.2)	105 (52.8)	185 (70.3)	125 (55.8)	260 (74.3)
Additional Immunotherapy						
Yes	23 (12.3)	13 (5.7)	24 (12.1)	14 (5.3)	27 (12.1)	20 (5.7)
No	164 (87.7)	214 (94.3)	175 (87.9)	249 (94.7)	197 (88.0)	330 (94.3)
Additional Other Therapy						
Yes	1 (0.5)	3 (1.3)	1 (0.5)	3 (1.1)	1 (0.5)	3 (0.9)
No	186 (99.5)	224 (98.7)	198 (99.5)	260 (98.9)	223 (99.6)	347 (99.1)
Comorbid Conditions						
Anxiety +	29 (15.5)	74 (32.6)	33 (16.6)	79 (30.0)	39 (17.4)	96 (27.4)
Anxiety -	158 (84.5)	153 (67.4)	166 (83.4)	184 (70.0)	185 (82.6)	254 (72.6)
Arthritis +	40 (21.4)	83 (36.6)	42 (21.1)	99 (37.6)	47 (21.0)	123 (35.1)
Arthritis -	147 (78.6)	144 (63.4)	157 (78.9)	164 (62.4)	177 (79.0)	227 (64.9)
Back Pain +	33 (17.7)	96 (42.3)	34 (17.1)	113 (43.0)	38 (17.0)	145 (41.4)
Back Pain -	154 (82.4)	131 (57.7)	165 (82.9)	150 (57.0)	186 (83.0)	205 (58.6)
Depression +	28 (15.0)	63 (27.8)	30 (15.1)	71 (27.0)	36 (16.1)	88 (25.1)
Depression -	159 (85.0)	164 (72.3)	169 (84.9)	192 (73)	188 (83.9)	262 (74.9)
Diabetes +	34 (18.2)	52 (22.9)	37 (18.6)	63 (24.0)	45 (20.1)	83 (23.7)
Diabetes -	153 (81.8)	175 (77.1)	162 (81.4)	200 (76.1)	179 (79.9)	267 (76.3)
Heart Disease +	48 (25.7)	94 (41.4)	53 (26.6)	114 (43.4)	62 (27.7)	147 (42.0)
Heart Disease -	139 (74.3)	133 (58.6)	146 (73.4)	149 (56.7)	162 (72.3)	203 (58.0)
Hypertension +	78 (41.7)	138 (60.8)	83 (41.7)	166 (63.1)	97 (43.3)	219 (62.6)
Hypertension -	109 (58.3)	89 (39.2)	116 (58.3)	97 (36.9)	127 (56.7)	131 (37.4)
Lung Disease +	30 (16.0)	76 (33.5)	31 (15.6)	93 (35.4)	41 (18.3)	122 (34.9)
Lung Disease -	157 (84.0)	151 (66.5)	168 (84.4)	170 (64.6)	183 (81.7)	228 (65.1)
Substance Use						
Alcohol +	9 (4.8)	31 (13.7)	9 (4.5)	35 (13.3)	11 (4.9)	42 (12.0)
Alcohol -	178 (95.2)	196 (86.3)	190 (95.5)	228 (86.7)	213 (95.1)	308 (88.0)
Nicotine +	35 (18.7)	109 (48.0)	38 (19.1)	124 (47.2)	42 (18.8)	154 (44.0)
Nicotine -	152 (81.3)	118 (52.0)	161 (80.9)	139 (52.9)	182 (81.3)	196 (56.0)
Other Opioid +	2 (1.1)	5 (2.2)	2 (1.0)	6 (2.3)	2 (0.9)	7 (2.0)

Other Opioid -	185 (98.9)	222 (97.8)	197 (99.0)	257 (97.7)	222 (99.1)	343 (98.0)
Other Drug +	7 (3.7)	26 (11.5)	8 (4.0)	30 (11.4)	8 (3.6)	37 (10.6)
Other Drug -	180 (96.3)	201 (88.6)	191 (96.0)	233 (88.6)	216 (96.4)	313 (89.4)

** Number of prescriptions includes prescriptions written during radiation therapy that were not included in this analysis; Std: Standard Deviation; IQR: Interquartile Range; OE: Opioid Exposed; 5CS: 5-Year Cancer Survivors; 3CS: 3-Year Cancer Survivors; 1CS: 1-Year Cancer Survivors; POU: Pervious Opioid User; COU: Continued Opioid User; IMRT: Intensity Modulated Radiation Therapy; VCC: Virginia Coordinated Care

Table 3.11: NPOU Final Binary Logistic Regressions for ON 5CS, 3CS, and 1CS

	5-year Cancer survivors (n = 3,269)		**3-year Cancer Survivors (n = 3,456)**		**1-year Cancer Survivors (n = 4,135)**	
NPOU, NOU = reference	Stepwise	Stepwise + Theoretical	Stepwise	Stepwise + Theoretical	Stepwise	Stepwise + Theoretical
Covariates						
Age	**0.98 (0.97, 0.99)**	**0.98 (0.97, 0.99)**	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)	**0.98 (0.97, 0.99)**	**0.98 (0.97, 0.99)**
Race						
African American	**1.38 (1.11, 1.71)**	**1.38 (1.11, 1.71)**	**1.42 (1.16, 1.75)**	**1.42 (1.15, 1.74)**	**1.38 (1.15, 1.65)**	**1.37 (1.15, 1.64)**
Other	0.75 (0.46, 1.23)	0.75 (0.46, 1.22)	0.88 (0.56, 1.38)	0.88 (0.56, 1.37)	0.85 (0.56, 1.29)	0.85 (0.56, 1.29)
White	Reference					
Gender						
Male		1.01 (0.76, 1.34)		0.95 (0.73, 1.24)		1.01 (0.81, 1.26)
Female	Reference					
Insurance Type						
Commercial	Reference					
VCC	**1.61 (1.07, 2.44)**	**1.60 (1.06, 2.42)**	**1.64 (1.11, 2.44)**	**1.64 (1.10, 2.44)**	**1.58 (1.10, 2.26)**	**1.59 (1.11, 2.27)**
Insurance, Not Specified	**1.47 (1.02, 2.12)**	**1.47 (1.02, 2.12)**	**1.47 (1.03, 2.10)**	**1.48 (1.04, 2.10)**	**1.53 (1.11, 2.11)**	**1.52 (1.10, 2.10)**
Medicaid	**2.08 (1.35, 3.23)**	**2.08 (1.34, 3.21)**	**2.16 (1.43, 3.26)**	**2.14 (1.41, 3.23)**	**2.03 (1.42, 2.90)**	**2.01 (1.41, 2.88)**
Medicare	**1.53 (1.14, 2.04)**	**1.52 (1.14, 2.03)**	**1.47 (1.12, 1.93)**	**1.46 (1.11, 1.92)**	**1.35 (1.06, 1.72)**	**1.35 (1.06, 1.72)**
Military	0.92 (0.34, 2.49)	0.93 (0.34, 2.52)	0.77 (0.29, 2.06)	0.78 (0.29, 2.09)	0.93 (0.40, 2.19)	0.93 (0.40, 2.19)
Self-Pay	**1.97 (1.30, 2.98)**	**1.96 (1.30, 2.97)**	**1.88 (1.26, 2.80)**	**1.87 (1.26, 2.80)**	**1.94 (1.36, 2.78)**	**1.93 (1.34, 2.76)**
Cancer Type						
Breast	Reference					
Colorectal	**3.26 (2.21, 4.81)**	**3.09 (2.03, 4.69)**	**2.98 (2.06, 4.32)**	**2.84 (1.91, 4.22)**	**2.66 (1.86, 3.80)**	**2.63 (1.81, 3.81)**
Female Genital	**2.72 (1.74, 4.26)**	**2.57 (1.62, 4.08)**	**2.50 (1.67, 3.74)**	**2.31 (1.52, 3.51)**	**1.90 (1.28, 2.81)**	**1.88 (1.27, 2.79)**
Gastrointestinal	**3.48 (1.90, 6.37)**	**3.24 (1.70, 6.19)**	**3.70 (2.18, 6.25)**	**3.48 (1.97, 6.16)**	**3.65 (2.42, 5.49)**	**3.60 (2.33, 5.54)**
Head and Neck	**4.27 (3.10, 5.89)**	**3.90 (2.59, 5.86)**	**3.82 (2.81, 5.19)**	**3.50 (2.37, 5.15)**	**2.37 (1.69, 3.32)**	**2.35 (1.62, 3.39)**
Leukemia, Lymphoma, Other Hematopoietic	**1.69 (1.01, 2.84)**	1.48 (0.82, 2.66)	**1.77 (1.08, 2.89)**	1.51 (0.86, 2.65)	1.48 (0.91, 2.40)	1.45 (0.88, 2.40)
Lung and Bronchus	**2.91 (1.96, 4.31)**	**2.52 (1.55, 4.10)**	**3.02 (2.12, 4.31)**	**2.55 (1.64, 3.98)**	**1.81 (1.23, 2.66)**	**1.79 (1.20, 2.67)**
Other	**4.84 (3.33, 7.02)**	**4.48 (2.93, 6.85)**	**5.26 (3.64, 7.60)**	**4.88 (3.19, 7.46)**	**4.00 (2.81, 5.69)**	**3.96 (2.72, 5.77)**
Prostate	0.85 (0.51, 1.40)	0.72 (0.38, 1.37)	0.79 (0.49, 1.29)	0.68 (0.37, 1.24)	**0.41 (0.24, 0.69)**	**0.40 (0.23, 0.71)**
Clinical Stage						
0	Reference					
1	1.06 (0.65, 1.74)	1.07 (0.66, 1.75)	1.18 (0.73, 1.91)	1.19 (0.74, 1.94)	1.25 (0.78, 1.99)	1.25 (0.78, 1.99)
2	1.16 (0.69, 1.96)	1.18 (0.70, 1.98)	1.32 (0.79, 2.20)	1.34 (0.80, 2.23)	1.50 (0.93, 2.43)	1.50 (0.93, 2.43)

3	**1.74 (1.00, 3.03)**	**1.75 (1.01, 3.05)**	**1.82 (1.06, 3.12)**	**1.84 (1.07, 3.15)**	**2.01 (1.22, 3.31)**	**2.01 (1.22, 3.32)**
Additional Chemotherapy	**1.58 (1.23, 2.02)**	**1.55 (1.21, 1.98)**	**1.55 (1.23, 1.95)**	**1.51 (1.20, 1.91)**	**1.29 (1.05,1.60)**	**1.29 (1.05, 1.60)**
Additional Surgery		0.86 (0.65, 1.14)		0.80 (0.62, 1.05)	**0.71 (0.56, 0.89)**	**0.71 (0.56, 0.90)**
Death After 5, 3, 1 or more years of Diagnosis					**1.72 (1.40, 2.11)**	**1.72 (1.40, 2.11)**
Recurrence After 5, 3, 1 or more years of Diagnosis					**1.83 (1.36, 2.45)**	**1.83 (1.36, 2.45)**
Comorbid conditions						
Anxiety	**1.52 (1.11, 2.08)**	**1.52 (1.11, 2.08)**	**1.54 (1.14, 2.08)**	**1.53 (1.13, 2.07)**	**1.52 (1.15, 2.00)**	**1.51 (1.15, 2.00)**
Arthritis	**1.56 (1.15, 2.13)**	**1.58 (1.16, 2.15)**	**1.51 (1.13, 2.03)**	**1.53 (1.14, 2.06)**	**1.53 (1.18, 2.00)**	**1.53 (1.18, 2.00)**
Back Pain	**1.94 (1.46, 2.58)**	**1.94 (1.46, 2.58)**	**1.79 (1.37, 2.35)**	**1.79 (1.36, 2.34)**	**1.88 (1.46, 2.42)**	**1.88 (1.46, 2.42)**
Depression	**1.55 (1.08, 2.23)**	**1.56 (1.08, 2.25)**	**1.61 (1.14, 2.28)**	**1.62 (1.15, 2.30)**	**1.57 (1.14, 2.15)**	**1.56 (1.13, 2.15)**
Lung Disease	**1.84 (1.39, 2.43)**	**1.84 (1.39, 2.43)**	**1.81 (1.39, 2.35)**	**1.81 (1.39, 2.35)**	**1.88 (1.49, 2.36)**	**1.87 (1.48, 2.35)**
Substance Use						
Nicotine Use	**1.59 (1.21, 2.08)**	**1.58 (1.21, 2.08)**	**1.57 (1.21, 2.03)**	**1.56 (1.20, 2.02)**	**1.63 (1.29, 2.05)**	**1.61 (1.28, 2.03)**
Other Opioid Use	**3.14 (1.05, 9.38)**	**3.05 (1.02, 9.13)**	**3.03 (1.02, 9.04)**	2.95 (0.99, 8.82)		1.68 (0.63, 4.50)
Radiation Modality						
Brachytherapy					**0.63 (0.42, 0.94)**	**0.63 (0.43, 0.94)**
Conformal or 3-D					**0.63 (0.45, 0.89)**	**0.63 (0.45, 0.89)**
External Beam					**0.57 (0.43, 0.76)**	**0.57 (0.43, 0.76)**
IMRT	Reference					
Other					**0.86 (0.52, 1.40)**	**0.86 (0.53, 1.41)**
Photons					**0.70 (0.54, 0.91)**	**0.70 (0.54, 0.91)**
Stereotactic Radiosurgery					**0.66 (0.40, 1.07)**	**0.66 (0.40, 1.08)**

Bold denotes statistical significance; ON: Opioid Naïve; 5CS: 5-Year Cancer Survivors; 3CS: 3-Year Cancer Survivors; 1CS: 1-Year Cancer Survivors; NPOU: New Persistent Opioid User; NOU: Never Opioid User; VCC: Virginia Coordinated Care; OR: Odds Ratio; 95% CI: 95% Confidence Interval

Table 3.12: COU Final Binary Logistic Regressions for OE 5CS, 3CS, and 1CS

	5-year Cancer survivors (n = 414)		**3-year Cancer Survivors (n = 462)**		**1-year Cancer Survivors (n = 674)**	
COU, POU = reference	Stepwise	Stepwise + Theoretical	Stepwise	Stepwise + Theoretical	Stepwise	Stepwise + Theoretical
Covariates						
Age		0.98 (0.96, 1.01)		0.98 (0.96, 1.00)	**0.98 (0.96, 0.99)**	0.98 (0.96, 1.00)
Race						
African American		1.29 (0.76, 2.18)		0.93 (0.57, 1.54)		1.08 (0.69, 1.68)
Other		1.88 (0.64, 5.50)		1.47 (0.51, 4.25)		1.97 (0.72, 5.40)
White	Reference					
Gender						
Male		1.16 (0.51, 2.64)	**1.69 (1.01, 2.81)**	1.32 (0.62, 2.85)		1.81 (0.93, 3.54)
Female	Reference					
Insurance Type						
Commercial	Reference					
VCC		**2.39 (1.00, 5.73)**		**3.02 (1.29, 7.06)**		**2.59 (1.18, 5.68)**

Insurance, Not Specified		1.28 (0.53, 3.11)		1.15 (0.48, 2.75)		1.28 (0.59, 2.80)
Medicaid		1.62 (0.65, 4.04)		1.79 (0.77, 4.20)		1.49 (0.67, 3.31)
Medicare		1.25 (0.63, 2.48)		1.55 (0.83, 2.91)		1.51 (0.85, 2.71)
Military		0.93 (0.12, 7.29)		1.17 (0.15, 8.97)		1.21 (0.17, 8.69)
Self-Pay		2.89 (0.87, 9.62)		1.97 (0.69, 5.56)		1.70 (0.66, 4.37)
Cancer Type						
Breast	Reference					
Colorectal	**4.67 (1.07, 20.49)**	4.23 (0.83, 21.53)		3.99 (0.82, 19.44)	**6.62 (1.79, 24.45)**	**4.89 (1.10, 21.67)**
Female Genital	1.33 (0.31, 5.71)	0.71 (0.15, 3.40)		0.89 (0.23, 3.46)	1.45 (0.52, 4.06)	1.43 (0.45, 4.52)
Gastrointestinal	**5.15 (1.47, 18.07)**	4.03 (1.02, 15.98)		3.80 (0.96, 15.08)	3.33 (1.43, 7.80)	2.29 (0.84, 6.25)
Head and Neck	2.34 (0.90, 6.03)	1.76 (0.53, 5.89)		2.14 (0.66, 6.95)	**3.84 (1.68, 8.78)**	**2.34 (0.80, 6.88)**
Leukemia, Lymphoma, Other Hematopoietic	1.06 (0.39, 2.84)	0.59 (0.14, 2.50)		0.52 (0.13, 2.11)	0.80 (0.32, 1.96)	0.46 (0.13, 1.64)
Lung and Bronchus	1.19 (0.46, 3.07)	0.99 (0.25, 3.98)		1.07 (0.27, 4.27)	1.85 (0.88, 3.92)	0.82 (0.25, 2.69)
Other	**5.19 (2.07, 13.00)**	4.49 (1.53, 13.22)		2.77 (0.96, 8.01)	**2.33 (1.15, 4.73)**	2.08 (0.82, 5.29)
Prostate	**2.72 (1.02, 7.26)**	1.54 (0.32, 7.44)		1.43 (0.31, 6.66)	2.52 (1.00, 6.37)	0.84 (0.21, 3.37)
Clinical Stage						
0	Reference					
1	0.47 (0.14, 1.64)	0.46 (0.12, 1.76)		0.54 (0.16, 1.82)		0.95 (0.32, 2.86)
2	0.67 (0.20, 2.30)	0.46 (0.16, 2.55)		0.61 (0.17, 2.14)		1.01 (0.33, 3.14)
3	0.89 (0.23, 3.40)	0.79 (0.17, 3.66)		0.78 (0.2, 3.11)		1.33 (0.39, 4.50)
Additional Chemotherapy		0.85 (0.46, 1.57)		0.92 (0.51, 1.65)		0.92 (0.54, 1.56)
Additional Surgery		0.70 (0.29, 1.66)		0.73 (0.32, 1.67)		0.69 (0.33, 1.44)
Additional Hormonal Therapy			**0.61 (0.39, 0.95)**	0.83 (0.48, 1.44)		0.87 (0.52,1.45)
Death After 5 years or more of Diagnosis					**2.83 (1.76, 4.55)**	**2.48 (1.50, 4.10)**
Comorbid conditions						
Anxiety	**1.91 (1.10, 3.31)**	**2.00 (1.11, 3.60)**		1.47 (0.84, 2.57)		1.31 (0.78, 2.19)
Arthritis					**1.71 (1.06, 2.76)**	1.63 (0.99, 2.67)
Back Pain	**3.17 (1.88, 5.35)**	**2.83 (1.65, 4.86)**	**3.22 (1.99, 5.24)**	**3.09 (1.84, 5.17)**	**2.95 (1.87, 4.65)**	**2.98 (1.84, 4.81)**
Hypertension	**1.85 (1.16, 2.93)**	**1.77 (1.06, 2.96)**	**1.69 (1.10, 2.58)**	**1.78 (1.10, 2.89)**	**1.62 (1.07, 2.45)**	1.47 (0.94, 2.29)
Lung Disease			**1.84 (1.11, 3.05)**	**1.77 (1.02, 3.07)**		1.36 (0.83, 2.24)
Substance Use						
Nicotine Use	**3.27 (1.96, 5.47)**	**2.60 (1.46, 4.64)**	**2.71 (1.70, 4.34)**	**2.07 (1.20, 3.54)**	**2.23 (1.41, 3.53)**	**1.90 (1.15, 3.13)**

Bold denotes statistical significance; OE: Opioid Exposed; 5CS: 5-Year Cancer Survivors; 3CS: 3-Year Cancer Survivors; 1CS: 1-Year Cancer Survivors; COU: Chronic Opioid User; POU: Previous Opioid User; VCC: Virginia Coordinated Care; OR: Odds Ratio; 95% CI: 95% Confidence Interval

Subgroup and Sensitivity Analysis Robustness

The use of the VCC subgroup, as well as the 3CS and 1CS sensitivity analyses, generally supported our results for incidence and associated factors with NPOU and COU. From the VCC subgroup, we could see that patients VCC may have been sicker (with higher proportions of comorbid diseases). Therefore, NPOU and COU incidence was higher in 5CS with VCC. Additionally, there were less significant factor associations with NPOU, but factors that were significant in this group were also significant in the entire sample. Due to insufficient power, we could not replicate COU results with the VCC subgroup. However, 3CS and 1CS sensitivity analysis groups resulted in similar incidence estimates and odds of associated factors with NPOU and COU.

Discussion

This is the first study to evaluate incidence and associated risks of NPOU and COU in patients that received radiation. While previous studies have investigated opioid use in curative intent surgery and chemotherapy in specific cancer types, to the best of our knowledge, no study has elucidated risks for patients specifically receiving radiation.[16,34–37] In this study, we determined that 19.7% (VCC subgroup: 31.4%; 3CS and 1CS SA: 20.9-25.0%) of opioid naïve patients with cancer that receive radiation develop NPOU. Additionally, 54.8% (VCC subgroup: 75.6%; 3CS and 1CS SA: 56.9-61.0%) of patients with cancer and opioid exposure prior to radiation continue opioid use after CIR. These results are similar to previously published results from a smaller study of comparable patient demographics. That study reported 19.7% (range: 6.6-31.6%) of patients at Grady Health System (GHS) in Atlanta, Georgia with any combination of cancer therapies continued opioid use after curative intent therapy.[34] It should be noted that this study did not control for opioid exposure prior to curative intent therapy. Lee et al. reported from a nationally representative sample that “among previously opioid naïve

patients, 4,159 or 10% (95% CI, 10.1% to 10.7%) developed new persistent opioid use after curative-intent surgery."[16] Such wide prescribing of opioids after curative intent treatment calls for evidence-based recommendations and guidelines for opioid use that emphasize discontinuation in cancer survivors.

Undergoing radiation therapy can subject patients to significant morbidity that can vary by treatment site, with patients treated for head and neck cancer tending to have a significant burden of radiation-related acute and late toxicity.[4–6,38] There has been some attention to opioid use specifically in patients with head and neck cancers in the literature.[4,17,39,40] In these studies, 15.4%-63% or 7%-33% of patients with head and neck cancers develop persistent opioid use following 3 or at least 6 months of radiation therapy, respectively.[4,17,39,40] In our study, we observed that 5CS with head and neck cancers had higher odds of developing NPOU (3.90) compared to breast cancer, controlling for other factors. Supplemental multinomial logistic regression supported these results (Supplementary Tables 2-8).

From the studies of patients with head and neck cancers in the literature, chemotherapy, alcohol use, and opioid use before and during treatment were significantly associated with persistent opioid use.[4,17,39,40] In our patient sample, of all cancer types, additional chemotherapy, as well as comorbid conditions such as anxiety, arthritis, back pain, depression, lung disease and nicotine and other opioid use were significantly associated with NPOU.

While head and neck cancers are notoriously caustic, from this study, we were able to show that patients with other cancers such as colorectal, female genital, gastrointestinal, and lung and bronchial also carry significant risk of NPOU when compared to breast cancer controlling for other factors.[4,17,39,40] This may be because in comparison to other cancers, patients with breast cancer have been shown to have lower opioid use.[41]

This study highlighted socioeconomic and health disparity differences that exist in patients receiving radiation that developed NPOU and COU. Just as health disparities exist in cancer and opioid prescribing independently, we were able to show that significant health disparities exist in development of NPOU and COU across models in this study.[42–44] African American patients were at 38% increased odds of developing NPOU. Those of lower socioeconomic status (requiring indigent, charity insurance - VCC) were at 60% and 2.39 times increased estimated odds of developing NPOU and COU, respectively. Additionally, those using Medicaid had 2.08 greater odds to develop NPOU. The results of higher opioid prescription use in low income insurance types following radiation therapy may be due to the fact that patients in disadvantaged sociodemographic positions have poorer outcomes, or due to inherent administrative forces from commercial insurers. A recent study published in JAMA Open comparing opioid prescribing patterns found that "a third of privately insured patients with cancer received an opioid prescription compared with more than half of patients with Medicaid. Patients with Medicaid received a higher days' supply and dosage compared with privately insured patients."[45] Insurers may have exerted prescriptive control with utilization management strategies (prior authorizations, step-therapy, or day-supply quantity limits) to limit opioid prescribing for their beneficiaries. There is evidence to suggest that public insurers have been stronger in implementing utilization control measures.[46] It is also possible that insurer preferred pharmacy coverage practices may have driven patients to obtain opioid prescriptions from outside of the academic institution studied, which were not included in our analyses. Our concerns for these scenarios reinforced the need for a subgroup analysis with full patient prescription data in the VCC subgroup. From our study, we observed that patients with lower presumed income (based on use of Medicaid or institution charity care VCC) carry greater odds of developing NPOU or COU. From the VCC subgroup analysis, higher disease

burden in indigent patients resulted in odds ratios of significant associations with NPOU of much higher magnitudes.

Health disparities in cancer survivors were echoed in this study with chronic conditions and substance use, which are highly prevalent in lower socioeconomic patient populations and may confer poorer outcomes.[47] In this study, cancer survivors with comorbid conditions such as anxiety, arthritis, back pain, depression, hypertension, and lung disease were at higher odds of developing NPOU or COU controlling for other factors. Additionally, patients with nicotine use were consistently at greater odds of developing NPOU and COU controlling for other factors across models.

Lastly, across models, we observed a small decreased risk of NPOU with increasing age at diagnosis, controlling for other factors, suggesting that younger age at diagnosis results in slightly greater odds of developing NPOU. The mean patient age with cancer receiving radiation in this sample was between 55 and 60, whereas those with VCC (which may be a sicker subgroup) was between 50 and 56. It could be that patients of younger age have more aggressive disease, or are given a more aggressive treatment strategy to prolong life. Either scenario may ultimately result in a higher opioid requirement that increases risk of NPOU and COU. Additionally, physicians may be more cautious in opioid prescribing for older patients of due to concerns related to opioids including sedation, fall risk, and risk of side effects including opioid induced constipation.

Limitations

This study had several limitations. First, this study only included patients at a single, urban hospital affiliated with an academic institution. Its providers may have different pain management practices or preferences that may not be nationally representative and thus, the results of this study may only be generalizable to other academic institutions of similar size

patient population, prescribing practices and geography. Second, this study utilized prescribing data rather than fill data. This raises the possibility of patients not filling prescriptions. In addition, due to a lack of access to opioid prescriptions written by doctors outside of the institution, we may have missed opioid prescriptions prescribed outside our institution. This could have resulted in underestimation of opioid use overall or under- or overestimation of NPOU. In order to address this, we conducted the subgroup analysis with VCC patients for which we have all prescribing data. Third, we could not differentiate indication of opioid prescription to be due to cancer or non-cancer pain. Opioid prescriptions due to cancer pain would be, in theory, easier to discontinue than non-cancer pain after curative intent therapy that decreases or eliminates the source of the underlying cancer pain (i.e. tumor burden). Lastly, this study can only be generalized to patients with cancer that receive radiation.

Conclusion

In conclusion, we determined that 19.7% of patients with no prior opioid exposure and with cancer that receive radiation develop NPOU. Further, 54.8% patients with cancer and opioid exposure prior to radiation continue opioid use after CIR. Patients with head and neck cancers may be at highest risk of NPOU, but other cancers such as colorectal, female genital, gastrointestinal, and lung and bronchial also carry significant risk. Comorbidities such as anxiety, arthritis, back pain, depression, lung disease, and nicotine were significantly associated with NPOU. Anxiety, back pain, hypertension, and nicotine use were significantly associated with COU. This study highlighted socioeconomic and health disparity differences resulting in increased odds of NPOU and COU in those receiving radiation using low income-based insurance. These findings warrant evidence-based recommendations and guidelines for opioid use and discontinuation in cancer survivors receiving radiation to prevent misuse and opioid related deaths.

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Appendix

Supplemental Table 3.1: Type 3 Analysis of Effects for Overall Significance of Variables

Covariates	5CS NPOU	5CS COU	5CS VCC NPOU	3CS NPOU	3CS COU	1CS NPOU	1CS COU
Age	0.0009	0.1816	0.0749	0.0023	0.0749	<0.0001	0.025
Race	0.004	0.4121	0.7008	0.002	0.7008	0.0011	0.4193
Gender	0.9512	0.7207	0.4738	0.7119	0.4738	0.9009	0.0804
Insurance Type	0.0013	0.4353	0.257	0.0005	0.257	0.0002	0.3986
Cancer Type	<0.0001	0.0279	0.1158	<0.0001	0.1158	<0.0001	0.0455
Clinical Stage	0.0109	0.0548	0.2763	0.0131	0.2763	0.0002	0.3577
Additional Chemotherapy	0.0006	0.6025	0.7696	0.0005	0.7696	0.0168	0.7543
Additional Surgery	0.2804	0.4157	0.4582	0.109	0.4582	0.0037	0.3189
Additional Hormonal Therapy			0.4998		0.4998		0.5804
Death After 5, 3, 1 or more years of Diagnosis						<0.0001	0.0004
Recurrence After 5, 3, 1 or more years of Diagnosis						<0.0001	
Anxiety	0.0093	0.0207	0.1815	0.006	0.1815	0.0034	0.3096
Arthritis	0.0039			0.0047		0.0016	0.0544
Back Pain	<0.0001	0.0002	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Depression	0.0175			0.0062		0.0064	0.0902
Hypertension		0.0288	0.0189		0.0189		
Lung Disease	<0.0001		0.044	<0.0001	0.044	<0.0001	0.2254
Nicotine Use	0.001	0.0012	0.0084	0.0008	0.0084	<0.0001	0.0122
Other Opioid Use	0.0463			0.0523		0.3039	
Radiation Modality	.					0.0072	

5CS: 5-Year Cancer Survivor; 3CS: 3-Year Cancer Survivor; 1-CS: 1-Year Cancer Survivor; NPOU: New Persistent Opioid User; COU: Continued Opioid User

Supplemental Table 3.2: NPOU Radiation Specific Multinomial Logistic Regression

NOU = reference	COU			NPOU			POU			UTOE		
Radiation Modality	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High
Brachytherapy	**0.229**	**0.067**	**0.784**	**0.328**	**0.157**	**0.685**	1.014	0.285	3.605	0.996	0.347	2.859
Conformal or 3-D	**0.329**	**0.189**	**0.573**	**0.425**	**0.288**	**0.626**	1.859	0.935	3.697	0.906	0.531	1.544
Electrons	**0.085**	**0.009**	**0.772**	0.318	0.098	1.034	N/A	N/A	N/A	0.755	0.163	3.494
External Beam	**0.136**	**0.079**	**0.237**	**0.313**	**0.227**	**0.432**	0.696	0.34	1.426	**0.463**	**0.279**	**0.769**
IMRT	Reference											
Other	0.351	0.038	3.232	0.62	0.141	2.725	2.386	0.25	22.761	1.135	0.125	10.266
Photons (11-19 MV)	**0.221**	**0.099**	**0.493**	**0.427**	**0.263**	**0.692**	1.735	0.712	4.228	0.537	0.236	1.225
Photons (2-5 MV)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Photons (6-10 MV)	**0.233**	**0.142**	**0.383**	**0.409**	**0.299**	**0.561**	1.282	0.677	2.429	**0.488**	**0.297**	**0.803**
Photons (>19 MV)	18.296	N/A	N/A	46.436	N/A	N/A	N/A	N/A	N/A	55.731	N/A	N/A
Photons (Mixed energies)	**0.228**	**0.129**	**0.402**	**0.524**	**0.368**	**0.746**	1.57	0.798	3.091	0.674	0.392	1.159
Photons and Electrons	**0.214**	**0.076**	**0.605**	**0.235**	**0.095**	**0.584**	1.943	0.718	5.256	0.955	0.397	2.299
Radiation Site												
Abdomen	**4.95**	**2.415**	**10.147**	**2.637**	**1.371**	**5.07**	1.698	0.637	4.529	**3.676**	**1.799**	**7.512**
Brain/Spinal cord	0.419	0.098	1.796	**2.276**	**1.296**	**3.998**	0.371	0.086	1.597	1.958	0.908	4.22
Breast	Reference											
Chest	**2.769**	**1.818**	**4.217**	**3.144**	**2.302**	**4.295**	**1.736**	**1.120**	**2.691**	**2.298**	**1.521**	**3.472**
Extremity bone	**5.823**	**2.489**	**13.622**	**6.432**	**3.295**	**12.555**	1.858	0.542	6.370	1.260	0.290	5.473
Head and neck	**2.818**	**1.700**	**4.671**	**5.511**	**3.997**	**7.599**	0.965	0.487	1.910	**2.825**	**1.751**	**4.558**
Lung	1.112	0.405	3.056	**4.380**	**2.433**	**7.884**	0.777	0.248	2.434	**2.841**	**1.253**	**6.442**
Lymph node region	N/A	N/A	N/A	1.489	0.433	5.116	**3.263**	**1.065**	**9.996**	1.560	0.354	6.871
Other	1.066	0.248	4.581	**3.556**	**1.817**	**6.962**	**2.610**	**1.040**	**6.548**	1.306	0.388	4.392
Pelvis	1.894	1.124	3.193	**4.585**	**3.379**	**6.222**	0.557	0.266	1.164	1.528	0.921	2.534
Prostate	0.951	0.476	1.901	0.727	0.439	1.203	0.507	0.216	1.189	**0.347**	**0.142**	**0.845**
Skin	1.669	0.181	15.367	0.661	0.079	5.561	1.893	0.222	16.112	N/A	N/A	N/A
Soft tissue	**3.941**	**1.090**	**14.257**	**3.238**	**1.139**	**9.206**	N/A	N/A	N/A	2.126	0.469	9.638
Spine	2.812	0.616	12.833	**8.929**	**4.085**	**19.521**	2.192	0.477	10.068	1.136	0.146	8.841
Uterus and cervix	N/A	N/A	N/A	**4.086**	**1.246**	**13.405**	N/A	N/A	N/A	N/A	N/A	N/A
Whole body	3.405	0.946	12.252	**6.487**	**2.834**	**14.850**	1.001	0.129	7.751	N/A	N/A	N/A

Supplemental Table 3.3: NPOU Radiation Specific Clinical Multinomial Logistic Regression

NOU = reference	COU			NPOU			POU			UTOE		
Cancer Type	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High
Anus	2.012	0.724	5.592	**5.647**	**3.011**	**10.59**	0.779	0.162	3.737	**3.816**	**1.433**	**10.16**

	Brain and Nervous System	0.117	0.013	1.05	0.877	0.382	2.014	0.37	0.076	1.797	1.943	0.477	7.919
	Breast	Reference											
	Cervix	0.769	0.17	3.485	**6.905**	**3.723**	**12.807**	0.829	0.178	3.873	2.516	0.795	7.963
	Colorectal	0.499	0.19	1.311	**2.667**	**1.658**	**4.287**	**0.121**	**0.016**	**0.898**	0.769	0.288	2.053
	Corpus and Uterus	0.663	0.151	2.914	**3.101**	**1.675**	**5.74**	1.118	0.37	3.378	1.367	0.389	4.806
	Esophagus	2.217	0.445	11.055	**6.961**	**2.594**	**18.677**	N/A	N/A	N/A	1.698	0.202	14.245
	Hodgkin's Disease	0.452	0.056	3.62	1.261	0.407	3.908	2.939	0.93	9.29	1.522	0.323	7.16
	Larynx	2.308	0.885	6.017	**6.094**	**3.393**	**10.945**	0.444	0.055	3.569	**5.475**	**2.393**	**12.526**
	Leukemia, Lymphoma, Other Hematopoietic	1.122	0.432	2.913	1.352	0.704	2.597	0.857	0.306	2.402	0.47	0.105	2.101
	Liver	2.552	0.651	9.996	1.391	0.377	5.137	N/A	N/A	N/A	**6.723**	**2.095**	**21.573**
	Lung and Bronchus	1.98	0.914	4.289	**4.503**	**2.749**	**7.376**	1.439	0.539	3.841	**4.261**	**2.064**	**8.798**
	Multiple Myeloma	2.021	0.406	10.062	**3.921**	**1.488**	**10.331**	N/A	N/A	N/A	3.588	0.615	20.953
	Oral Cavity and Pharynx	**2.5**	**1.273**	**4.912**	**5.826**	**3.712**	**9.143**	0.96	0.349	2.638	**4.401**	**2.28**	**8.495**
	Other	2.883	0.971	8.558	**2.442**	**1.018**	**5.861**	2.392	0.734	7.797	2.578	0.698	9.529
	Other Respiratory and Thoracic Organs	3.772	0.69	20.616	**5.242**	**1.535**	**17.907**	2.231	0.243	20.497	**5.966**	**1.082**	**32.907**
	Other Female Genital	0.774	0.099	6.062	**3.731**	**1.524**	**9.133**	N/A	N/A	N/A	3.427	0.941	12.473
	Pancreas	2.81	0.555	14.22	0.904	0.108	7.54	**6.106**	**1.664**	**22.405**	**6.565**	**1.591**	**27.094**
	Prostate	1.145	0.529	2.478	1.058	0.602	1.861	0.766	0.279	2.102	0.642	0.259	1.594
	Skin	2.33	0.627	8.663	1.31	0.361	4.749	1.945	0.414	9.142	3.316	0.888	12.38
	Soft Tissue including Heart	2.493	0.954	6.516	**5.693**	**3.051**	**10.623**	1.12	0.254	4.94	1.637	0.464	5.774
	Stomach	**4.475**	**1.469**	**13.631**	**3.307**	**1.187**	**9.213**	N/A	N/A	N/A	2.826	0.595	13.415
	Unknown	**3.736**	**1.026**	**13.611**	1.523	0.547	4.242	1.293	0.24	6.973	3.262	0.583	18.257
Clinical Stage													
	0	Reference											
	1	1.623	0.768	3.429	1.118	0.691	1.808	**2.887**	**1.119**	**7.445**	0.67	0.398	1.128
	2	**2.7**	**1.246**	**5.849**	1.31	0.787	2.181	**3.308**	**1.241**	**8.821**	0.911	0.512	1.62
	3	2.29	0.979	5.356	**1.915**	**1.116**	**3.286**	2.363	0.794	7.029	1.019	0.528	1.965
	Criteria Met but unknown	1.057	0.469	2.381	0.999	0.597	1.673	2.505	0.935	6.716	**0.39**	**0.208**	**0.731**
	Not Applicable	2.956	0.935	9.345	**3.498**	**1.623**	**7.538**	**5.36**	**1.317**	**21.82**	0.8	0.23	2.782
Additional Chemotherapy		**1.625**	**1.123**	**2.351**	**1.655**	**1.299**	**2.107**	**2.367**	**1.604**	**3.495**	1.352	0.947	1.931
Additional Surgery		1.355	0.805	2.279	1.08	0.787	1.484	1.402	0.691	2.845	1.538	0.939	2.521
Additional Hormonal Therapy		0.728	0.502	1.057	1.057	0.794	1.407	1.105	0.759	1.609	1.235	0.832	1.831
Additional Immunotherapy		1.105	0.586	2.082	0.925	0.57	1.502	**1.938**	**1.159**	**3.24**	0.914	0.449	1.861
Additional Other Therapy		2.019	0.579	7.037	1.116	0.399	3.117	0.552	0.072	4.208	2.396	0.779	7.371

Supplemental Table 3.4: NPOU Non-Radiation Specific Clinical Multinomial Logistic Regression

NOU = reference	COU			NPOU			POU			UTOE		
Cancer Type	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High
Anus	2.619	0.981	6.991	**6.248**	**3.551**	**10.993**	0.712	0.165	3.069	**2.688**	**1.136**	**6.359**
Brain and Nervous System	0.18	0.019	1.712	1.02	0.437	2.383	0.42	0.085	2.072	1.757	0.431	7.169
Breast	Reference											
Cervix	0.562	0.119	2.648	**5.76**	**3.252**	**10.203**	0.676	0.158	2.900	1.716	0.583	5.052
Colorectal	0.906	0.339	2.421	**3.271**	**2.086**	**5.128**	**0.131**	**0.018**	**0.959**	0.627	0.244	1.613
Corpus and Uterus	0.474	0.106	2.119	**2.011**	**1.097**	**3.688**	0.664	0.223	1.979	1.502	0.432	5.216
Esophagus	4.657	0.933	23.252	**8.255**	**3.119**	**21.846**	N/A	N/A	N/A	1.346	0.163	11.09
Hodgkin's Disease	0.638	0.076	5.37	1.437	0.472	4.373	**3.157**	**1.211**	**8.228**	0.929	0.212	4.074
Larynx	**2.775**	**1.117**	**6.896**	**5.944**	**3.598**	**9.822**	0.281	0.038	2.076	**3.173**	**1.608**	**6.261**
Leukemia, Lymphoma, Other Hematopoietic	1.408	0.535	3.704	1.479	0.791	2.763	0.985	0.399	2.431	0.367	0.087	1.557
Liver	3.267	0.883	12.083	1.132	0.319	4.018	N/A	N/A	N/A	**4.504**	**1.554**	**13.052**
Lung and Bronchus	1.144	0.606	2.158	**3.124**	**2.158**	**4.523**	0.79	0.384	1.626	**2.537**	**1.511**	**4.257**
Multiple Myeloma	2.559	0.481	13.615	**4.744**	**1.833**	**12.279**	N/A	N/A	N/A	2.758	0.497	15.3
Oral Cavity and Pharynx	**2.711**	**1.440**	**5.104**	**5.216**	**3.515**	**7.741**	0.687	0.268	1.758	**3.043**	**1.727**	**5.364**
Other	2.975	0.931	9.505	1.995	0.824	4.83	1.831	0.559	5.999	2.24	0.61	8.222
Other Respiratory and Thoracic Organs	5.614	0.887	35.514	**5.396**	**1.522**	**19.122**	2.04	0.222	18.766	5.192	0.938	28.742
Other Female Genital	0.446	0.049	4.105	**2.827**	**1.13**	**7.071**	N/A	N/A	N/A	3.026	0.852	10.744
Pancreas	2.863	0.495	16.563	0.937	0.111	7.929	**4.605**	**1.231**	**17.227**	**5.918**	**1.456**	**24.045**
Prostate	0.617	0.342	1.113	0.661	0.417	1.048	**0.258**	**0.121**	**0.549**	**0.375**	**0.176**	**0.800**
Skin	3.074	0.811	11.651	1.114	0.313	3.971	1.129	0.249	5.114	2.408	0.665	8.727
Soft Tissue including Heart	**3.825**	**1.466**	**9.978**	**5.103**	**2.816**	**9.248**	0.732	0.171	3.141	1.212	0.359	4.089
Stomach	**5.306**	**1.558**	**18.068**	**3.418**	**1.214**	**9.624**	N/A	N/A	N/A	2.542	0.544	11.876
Unknown	**4.391**	**1.121**	**17.201**	1.794	0.654	4.927	1.318	0.266	6.536	2.102	0.398	11.096
Clinical Stage												
0	Reference											
1	1.445	0.657	3.18	1.118	0.692	1.806	**3.974**	**1.564**	**10.094**	0.792	0.477	1.314
2	**3.181**	**1.46**	**6.93**	**1.672**	**1.028**	**2.718**	**6.402**	**2.506**	**16.355**	1.247	0.741	2.097
3	**3.049**	**1.306**	**7.115**	**2.683**	**1.612**	**4.467**	**5.431**	**1.921**	**15.357**	1.331	0.74	2.394
Criteria Met but unknown	1.343	0.573	3.146	1.256	0.756	2.087	**3.935**	**1.489**	**10.4**	**0.47**	**0.256**	**0.863**
Not Applicable	1.683	0.494	5.738	**2.96**	**1.369**	**6.401**	**5.994**	**1.494**	**24.049**	0.854	0.246	2.959

Death After 5 years or more after Diagnosis	1.539	0.743	3.187	1.107	0.683	1.794	0.971	0.398	2.368	0.567	0.222	1.444
Recurrence 5 years or more after Diagnosis	N/A	N/A	N/A	0.459	0.118	1.782	N/A	N/A	N/A	N/A	N/A	N/A
Anxiety	**2.277**	**1.548**	**3.351**	**1.573**	**1.165**	**2.124**	1.249	0.778	2.005	1.362	0.805	2.304
Arthritis	**2.755**	**1.924**	**3.945**	**1.41**	**1.045**	**1.901**	**1.979**	**1.303**	**3.006**	0.887	0.491	1.601
Back Pain	**4.099**	**2.895**	**5.803**	**2.142**	**1.626**	**2.823**	**1.689**	**1.09**	**2.617**	1.207	0.709	2.055
Depression	**2.544**	**1.675**	**3.863**	**1.729**	**1.22**	**2.451**	**1.991**	**1.221**	**3.248**	0.751	0.36	1.569
Diabetes	1.049	0.699	1.573	0.915	0.675	1.24	1.445	0.922	2.264	1.083	0.623	1.883
Heart Disease	1.32	0.936	1.861	1.225	0.958	1.567	1.061	0.718	1.569	**0.546**	**0.333**	**0.894**
Hypertension	**1.441**	**1.02**	**2.036**	**1.308**	**1.04**	**1.644**	1.126	0.778	1.63	0.568	0.382	0.843
Lung Disease	**2.806**	**1.941**	**4.056**	**2.133**	**1.631**	**2.789**	1.554	0.988	2.447	1.182	0.72	1.939
Psychosis	0.726	0.194	2.719	0.612	0.219	1.708	0.932	0.198	4.38	N/A	N/A	N/A
Stroke	1.565	0.772	3.174	0.859	0.498	1.482	0.627	0.213	1.852	1.179	0.466	2.982

Supplemental Table 3.5: NPOU Sociodemographic Multinomial Logistic Regression

NOU = reference	COU			NPOU			POU			UTOE		
	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High
Age	**0.973**	**0.959**	**0.988**	**0.976**	**0.967**	**0.985**	0.984	0.968	1	0.998	0.984	1.013
Race												
American Indian-Alaskan	1.759	0.178	17.363	N/A	N/A	N/A	1.846	0.229	14.891	2.391	0.51	11.216
Asian	1.189	0.256	5.514	0.833	0.312	2.228	0.604	0.081	4.528	0.685	0.159	2.957
Black of African American	**1.601**	**1.182**	**2.168**	**1.255**	**1.035**	**1.522**	**1.379**	**1.005**	**1.893**	0.807	0.594	1.096
Other	1.253	0.505	3.111	0.542	0.268	1.096	0.486	0.117	2.019	1.189	0.556	2.545
Other of Hispanic or Latino or Spanish Origin	**10.336**	**3.565**	**29.97**	2.005	0.674	5.959	**6.974**	**2.123**	**22.913**	0.79	0.099	6.297
White	Reference											
White of Hispanic or Latino or Spanish Origin	N/A	N/A	N/A	1.301	0.41	4.127	N/A	N/A	N/A	1.332	0.296	5.989
Gender												
Male	0.875	0.625	1.225	**1.645**	**1.353**	**2.001**	**0.551**	**0.367**	**0.827**	1.133	0.838	1.531
Female	Reference											
Insurance Type												
Commercial/HMO	Reference											
VCC	**2.61**	**1.583**	**4.303**	**2.028**	**1.392**	**2.954**	1.038	0.526	2.049	0.483	0.173	1.348
Insurance, NOS	1.422	0.803	2.517	**1.686**	**1.203**	**2.361**	1.204	0.674	2.153	1.505	0.91	2.489
Medicaid	**2.454**	**1.424**	**4.231**	**2.543**	**1.723**	**3.754**	1.389	0.71	2.719	**2.774**	**1.559**	**4.934**

Medicare	**1.86**	**1.195**	**2.895**	**1.808**	**1.379**	**2.37**	1.394	0.9	2.16	1.369	0.925	2.027
Military	0.976	0.222	4.286	0.678	0.259	1.775	1.471	0.438	4.943	0.658	0.155	2.803
Self-Pay	**2.039**	**1.145**	**3.63**	**2.564**	**1.759**	**3.738**	0.64	0.246	1.663	**2.702**	**1.528**	**4.776**
Unknown	1.968	0.362	10.689	**3.5**	**1.184**	**10.345**	3.392	0.662	17.363	3.464	0.709	16.93
Alcohol Use	**3.228**	**1.792**	**5.814**	1.243	0.737	2.096	**2.727**	**1.19**	**6.246**	1.641	0.7	3.848
Nicotine Use	**5.679**	**4.056**	**7.951**	**2.616**	**2.051**	**3.336**	**1.934**	**1.247**	**3**	0.981	0.615	1.566
Other Opioid Use	1.901	0.494	7.316	**4.69**	**1.642**	**13.395**	2.54	0.431	14.95	N/A	N/A	N/A
Other Drug Use	1.412	0.737	2.706	1.074	0.612	1.882	1.299	0.486	3.477	0.256	0.033	1.959

Supplemental Table 3.6: NPOU Medications Multinomial Logistic Regression

NOU = reference	COU			NPOU			POU			UTOE		
Number of Opioid Prescriptions	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High
Buprenorphine	**15.18**	**14.564**	**15.822**	**2.021**	**1.913**	**2.135**	**56.496**	**54.027**	**59.078**	**0.761**	**0.591**	**0.982**
Codeine	**50.3**	**49.602**	**51.009**	**3.92**	**3.841**	**4**	**9.222**	**9.011**	**9.438**	**4.693**	**4.58**	**4.808**
Dihydrocodeine	N/A	N/A	N/A	0.523	N/A	N/A	0.197	N/A	N/A	0.056	N/A	N/A
Fentanyl	**3.425**	**3.39**	**3.46**	**7.223**	**7.163**	**7.284**	**0.288**	**0.274**	**0.302**	**0.904**	**0.885**	**0.923**
Hydrocodone	**13.134**	**13.045**	**13.225**	**6.093**	**6.054**	**6.132**	**12.662**	**12.554**	**12.77**	**43.05**	**42.812**	**43.29**
Hydromorphone	**7.784**	**7.7**	**7.868**	**4.753**	**4.706**	**4.801**	**2.711**	**2.646**	**2.778**	2.902	2.84	2.965
Meperidine	**6.871**	**5.004**	**9.434**	**21.97**	**19.988**	**24.149**	**19.96**	**17.166**	**23.21**	**516**	**481.031**	**553.512**
Methadone	**2.808**	**2.768**	**2.849**	**1.273**	**1.254**	**1.291**	**0.138**	**0.128**	**0.149**	**0.15**	**0.14**	**0.161**
Morphine	**4.018**	**3.983**	**4.054**	**3.165**	**3.139**	**3.192**	**0.339**	**0.326**	**0.352**	**0.396**	**0.384**	**0.407**
Oxycodone	**46.437**	**46.247**	**46.627**	**19.824**	**19.749**	**19.898**	**13.919**	**13.824**	**14.015**	**12.734**	**12.656**	**12.812**
Oxymorphone	**201.248**	**184.217**	**219.853**	0.073	0.002	2.493	N/A	N/A	N/A	0.118	N/A	40.677
Tapentadol	**592.932**	**158.579**	**N/A**	N/A	N/A	N/A	26.005	0.001	N/A	0.032	N/A	N/A
Tramadol	**26.189**	**26.028**	**26.35**	**12.165**	**12.097**	**12.234**	**13.246**	**13.134**	**13.359**	**3.206**	**3.168**	**3.245**

Supplemental Table 3.7: NPOU Stepwise Multinomial Logistic Regression

NOU = reference	COU			NPOU			POU			UTOE		
Radiation Modality	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High
Brachytherapy	**0.298**	**0.142**	**0.623**	**0.224**	**0.149**	**0.337**	1.407	0.659	3.005	**0.285**	**0.161**	**0.505**
Conformal or 3-D	0.895	0.508	1.576	**0.268**	**0.183**	**0.392**	**3.75**	**2.044**	**6.879**	**0.477**	**0.292**	**0.778**
Electrons	0.536	0.058	4.957	0.359	0.118	1.086	N/A	N/A	N/A	0.301	0.068	1.336

	External Beam	0.611	0.341	1.095	**0.338**	**0.245**	**0.466**	1.555	0.803	3.012	**0.238**	**0.145**	**0.391**
	IMRT	Reference											
	Other	1.964	0.193	20.011	0.596	0.124	2.87	6.815	0.744	62.464	0.611	0.07	5.333
	Photons (11-19 MV)	0.646	0.28	1.494	**0.338**	**0.207**	**0.552**	**2.659**	**1.148**	**6.156**	**0.3**	**0.134**	**0.669**
	Photons (2-5 MV)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Photons (6-10 MV)	**0.545**	**0.333**	**0.892**	**0.241**	**0.178**	**0.327**	**2.449**	**1.412**	**4.249**	**0.23**	**0.144**	**0.368**
	Photons (>19 MV)	555.85	N/A	N/A	67.606	N/A	N/A	N/A	N/A	N/A	46.611	N/A	N/A
	Photons (Mixed energies)	0.567	0.321	1.001	**0.316**	**0.226**	**0.441**	**2.754**	**1.527**	**4.969**	**0.35**	**0.214**	**0.574**
	Photons and Electrons	0.73	0.243	2.192	**0.147**	**0.059**	**0.364**	**3.85**	**1.496**	**9.908**	0.471	0.203	1.092
Clinical Stage													
	0	Reference											
	1	1.445	0.647	3.227	1.326	0.819	2.148	**2.719**	**1.049**	**7.05**	0.695	0.414	1.165
	2	2.158	0.969	4.806	1.242	0.758	2.034	2.617	0.994	6.89	0.762	0.44	1.318
	3	1.984	0.825	4.773	**2.816**	**1.67**	**4.748**	1.674	0.574	4.887	1.119	0.604	2.077
	Criteria Met but unknown	1.185	0.502	2.796	1.373	0.834	2.262	2.33	0.87	6.238	**0.445**	**0.245**	**0.808**
	Not Applicable	1.565	0.618	3.964	**2.52**	**1.454**	**4.368**	2.358	0.772	7.2	0.987	0.488	1.996
Additional Chemotherapy		**1.48**	**1.024**	**2.138**	**1.834**	**1.467**	**2.294**	**2.54**	**1.761**	**3.664**	**1.553**	**1.121**	**2.152**
Comorbid Conditions													
	Anxiety	**1.964**	**1.318**	**2.925**	**1.483**	**1.099**	**2**	1.166	0.72	1.889	1.473	0.869	2.498
	Arthritis	**3.265**	**2.243**	**4.753**	**1.357**	**1.006**	**1.829**	**2.24**	**1.458**	**3.441**	0.89	0.491	1.614
	Back Pain	**3.29**	**2.313**	**4.68**	**1.884**	**1.433**	**2.477**	1.544	0.993	2.402	1.199	0.701	2.053
	Depression	**2.302**	**1.506**	**3.518**	1.397	0.989	1.971	**1.913**	**1.168**	**3.135**	0.697	0.334	1.456
	Heart Disease	1.353	0.959	1.908	1.108	0.871	1.41	1.043	0.706	1.54	**0.536**	**0.329**	**0.875**
	Hypertension	1.378	0.97	1.957	1.194	0.954	1.493	1.133	0.785	1.637	**0.565**	**0.385**	**0.83**
	Lung Disease	**1.775**	**1.215**	**2.593**	**2.019**	**1.546**	**2.638**	1.299	0.819	2.061	1.233	0.744	2.042
Age		**0.971**	**0.955**	**0.987**	**0.984**	**0.974**	**0.994**	0.99	0.974	1.007	1.007	0.992	1.023
Race													
	American Indian-Alaskan	2.983	0.328	27.102	N/A	N/A	N/A	1.982	0.241	16.319	1.657	0.342	8.019
	Asian	0.877	0.176	4.384	0.795	0.287	2.206	0.531	0.069	4.075	0.894	0.206	3.88
	Black of African American	**1.426**	**1.016**	**2.003**	1.216	0.986	1.5	1.287	0.917	1.805	0.866	0.628	1.192
	Other	1.365	0.509	3.657	0.56	0.271	1.159	0.51	0.121	2.14	1.187	0.543	2.594
	Other of Hispanic or Latino or Spanish Origin	**12.038**	**3.769**	**38.452**	2.074	0.672	6.397	**7.599**	**2.203**	**26.213**	0.82	0.1	6.703
	White	Reference											
	White of Hispanic or Latino or Spanish Origin	N/A	N/A	N/A	1.576	0.477	5.204	N/A	N/A	N/A	1.414	0.307	6.511
Insurance													
	Commercial/HMO	Reference											
	VCC	**1.84**	**1.078**	**3.141**	**1.804**	**1.216**	**2.675**	0.916	0.455	1.845	0.56	0.197	1.589
	Insurance, NOS	1.672	0.921	3.035	**1.645**	**1.154**	**2.345**	1.352	0.747	2.447	1.372	0.815	2.309
	Medicaid	**1.872**	**1.032**	**3.396**	**2.305**	**1.527**	**3.478**	1.29	0.647	2.571	**2.831**	**1.573**	**5.095**
	Medicare	1.543	0.963	2.474	**1.6**	**1.206**	**2.123**	1.297	0.83	2.027	1.36	0.909	2.034
	Military	1.343	0.297	6.065	0.817	0.305	2.191	1.502	0.436	5.175	0.608	0.14	2.652

Self-Pay	1.845	0.995	3.422	**2.4**	**1.616**	**3.562**	0.64	0.245	1.671	**2.52**	**1.389**	**4.572**
Unknown	1.709	0.312	9.371	2.236	0.69	7.248	2.726	0.518	14.355	3.251	0.641	16.491
Substance Use												
Alcohol Use	**2.711**	**1.495**	**4.918**	1.091	0.633	1.881	**2.249**	**1.002**	**5.046**	1.891	0.792	4.515
Nicotine Use	**3.55**	**2.48**	**5.083**	**1.814**	**1.397**	**2.356**	1.525	0.977	2.38	0.863	0.518	1.439

Supplemental Table 3.8: NPOU Final Multinomial Logistic Regression (Stepwise + Theoretical)

NOU = reference	COU			NPOU			POU			UTOE		
Radiation Modality	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High	OR	95% CI Low	95% CI High
Brachytherapy	**0.227**	**0.1**	**0.513**	**0.514**	**0.319**	**0.829**	**0.36**	**0.152**	**0.857**	**0.429**	**0.214**	**0.86**
Conformal or 3-D	0.667	0.344	1.294	**0.5**	**0.325**	**0.771**	0.913	0.429	1.943	0.774	0.431	1.389
Electrons	0.185	0.017	2.021	0.691	0.209	2.291	N/A	N/A	N/A	0.475	0.093	2.412
External Beam	**0.416**	**0.217**	**0.797**	**0.512**	**0.357**	**0.735**	**0.418**	**0.193**	**0.906**	**0.331**	**0.188**	**0.583**
IMRT	Reference											
Other	1.371	0.134	14.064	0.792	0.162	3.882	2.225	0.219	22.58	1.268	0.133	12.1
Photons (11-19 MV)	0.469	0.187	1.181	**0.467**	**0.27**	**0.808**	0.792	0.306	2.05	0.476	0.196	1.156
Photons (2-5 MV)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Photons (6-10 MV)	**0.37**	**0.207**	**0.658**	**0.514**	**0.359**	**0.736**	0.56	0.277	1.132	**0.391**	**0.223**	**0.686**
Photons (>19 MV)	N/A	N/A	N/A	256.476	N/A	N/A	N/A	N/A	N/A	116.776	N/A	N/A
Photons (Mixed energies)	**0.403**	**0.206**	**0.79**	0.699	0.468	1.042	0.631	0.299	1.336	0.589	0.322	1.077
Photons and Electrons	0.538	0.166	1.741	0.466	0.182	1.192	0.81	0.28	2.345	0.855	0.336	2.173
Clinical Stage												
0	Reference											
1	1.565	0.683	3.588	1.049	0.635	1.73	**2.659**	**1.01**	**7.001**	0.592	0.344	1.017
2	**2.38**	**1.011**	**5.603**	1.155	0.682	1.959	**2.93**	**1.079**	**7.956**	0.82	0.452	1.486
3	1.952	0.763	4.99	1.617	0.92	2.841	2.214	0.733	6.684	0.876	0.444	1.731
Criteria Met but unknown	0.984	0.395	2.448	1.002	0.587	1.712	2.475	0.903	6.789	0.356	0.187	0.675
Not Applicable	1.003	0.279	3.614	**2.29**	**1.009**	**5.198**	4.024	0.957	16.929	0.792	0.219	2.864
Additional Chemotherapy	1.382	0.896	2.132	**1.539**	**1.179**	**2.009**	**2.742**	**1.81**	**4.154**	**1.476**	**1.014**	**2.148**
Comorbid Conditions												
Anxiety	**2.123**	**1.404**	**3.21**	**1.496**	**1.095**	**2.044**	1.219	0.746	1.992	1.48	0.864	2.538
Arthritis	**3.342**	**2.27**	**4.921**	**1.516**	**1.113**	**2.066**	**2.198**	**1.421**	**3.4**	0.935	0.512	1.71
Back Pain	**3.405**	**2.365**	**4.902**	**1.924**	**1.449**	**2.554**	1.526	0.974	2.39	1.239	0.718	2.138
Depression	**2.271**	**1.464**	**3.522**	**1.557**	**1.09**	**2.225**	**1.784**	**1.08**	**2.949**	0.742	0.353	1.559
Heart Disease	1.313	0.92	1.873	1.175	0.914	1.511	0.958	0.643	1.427	**0.523**	**0.318**	**0.862**
Hypertension	1.299	0.905	1.863	1.183	0.937	1.494	1.166	0.802	1.695	**0.55**	**0.371**	**0.816**
Lung Disease	**1.891**	**1.273**	**2.809**	**1.811**	**1.37**	**2.395**	1.289	0.801	2.074	1.171	0.701	1.956
Age	**0.966**	**0.949**	**0.984**	**0.981**	**0.97**	**0.991**	**0.997**	0.979	1.015	1.007	0.99	1.023

Race												
American Indian-Alaskan	4.949	0.562	43.623	N/A	N/A	N/A	2.045	0.244	17.15	1.657	0.328	8.363
Asian	0.883	0.177	4.415	0.715	0.258	1.983	0.567	0.071	4.542	0.805	0.18	3.596
Black of African American	**1.564**	**1.093**	**2.238**	**1.37**	**1.097**	**1.709**	1.27	0.895	1.801	0.948	0.683	1.317
Other	1.406	0.522	3.791	0.532	0.252	1.126	0.502	0.118	2.141	1.151	0.517	2.561
Other of Hispanic or Latino or Spanish Origin	13.022	3.939	43.048	2.083	0.655	6.618	**8.857**	**2.419**	**32.435**	0.841	0.098	7.21
White	Reference											
White of Hispanic or Latino or Spanish Origin	N/A	N/A	N/A	1.358	0.389	4.742	N/A	N/A	N/A	0.921	0.189	4.497
Insurance												
Commercial/HMO	Reference											
VCC	**2.171**	**1.246**	**3.784**	**1.735**	**1.15**	**2.618**	0.929	0.452	1.91	0.524	0.183	1.505
Insurance, NOS	1.699	0.928	3.111	**1.538**	**1.069**	**2.213**	1.44	0.788	2.629	1.345	0.793	2.28
Medicaid	**1.936**	**1.046**	**3.584**	**2.175**	**1.418**	**3.336**	1.37	0.676	2.778	**2.894**	**1.593**	**5.258**
Medicare	**1.634**	**1.005**	**2.658**	**1.538**	**1.149**	**2.06**	1.341	0.847	2.123	1.362	0.907	2.045
Military	1.194	0.237	6.027	0.922	0.337	2.523	1.924	0.55	6.727	0.79	0.178	3.506
Self-Pay	**2.076**	**1.089**	**3.957**	**2.191**	**1.449**	**3.313**	0.891	0.333	2.385	**2.567**	**1.383**	**4.767**
Unknown	1.704	0.3	9.677	2.204	0.679	7.153	4.182	0.753	23.216	3.505	0.66	18.622
Substance Use												
Alcohol Use	**2.478**	**1.31**	**4.686**	0.851	0.482	1.502	**2.956**	**1.243**	**7.031**	1.506	0.611	3.71
Nicotine Use	**3.729**	**2.559**	**5.434**	**1.625**	**1.235**	**2.138**	**1.665**	**1.048**	**2.643**	0.719	0.426	1.213
Sex												
Male	0.609	0.36	1.029	0.978	0.727	1.314	0.637	0.344	1.18	0.841	0.538	1.315
Female	Reference											
Additional Surgery	1.136	0.615	2.098	0.978	0.694	1.376	1.562	0.731	3.336	**1.962**	**1.162**	**3.311**
Additional Hormonal Therapy	0.734	0.48	1.124	1.109	0.823	1.495	1.185	0.804	1.745	1.217	0.815	1.817
Cancer Type												
Anus	1.761	0.522	5.942	**4.583**	**2.266**	**9.268**	0.801	0.151	4.248	**4.334**	**1.499**	**12.529**
Brain and Nervous System	0.189	0.018	1.972	0.772	0.3	1.984	0.351	0.062	2.002	1.913	0.42	8.705
Breast	Reference											
Cervix	**0.185**	**0.035**	**0.977**	**3.422**	**1.696**	**6.904**	0.528	0.103	2.709	3.086	0.891	10.692
Colorectal	0.705	0.237	2.101	**3.161**	**1.836**	**5.442**	0.129	0.017	1.001	0.716	0.254	2.022
Corpus and Uterus	0.647	0.131	3.202	**2.509**	**1.264**	**4.977**	1.159	0.354	3.793	2.06	0.554	7.651
Esophagus	**6.45**	**1.091**	**38.125**	**8.563**	**2.961**	**24.766**	N/A	N/A	N/A	1.949	0.22	17.233
Hodgkin's Disease	0.41	0.043	3.913	1.113	0.335	3.698	**5.102**	**1.423**	**18.294**	2.441	0.486	12.252
Larynx	2.459	0.724	8.349	6.236	3.09	12.585	0.69	0.077	6.18	**8.366**	**3.125**	**22.393**
Leukemia, Lymphoma, Other Hematopoietic	2.259	0.71	7.192	1.396	0.67	2.911	1.531	0.484	4.847	0.622	0.135	2.872
Liver	**6.645**	**1.075**	**41.073**	1.906	0.478	7.61	N/A	N/A	N/A	**11.737**	**3.087**	**44.625**

	Lung and Bronchus	0.691	0.236	2.027	**3.106**	**1.699**	**5.679**	0.597	0.169	2.114	**4.181**	**1.804**	**9.687**
	Multiple Myeloma	**6.342**	**1.015**	**39.648**	**5.369**	**1.866**	**15.453**	N/A	N/A	N/A	4.297	0.695	26.583
	Oral Cavity and Pharynx	2.342	0.936	5.857	**5.184**	**2.956**	**9.092**	0.881	0.26	2.991	**4.85**	**2.13**	**11.041**
	Other	2.547	0.683	9.506	1.929	0.733	5.075	2.857	0.794	10.279	3.12	0.8	12.167
	Other Respiratory and Thoracic Organs	6.473	0.918	45.634	**5.328**	**1.417**	**20.04**	2.947	0.288	30.116	**6.832**	**1.114**	**41.891**
	Other Female Genital	0.299	0.026	3.483	2.245	0.836	6.025	N/A	N/A	N/A	3.713	0.95	14.51
	Pancreas	3.137	0.454	21.671	0.998	0.115	8.636	**4.852**	**1.102**	**21.37**	8.5	1.834	39.401
	Prostate	1.109	0.37	3.32	0.774	0.387	1.548	0.976	0.266	3.585	0.967	0.324	2.886
	Skin	**7.256**	**1.657**	**31.784**	1.576	0.404	6.146	3.6	0.708	18.321	3.863	0.942	15.834
	Soft Tissue including Heart	**4.855**	**1.593**	**14.79**	**6.575**	**3.297**	**13.111**	1.458	0.31	6.861	1.826	0.492	6.776
	Stomach	**5.796**	**1.441**	**23.314**	**3.483**	**1.144**	**10.61**	N/A	N/A	N/A	3.217	0.623	16.599
	Unknown	5.004	0.937	26.716	1.701	0.542	5.342	1.674	0.257	10.907	3.473	0.55	21.932

CHAPTER 4: PRESCRIBED OPIOID DOSES IN CANCER SURVIVORS PRE- AND POST-CURATIVE INTENT RADIATION

Abstract

Background: Improvements in cancer therapy have led to an increase in the aggregate number of cancer survivors and the duration of time spent in the survivorship period. There is growing awareness of opioid use in cancer survivors as the population increases. Pain management is an important consideration for patients with cancer, as malignancies, invasive surgery, chemotherapy, and radiation can all lead to significant pain. Approximately 50% of cancer patients will receive radiation therapy as a component of their treatment, for which opioid utilization is of increasing concern. Neither opioid dose utilization pre- and post-curative intent radiation (CIR) or the factors associated with opioid doses is known. Objective: Determine opioid oral morphine equivalent (OME) doses for cancer survivors after CIR and factors associated with higher opioid dose burden. Methods: Electronic medical record clinical and pharmacy data from cancer survivors receiving radiotherapy for any indication from a single academic cancer center from January 1, 2008 to December 31, 2018 was utilized to calculate OME doses before and after CIR. A panel data model was used to estimate factors associated with high opioid doses and a mixed linear model was used to predict average opioid dose used one year after CIR. Subgroup and sensitivity analyses were then conducted. Results: Cancer survivors that lived at least 5 years after diagnosis and had an opioid prescription prior to radiation were estimated to have, on average, 68.2 (95% CI: 62.8-73.6, panel data model) - 68.3 (95% CI: 62.9-73.7, mixed linear model) OMEs higher that those without an opioid prescription prior to radiation over the course of time, controlling for other factors. Across models and subgroups, patients with public insurance and comorbid conditions of anxiety, depression, and other drug use are associated with higher average OMEs over time, while

patients with diabetes and hypertension are associated with lower average OMEs over time. Controlling for other factors, we predict that patients that undergo radiation for their cancer will use, on average, 4.1 (95% CI: 3.1-5.1) OMEs one year after end of radiation. Discussion: From this study, we can see that many cancer survivors do not utilize opioids long-term before or after radiation. However, for those using opioids to manage cancer and treatment related pain, sustained high doses of opioids are used. Conclusion: Substantial opioid dosages in cancer survivors who received radiation therapy warrants evidence-based recommendations and guidelines for opioid use and discontinuation to prevent misuse and opioid related deaths.

Background

Five-year survival from cancer diagnosis has increased from less than 50% to a mean of 67% (with a large range based on cancer site) over the last several decades.[1,2] Increased survival, in part due to improvements in antineoplastic therapy, has led to an increase in both the aggregate number of cancer survivors and the duration of time patients spend in the survivorship period. Pain management is an important consideration for patients that receive cancer treatment. Opioids are a cornerstone of pain management in patients with cancer, as malignancies themselves can lead to significant pain, in addition to pain resulting from invasive surgery, chemotherapy, and radiation.[3–5] Approximately 50% of cancer patients will receive radiation therapy as a component of their treatment.[6] Undergoing radiation therapy can subject patients to significant morbidity that can vary by treatment site, with patients treated for head and neck cancer tending to have a significant burden of radiation-related acute and late toxicity.[4,7,8]

Thus, cancer survivors who have received radiation are an important demographic to consider, as opioid use and abuse have reached epidemic proportions in the United States.

There is emerging evidence of high rates of opioid misuse (use of opioids contrary to the directed or prescribed pattern of use, regardless of presence or absence of harm) in patients with cancer.[9–14] One study found that more than half (58%) of patients with cancer were noncompliant with their prescribed opioid therapy.[10] Ultimately, an estimated 29% of patients with cancer are at high-risk for misuse.[3,15] Additionally, recent evidence suggests that cancer-directed therapies (especially surgery and radiation directed to the head and neck) may promote opioid use long after the cancer therapy is concluded.[8,16–18]

While there are evidence based recommendations for opioid formulations to use for patients with cancer undergoing therapy, there are no daily oral morphine equivalent (OME) dose recommendations for patients with cancer.[19] The 2016 chronic opioid prescribing guidelines for non-cancer pain (cancer pain explicitly excluded) recommended avoiding daily OME doses greater than 90 and for prescribers to use caution with daily OME doses greater than 50.[20] Subsequently Guy Jr et al. noted that decreases in opioid prescriptions followed the "publication of two national guidelines defining high-dose opioid prescribing as >200 MME/day. […, These guidelines] coincided with studies demonstrating progressively increasing overdose risk at prescribed opioid dosages exceeding 20, 50, and 100 [OME] per day and publications highlighting associations of prescribed opioids with overdose deaths."[21]

It has been suggested that opioid utilization patterns (chronic opioid use by total daily dose, dose escalations, and dose reductions) are similar between patients with cancer pain and patients with non-cancer pain, although patients were not matched.[22,23] However, this has not been studied well in cancer survivors. Cancer survivors with chronic opioid use have been found to have a higher daily dose of opioids than controls in some cancers.[24] Patients with active cancer that were non-compliant with their prescribed opioid therapy have also been found to have higher morphine equivalent daily doses.[10] A review of 22 articles on opioid

analgesic dose and adverse health outcomes in non-cancer patients determined that "risk of misuse, overdose, and death increases with increasing opioid analgesic dose [but, there] is no clear dose inflection point beyond which the risk of these adverse health outcomes increases [and no] analgesic dose is without risk."[25] Presumably, increased doses of opioids confer similar risk for patients with cancer and cancer survivors long after curative intent therapy. However, opioid dose utilization in cancer survivors after curative intent radiation (CIR) has not been studied.

As more patients are surviving cancer, understanding opioid use, and specifically opioid dose, is of greater concern, especially as there is little to no consensus on the therapeutic framework of treating pain for these patients.[26] Understanding levels of opioid utilization and factors that may put patients at risk for higher opioid requirements may help identify patients that may have difficulty weaning off opioid regimens.

Methods

Data Source, Patient Identification, and Patient Covariates

In order to conduct this project, we utilized electronic medical record data from individuals receiving radiotherapy for any indication at Virginia Commonwealth University's Massey Cancer Center between January 1, 2008 to December 31, 2018. Patients 18 years of age or older with any cancer type and stage receiving radiation with or without any additional treatment modalities (surgery, chemotherapy) were included. Patients receiving radioisotopes or radium as their primary radiation therapy were excluded. We only included patients that classify as cancer survivors, defined as the absence of metastatic disease or recurrence within 5 years of diagnosis (5CS). Prisoners were excluded. Covariate information on the date of cancer diagnosis, cancer type, stage, treatment type, treatment details, comorbid conditions,

germane social history (including alcohol, tobacco, or illicit drug use), and demographic information (e.g., age, race, ethnicity and insurance status and type - including Virginia Coordinated Care [VCC], the institution sponsored health insurance for which all medical records should be available for these patients) was used. Prescribed opioid medications were included if written for the outpatient setting for at least a 14-day supply. Due to the differing approach to pain treatment acutely, inpatient opioids and prescriptions written during radiation treatment were excluded. Further, only patients with sufficient prescription information to calculate OMEs were included in this study.

Opioid Prescription Equivalencies

Medication prescribing data was coded to create a monthly longitudinal record of the average daily oral morphine equivalent (OME) dose for each patient as described in Chapter 2. Methods included utilizing outpatient prescriptions of at least 14 days supply coded with established OME conversion factors. Prescription OMEs were averaged for each patient at each of 5 time points as described in Figure 4.1. Univariate analysis of average OME at each time point per patient over time was then conducted.

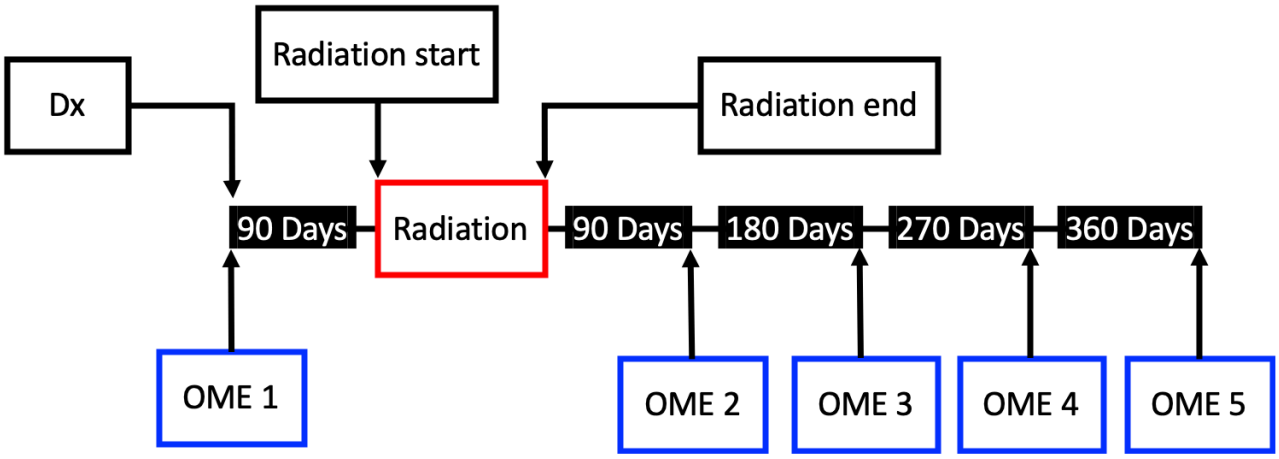

Figure 4.1: Timeline of Opioid Dose Assessment
Dx: Diagnosis date; OME: Oral morphine equivalent dose

Patient Grouping and Categorization

Patients were grouped based on variations in treatment and by cancer type. Patients that receive surgery versus those that do not may have different pain levels and thus a different average OME. Patients were classified by use criteria by methods described in Chapter 3, generally following Lee et al. and Silver et al (Table 4.1).[17,27] These groupings were used to inform accuracy of calculated OME doses based on opioid classification. OME doses from Figure 4.1 were verified to be correct based on Chapter 3's opioid use determined category. An accurate example being a patient classified as NPOU with zero calculated OME dose at time 1 and at time 2-5 calculated OME doses greater than zero. There were patients that could be categorized by opioid exposure based on date of prescription (and day supply) in Chapter 3, but were missing some information required to calculate OME. Patients that OME calculated doses did not fit their opioid exposure categorization were not included in this study. An excluded case example being a patient classified as COU based on date of prescription (and day supply), with calculated OME at time 1 as greater than zero, but at time OME 2-5, calculated OME was zero. The patient in this case was missing necessary information to calculate OME at times OME 2-5, and would appear in this study to be a POU when that was not the case.

Table 4.1: Summary of Patient Groups by Opioid Exposure

Group	Abbreviation	Definition
Chronic Opioid User	COU	Prescribed at least one opioid prescription 30 days before treatment (OE) and at least one opioid prescription 30 days after treatment
Never Opioid User	NOU	Had no known opioid prescription history before (ON) or after treatment
New Persistent Opioid User	NPOU	Previously ON who was prescribed at least one opioid prescription 30 after treatment
Previous Opioid User	POU	Prescribed at least one opioid prescription 30 days before treatment (OE) and no known opioid prescription history after treatment

Statistical Analysis: Panel Data Model and Mixed Linear Model

To estimate factors associated with average daily OME dose after CIR therapy, two model types were utilized. Dummy variables were created for all categorical covariates. For both models, a dummy variable of presence of OME dose at baseline, "Baseline Opioid Prescription" (yes = 1, no =0) was used. A dynamic panel data model (PDM) was built as, $OME_t = f(OME_{t-1}$, covariates), where t = 90 days before radiation start and 90, 180, 270, 360 days after radiation end (Figure 4.1; Specific Aim 3b, Tables 4.2 and 4.3). Two PDMs were built: (1) a significant model with only covariates included with p-values <0.05 and (2) a theoretical model with significant covariates from model 1 and important covariates to adjust for age, race, sex, treatment modality, comorbidities, and insurance. The second model, a mixed linear model (MLM), allowed for assessment of OME per day and was used to predict average daily OME after CIR. As with the PDMs, significant and theoretical models were created with covariates of age, race, sex, treatment modality, comorbidities, insurance (Specific Aim 3c, Tables 4.2 and 4.3). Results of the average OME per day variable from the MLM were then utilized to predict average OME dosages controlling for other factors at each time point following radiation. Resulting average OME dose per day was multiplied by the time point day to estimate total average OME dose predicted at each time point.

For the panel data model, the Breusch and Pagan Lagrangian Multiplier (LM) test for random effects resulted in a p-value < 0.0001. Therefore, a random effects model was used instead of the ordinary least squares (OLS) model. Additionally, the Hausman test for fixed versus random effects estimators supported use of random effects model. The random effect utilized in the MLM was the de-identified patient ID number. P-values of <0.05 were considered statistically significant. Statistical analyses were conducted using Stata v15.1 and SAS v9.4 (SAS Institute, Cary, NC).

Table 4.2: Methods for Specific Aim 3

Specific Aim 3		
In cancer survivors who received curative intent radiation therapy for their malignancy, examine new persistent and continued chronic opioid use and 30-day average daily OME dose after curative intent radiation therapy		Method
3b	Examine average daily OME dose for opioid use overall over time before and after curative intent radiation	Panel data models
3c	Predict average daily OME dose between new persistent and continued chronic opioid use in the year following radiation therapy	Mixed linear models

Table 4.3: Panel Data Model and Mixed Linear Models

Regression	Model Type	Model
Panel Data Model 1	Significant	$OME_t = \beta_0 + \beta_{1\ldots n}$(Clinical Significant Factors)+ $\beta_{n+1\ldots n+2}$ (Sociodemographic Significant Factors) + ε^a
Panel Data Model 2	Theoretical	$OME_t = \beta_0 + \beta_{1\ldots n}$(Clinical Significant Factors)+ $\beta_{n+1\ldots n+2}$ (Sociodemographic Significant Factors) + ε^a
Mixed Linear Model 1	Significant	$OME = \beta_0 + \beta_1(\mathrm{OME_{baseline}}) + \beta_2(\mathrm{Day}) + \beta_{3\ldots n}$ (Clinical Significant Factors)+ $\beta_{n+1\ldots n+2}$ (Sociodemographic Significant Factors) + ε^a
Mixed Linear Model 2	Theoretical	$OME = \beta_0 + \beta_1(\mathrm{OME_{baseline}}) + \beta_2(\mathrm{Day}) + \beta_{3\ldots n}$ (Clinical Significant Factors)+ $\beta_{n+1\ldots n+2}$ (Sociodemographic Significant Factors) + ε^a

Significant model includes significant covariates only; Theoretical model includes significant covariates and important non-significant covariates

Subgroup and Sensitivity Analyses

In order to assess the robustness of our results, we conducted four subgroup analyses. First, a subgroup analysis for patients with VCC was conducted to compare to patients without VCC to determine if differences existed due to potentially missed pre-radiation opioid prescriptions in patients without VCC. To further assess impact of missing prescriptions and assess the difference due to "0" OME doses for NOU, we conducted a subgroup analysis with patients with at least one calculated OME prescription (removed patients classified as NOU, i.e. those with OME doses of "0" before and after radiation). Lastly, we conducted sensitivity analyses of patients with cancer that received radiation and lived without recurrence, metastatic disease, or death for at least 1 (1-Year Cancer Survivors; 1CS) and 3 years (3-Year Cancer Survivors; 3CS) after diagnosis.

Results

Between January 1, 2008 and December 31, 2018, 7,767 patients over the age of 18 underwent radiation therapy for their malignancies at a single institution (Chapter 2). Of these patients, 1,059 had known opioid exposure status and survived without metastasis or recurrence of their disease beyond 5 years (5-Year Cancer Survivors; 5CS), but only 414 patients had sufficient prescription information to be able to calculate OME or be classified as never opioid users (Figure 4.2). In other words, 38.7% (414 / 1,059) of patients with opioid prescriptions had sufficient information to calculate OME corresponding to their assigned opioid use category. Patients with opioid prescriptions had an average of 6.2 prescriptions (Standard Deviation [SD]: 10.8, Median: 2, Interquartile Range [IQR]: 4, Range: 1-79) over the course of the study, with average days supply of 29.5 days (Standard Deviation [SD]: 10.7, Median: 30, Interquartile Range [IQR]: 0, Range: 14-90) per prescription.

Table 4.4 describes patient demographics, clinical characteristics, and opioid use categories for patients included in this study as well as those in subgroup analyses. Across samples, patients were majority female, white (except VCC being majority African American), did not have comorbid conditions (except VCC, with the majority of patients having hypertension), had additional surgery and the largest number carried commercial insurance. Breast cancer was the most common cancer type (54.2% in the base case). Most patients fell in the NOU (85.9%) category, except when NOU patients were removed for the “No NOU” group for which most patients were NPOUs. The VCC and No NOU groups were more likely to have comorbidities. Opioid use was much higher in VCC and No NOU groups. Table 4.5 describes summary statistics of daily OME for prescriptions at each time point. Average OME doses were higher following radiation therapy and decreased slightly over time.

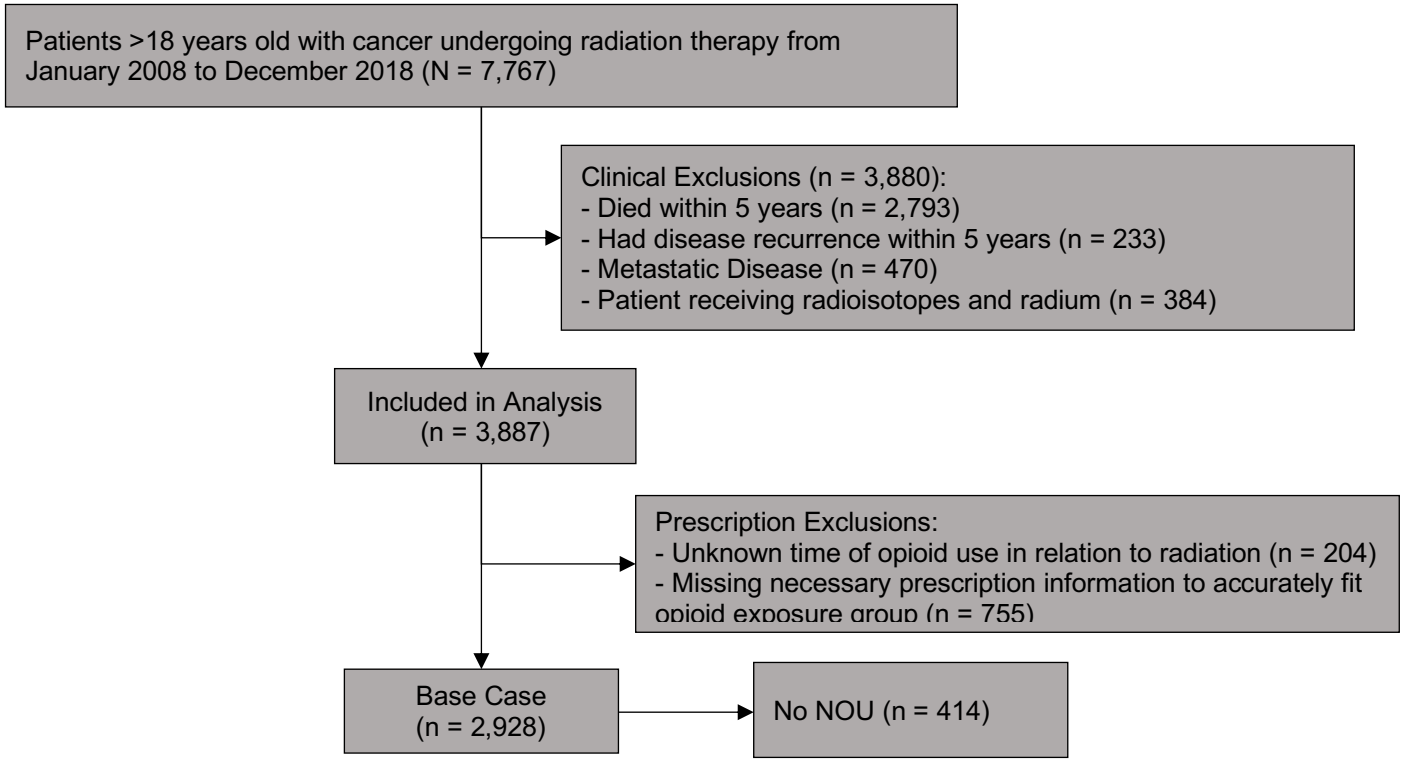

Figure 4.2: CONSORT Diagram

Table 4.4: Patient Demographics

	Base Case (n = 2,928)	VCC (n = 167)	No NOU (n = 414)	1 Year (n = 3,654)	3 Year (n = 3,115)
Age					
Mean (SD)	58.9 (12.1)	53.1 (10.4)	54.8 (12.7)	59.9 (12.4)	59.2 (12.2)
Median (IQR)	59 (16)	55 (14)	56 (16)	60 (16)	60 (15)
			N (%)		
Gender					
Female	2,097 (71.6)	122 (73.1)	230 (55.6)	2,492 (68.2)	2,212 (71.0)
Male	831 (28.4)	45 (17.0)	184 (44.4)	1,162 (31.8)	903 (29.0)
Race					
Black or African American	955 (32.6)	99 (59.3)	166 (40.1)	1,200 (32.84)	1,201 (32.8)
White	1,828 (62.4)	55 (32.9)	229 (55.3)	2,280 (62.4)	1,936 (62.2)
Other	145 (5.0)	13 (7.8)	19 (4.6)	174 (4.8)	158 (5.1)
Insurance Type					
Commercial	1,268 (43.3)	0 (0)	128 (30.9)	1,445 (39.6)	1,313 (42.2)
VCC	167 (5.7)	167 (100)	50 (12.1)	201 (5.5)	173 (5.6)
Insurance, Not Specified	212 (7.2)	0 (0)	35 (8.5)	247 (6.8)	218 (7.0)
Medicaid	131 (4.5)	0 (0)	45 (10.9)	176 (4.8)	139 (4.5)
Medicare	960 (32.8)	0 (0)	101 (24.4)	1,342 (36.7)	1,072 (34.4)
Military	40 (1.4)	0 (0)	2 (0.5)	47 (1.3)	42 (1.3)
Self-Pay	138 (4.7)	0 (0)	49 (11.8)	175 (4.8)	146 (4.7)
Unknown	12 (0.4)	0 (0)	4 (1.0)	21 (0.6)	12 (0.4)
Cancer Type					

Breast	1,586 (54.2)	82 (49.1)	100 (24.2)	1,716 (47.0)	1,647 (53.9)
Colorectal	164 (5.6)	9 (5.4)	55 (13.3)	219 (6.0)	181 (5.8)
Female Genital	113 (3.9)	33 (19.8)	22 (5.3)	142 (3.9)	120 (3.9)
Gastrointestinal	71 (2.4)	1 (0.6)	26 (6.3)	151 (4.1)	81 (2.6)
Head and Neck	196 (6.7)	8 (4.8)	69 (16.7)	252 (6.9)	212 (6.8)
Lung	158 (5.4)	3 (1.8)	42 (10.1)	376 (10.3)	195 (6.3)
Prostate	263 (9.0)	18 (10.8)	12 (2.9)	288 (7.9)	278 (8.9)
Other	377 (12.9)	13 (7.8)	88 (21.3)	510 (14.0)	401 (12.9)
Clinical Stage					
0	261 (9.0)	15 (9.0)	9 (2.2)	275 (76)	269 (8.7)
1	818 (28)	37 (22.2)	75 (18.4)	941 (25.8)	861 (27.8)
2	734 (25.2)	59 (35.3)	102 (25)	885 (24.3)	776 (25.0)
3	345 (11.8)	18 (10.8)	108 (26.5)	580 (15.9)	388 (12.5)
Unknown	757 (26.0	38 (22.8)	114 (27.9)	960 (26.4)	808 (26.1)
Additional Chemotherapy					
Chemotherapy +	1,254 (42.8)	80 (47.6)	289 (69.8)	1,699 (46.5)	1,354 (43.5)
Chemotherapy -	1,674 (57.2)	88 (52.4)	125 (30.2)	1,956 (53.5)	1,762 (56.6)
Additional Surgery					
Surgery +	2,093 (71.5)	121 (72.0)	231 (55.8)	2,416 (66.1)	2,195 (70.4)
Surgery -	836 (28.5)	47 (28.0)	183 (44.2)	1,239 (33.9)	921 (29.6)
Comorbid Conditions					
Anxiety +	302 (10.3)	38 (22.8)	105 (25.4)	370 (10.1)	321 (10.3)
Anxiety -	3,626 (89.7)	129 (77.3)	309 (74.6)	3,284 (89.9)	2,794 (89.7)
Back Pain +	309 (10.6)	45 (27.0)	118 (28.5)	395 (10.8)	337 (10.8)
Back Pain -	2,619 (89.5)	122 (73.05)	296 (71.5)	3,295 (89.2)	2,778 (89.2)
Depression +	208 (7.1)	23 (13.8)	77 (18.6)	258 (7.1)	223 (7.2)
Depression -	2,720 (92.9)	144 (86.2)	337 (81.4)	3,396 (92.9)	2,892 (92.8)
Hypertension +	949 (32.4)	104 (62.3)	204 (49.3)	1,210 (33.1)	1,018 (32.7)
Hypertension -	1,979 (67.6)	63 (37.7)	210 (50.7)	2,444 (66.9)	2,097 (67.3)
Lung Disease +	337 (11.5)	33 (19.8)	127 (30.7)	486 (13.3)	373 (12.0)
Lung Disease -	2,591 (88.5)	134 (80.2)	287 (69.3)	3,168 (86.7)	2,742 (88.0)
Substance Use					
Alcohol Use +	76 (2.6)	9 (5.4)	36 (8.7)	108 (3.0)	86 (2.8)
Alcohol Use -	2,852 (97.4)	158 (94.6)	378 (91.3)	3,546 (97.0)	3,029 (97.2)
Nicotine Use +	388 (13.3)	58 (34.7)	153 (37.0)	517 (14.2)	418 (13.4)
Nicotine Use -	2,540 (86.8)	109 (65.3)	261 (63.0)	3,137 (85.9)	2,697 (86.6)
Other Drug Use +	65 (2.2)	13 (7.8)	34 (8.2)	99 (2.7)	74 (2.4)
Other Drug Use -	2,863 (97.8)	154 (92.2)	380 (91.8)	3,555 (97.3)	3,041 (97.6)
Opioid Use Status					
COU	179 (6.1)	26 (15.5)	179 (43.2)	266 (7.3)	196 (6.3)
NPOU	220 (7.5)	22 (13.1)	220 (53.1)	352 (9.6)	242 (7.8)
POU	15 (0.5)	2 (1.2)	15 (3.6)	17 (0.5)	16 (0.5)
NOU	2514 (85.9)	118 (70.2)	0 (0)	3,020 (82.6)	2,662 (85.4)

COU: Chronic Opioid User; NPOU: New Persistent Opioid User; POU: Previous Opioid User; NOU: Never Opioid User; VCC: Virginia Coordinated Care

Table 4.5: Summary of Prescriptions by Time Point without NOU

Day	Number of Averaged Prescriptions	Average OME Dose (Std)	Median OME Dose (IQR)	Range
OME 1: -90	194	20.6 (65.7)	<0.1 (15.7)	<0.1 – 896.0
OME 2: 90	319	54.9 (132.4)	15.5 (50.4)	<0.1 – 1,480.9
OME 3: 180	362	53.4 (121.6)	17.1 (48.2)	<0.1 – 1,511.3
OME 4: 270	386	51.8 (108.2)	16.2 (46.2)	<0.1 – 1,104.6
OME 5: 360	406	51.9 (105.1)	16.2 (45.6)	<0.1 – 962.7
Total	1667	46.5 (109.6)	12.4 (42.5)	<0.1 – 1,511.3

OME: Oral Morphine Equivalent; Std: Standard Deviation; IQR: Interquartile Range; NOU: Never Opioid User

Panel Data and Mixed Linear Models

Estimation of both model methods resulted in similar estimates of average daily OME (Table 4.6). 5CS who had an opioid prescription with a calculated OME 90 days before radiation start had substantially higher average daily OME doses than those without an opioid before radiation. On average, the difference was 68.2 (95% CI: 62.8-73.6) from the PDM and 68.3 (95% CI: 62.9-73.7) from the MLM OMEs, controlling for other factors. Other characteristics that were associated with higher average OMEs over time, controlling for other factors, included public insurance compared to private or other types of insurance, comorbid conditions of anxiety and depression, and other drug use. Comorbid diabetes and hypertension consistently resulted in significantly lower OMEs across models, controlling for other factors. For 5CS, no cancer type was significantly associated with OME dose in the panel data model, whereas colorectal, female genital, and head and neck cancers were associated with increased OME in the mixed linear model.

Table 4.6: Panel Data and Mixed Linear Models of OME Over Time in 5CS (Base Case)

	Panel Data Model				Mixed Linear Model			
	Significant		Theoretical		Significant		Theoretical	
Characteristic	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
Intercept	-0.43 (-2.17, 1.31)	0.6290	3.30 (-5.67, 12.26)	0.4710	**-1.90 (-3.68, -0.12)**	**0.036**	-3.20 (-12.74, 6.33)	0.5099

Average OME Per Day	--	--	--	--	**0.01 (0.01, 0.01)**	**<0.0001**	**0.01 (0.01, 0.01)**	**<0.0001**
Baseline Opioid Prescription	**69.86 (64.55, 75.17)**	**<0.0001**	**68.19 (62.79, 73.60)**	**<0.0001**	**69.86 (64.54, 75.17)**	**<0.0001**	**68.33 (62.93, 73.74)**	**<0.0001**
Age at Diagnosis			-0.11 (-0.24, 0.02)	0.0850			-0.11 (-0.24, 0.02)	0.0925
Gender (Male)	**2.97 (0.13, 5.81)**	**0.0400**	3.16 (-1.38, 7.70)	0.1730	2.97 (0.13, 5.81)	0.0405	3.62 (-0.93, 8.17)	0.1185
Race (African American)			-2.25 (-5.08, 0.57)	0.1180			-2.29 (-5.12, 0.54)	0.1121
Insurance (Public)			**3.86 (0.85, 6.87)**	**0.0120**			**3.71 (0.71, 6.72)**	**0.0155**
Cancer Type								
Breast			1.35 (-4.42, 7.11)	0.6470			6.30 (-0.32, 12.92)	0.0619
Colorectal			0.85 (-5.92, 7.63)	0.8060			**8.94 (1.15, 16.72)**	**0.0244**
Female Genital			4.17 (-3.98, 12.31)	0.3160			**12.55 (3.47, 21.63)**	**0.0068**
Head and Neck			4.75 (-2.15, 11.65)	0.1770			**9.26 (1.83, 16.70)**	**0.0146**
Lung			2.09 (-5.27, 9.44)	0.5780			6.80 (-1.16, 14.75)	0.094
Prostate			-1.96 (-8.76, 4.83)	0.5720			2.51 (-4.80, 9.82)	0.5009
Other			3.39 (-2.90, 9.68)	0.2900			**9.78 (2.90, 16.66)**	**0.0054**
Comorbid Condition								
Anxiety	**12.76 (8.28, 17.24)**	**<0.0001**	**11.48 (6.93, 16.03)**	**<0.0001**	**12.76 (8.28, 17.25)**	**<0.0001**	**11.35 (6.81, 15.89)**	**<0.0001**
Back Pain			3.23 (-1.13, 7.59)	0.1460			2.99 (-1.37, 7.35)	0.1784
Depression	**7.46 (2.18, 12.75)**	**0.0060**	**6.90 (1.59, 12.21)**	**0.0110**	**7.46 (2.17, 12.75)**	**0.0057**	**7.12 (1.81, 12.42)**	**0.0086**
Diabetes	**-4.63 (-8.93, -0.34)**	**0.0340**	**-4.73 (-9.06, -0.40)**	**0.0320**	**-4.63 (-8.93, -0.34)**	**0.0345**	**-4.70 (-9.03, -0.38)**	**0.0332**
Hypertension	**-3.58 (-6.55, -0.62)**	**0.0180**	**-3.62 (-6.72, -0.53)**	**0.0220**	**-3.58 (-6.55, -0.62)**	**0.0180**	**-3.53 (-6.63, -0.44)**	**0.0254**
Substance Use								
Alcohol Use			6.40 (-2.18, 14.97)	0.1440			7.35 (-1.25, 15.95)	0.0937
Nicotine Use	**5.36 (1.31, 9.40)**	**0.0090**	**4.29 (0.06, 8.52)**	**0.0470**	**5.36 (1.31, 9.40)**	**0.0095**	4.16 (-0.05, 8.36)	0.0529
Other Drug Use	**29.82 (20.80, 38.83)**	**<0.0001**	**27.48 (18.15, 36.81)**	**<0.0001**	**29.82 (20.80, 38.83)**	**<0.0001**	**27.12 (17.79, 36.45)**	**<0.0001**

95% CI: 95% Confidence Interval; Bold indicates statistical significance, p-value <0.05;
5CS: 5-Year Cancer Survivors

Subgroup and Sensitivity Analyses

VCC Patients

In order to assess the robustness of our results, the first subgroup analysis conducted involved only patients receiving indigent charity VCC care for which patients receive all care at the institution. This group was identified to specifically address potential for and effects of missing prescriptions from outside institutions not captured in this study. In comparison to the base case model demographics, patients with VCC were slightly younger, and had a higher proportion of African Americans, female genital cancers, comorbid conditions, and substance use (Table 4.4). Additionally, there were higher proportions of opioid use including COU and NPOU. As in the base case, the PDM and MLM for the VCC group produced similar estimates across models (Table 4.7). Comparing the models, average OME over time with presence of OME at baseline and OME per day were slightly higher for patients with VCC than the base case. Unlike the base case, being of African American race resulted in statistically significant lower OME doses across models over time and controlling for other factors. Additionally, unlike the base case, there were no statistically significant clinical factors, such as cancer type, comorbid conditions, or substance use across VCC subgroup models, although a significant association with nicotine use was seen in the panel data model.

Table 4.7: Panel Data and Mixed Linear Models of OME Over Time in 5CS with VCC

	Panel Data Model				**Mixed Linear Model**			
	Significant		Theoretical		Significant		Theoretical	
Characteristic	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
Intercept	**55.35 (16.37, 94.33)**	**0.0050**	42.13 (-20.84, 105.10)	0.1900	**52.20 (12.88, 91.51)**	**0.0096**	31.66 (-41.60, 104.93)	0.3945
Average OME Per Day	--	--	--	--	**0.02 (0.01, 0.03)**	**0.0006**	**0.02 (0.01, 0.03)**	**0.0006**
Baseline Opioid Prescription	**71.56 (52.64, 90.47)**	**<0.0001**	**71.79 (51.66, 91.93)**	**<0.0001**	**71.56 (52.50, 90.61)**	**<0.0001**	**71.82 (51.51, 92.12)**	**<0.0001**
Age at Diagnosis	**-0.83 (-1.51, -0.15)**	**0.0170**	-0.69 (-1.49, 0.11)	0.0900	**-0.83 (-1.52, -0.14)**	**0.0183**	-0.68 (-1.49, 0.12)	0.0958

Gender (Male)			-12.85 (-57.12, 31.42)	0.5690			-8.83 (-52.61, 34.95)	0.6908
Race (African American)	**-14.96 (-29.20, -0.73)**	**0.0390**	**-15.82 (-31.56, -0.09)**	**0.0490**	**-14.96 (-29.30, -0.62)**	**0.041**	**-16.07 (-32.00, -0.14)**	**0.048**
Insurance (Public)	--	--	--	--	--	--	--	--
Cancer Type								
Breast			8.04 (-38.32, 54.39)	0.7340			15.39 (-46.14, 76.93)	0.6218
Colorectal			-10.60 (-69.28, 48.08)	0.7230			6.99 (-46.17, 60.16)	0.7953
Female Genital			3.24 (-63.23, 69.72)	0.9240			23.92 (-39.05, 86.89)	0.4541
Head and Neck			13.46 (-33.62, 60.55)	0.5750			17.26 (-38.24, 72.76)	0.5397
Lung			-8.07 (-72.60, 56.45)	0.8060			-2.49 (-76.31, 71.33)	0.947
Prostate			19.07 (-22.74, 60.88)	0.3710			22.52 (-27.88, 72.92)	0.3786
Other			13.40 (-44.49, 71.29)	0.6500			12.87 (-40.87, 66.61)	0.6367
Comorbid Condition								
Anxiety			11.67 (-7.86, 31.21)	0.2420			11.48 (-8.26, 31.22)	0.2522
Back Pain			-7.39 (-25.15, 10.37)	0.4150			-7.66 (-7.66, -25.66)	0.4018
Depression			-3.63 (-26.21, 18.95)	0.7530			-3.44 (-26.21, 19.34)	0.7659
Diabetes			-0.63 (-19.75, 18.49)	0.9490			-0.17 (-19.46, 19.13)	0.9865
Hypertension			-6.18 (-24.04, 11.69)	0.4980			-6.62 (-24.67, 11.44)	0.4703
Substance Use								
Alcohol Use			-21.62 (-57.99, 14.76)	0.2440			-22.75 (-58.43, 12.94)	0.2098
Nicotine Use			**17.86 (0.56, 35.16)**	**0.0430**			17.27 (-0.24, 34.78)	0.0532
Other Drug Use			-21.33 (-51.37, 8.72)	0.1640			-21.17 (-51.54, 9.19)	0.1702

N = 414; 95% CI: 95% Confidence Interval; Bold indicates statistical significance, p-value <0.05

No NOU

To further assess the effect of a large proportion of patients with no known opioid prescriptions, a second subgroup analysis was conducted excluding patients that fell in the NOU group (i.e. those that never had a known prescription, but who could have had outside prescriptions that were not captured). Compared to the base case group, the gender split was

much more even (far fewer females and breast cancers), suggesting that many females do not get opioid prescriptions or that they are not captured (Table 4.4). A lower proportion of patients received surgery, but higher proportions received chemotherapy, had comorbid diseases, and reported substance use. Comparing the models to the base case, average OME per day over time controlling for other factors was higher, while those with baseline opioid prescriptions were more than 10 OMEs lower overall across models (Table 4.8). Anxiety and other drug use remained statistically significant with OMEs more than double that of the base case overall, controlling for other factors and across models.

Table 4.8: Panel Data and Mixed Linear Models of OME Over Time in 5CS (No Unknown OME)

	Panel Data Model				**Mixed Linear Model**			
	Significant		Theoretical		Significant		Theoretical	
Characteristic	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
Intercept	4.89 (-7.97, 17.76)	0.4560	5.76 (-47.64, 59.16)	0.8330	-5.53 (-18.65, 7.60)	0.4082	-24.32 (-79.64, 31.01)	0.3880
Average OME Per Day	--	--	--	--	**0.06 (0.05, 0.08)**	**<0.0001**	**0.06 (0.05, 0.08)**	**<0.0001**
Baseline Opioid Prescription	**54.85 (37.31, 72.39)**	**<0.0001**	**55.75 (37.79, 73.70)**	**<0.0001**	**54.85 (37.26, 72.44)**	**<0.0001**	**56.53 (38.61, 74.44)**	**<0.0001**
Age at Diagnosis			-0.20 (-1.00, 0.59)	0.6160			-0.18 (-0.97, 0.62)	0.6657
Gender (Male)			15.60 (-7.58, 38.77)	0.1870			18.51 (-4.78, 41.80)	0.1190
Race (African American)			-11.81 (-30.94, 7.33)	0.2270			-13.71 (-32.85, 5.42)	0.1597
Insurance (Public)			16.09 (-2.44, 34.62)	0.0890			14.14 (-4.42, 32.70)	0.1350
Cancer Type								
Breast			0.97 (-32.20, 34.13)	0.9540			21.55 (-15.96, 59.07)	0.2594
Colorectal			-9.18 (-42.28, 23.91)	0.5870			23.27 (-13.68, 60.22)	0.2165
Female Genital			9.50 (-37.38, 56.38)	0.6910			45.42 (-5.73, 96.57)	0.0816
Head and Neck			5.27 (-27.49, 38.04)	0.7520			22.34 (-13.01, 57.70)	0.2149
Lung			5.23 (-31.67, 42.13)	0.7810			23.75 (-16.26, 63.76)	0.2440
Prostate			-27.72	0.3460			-10.09	0.7382

				(-85.42, 29.98)				(-69.38, 49.21)	
	Other			14.50 (-18.82, 47.81)	0.3940			**39.85 (4.44, 75.26)**	**0.0275**
Comorbid Condition									
	Anxiety	**41.22 (21.26, 61.18)**	**<0.0001**	**37.56 (14.97, 60.15)**	**0.0010**	**41.22 (21.21, 61.24)**	**<0.0001**	**36.13 (13.63, 58.63)**	**0.0017**
	Back Pain			6.72 (-13.92, 27.37)	0.5230			4.37 (-16.35, 25.09)	0.6784
	Depression			16.91 (-8.29, 42.12)	0.1880			18.12 (-7.05, 43.29)	0.1577
	Diabetes			-18.73 (-43.10, 5.63)	0.1320			-18.49 (-42.79, 5.81)	0.1354
	Hypertension			-16.70 (-36.42, 3.03)	0.0970			-16.85 (-36.53, 2.83)	0.0932
Substance Use									
	Alcohol Use			3.08 (-31.60, 37.76)	0.8620			5.34 (-29.33, 40.02)	0.7621
	Nicotine Use			10.54 (-9.95, 31.04)	0.3130			10.11 (-10.19, 30.41)	0.3282
	Other Drug Use	**66.44 (34.61, 98.28)**	**<0.0001**	**47.52 (12.31, 82.73)**	**0.0080**	**66.44 (34.52, 98.37)**	**<0.0001**	**48.43 (13.33, 83.53)**	**0.0070**

95% CI: 95% Confidence Interval; Bold indicates statistical significance, p-value <0.05

Sensitivity Analysis 3: Lived Without Recurrence, Metastatic Disease, or Death for at Least 3 Years

The next sensitivity analysis allowed for patients who only survived a minimum of 3 years beyond cancer diagnosis without recurrence or death (3CS) to be included. The additional two years of data resulted in an additional 187 patients compared to the base case. The demographics of patients in this group were very similar to that of the base case (Table 4.4). Comparing the estimates of the models to the base case, average OME per day was very similar, while those with a baseline prescription, public insurance, certain cancers, depression, alcohol use, and other drug use had higher OMEs across models (Table 4.9).

Table 4.9: Panel Data and Mixed Linear Models of OME Over Time in Cancer (3CS)

	Panel Data Model				**Mixed Linear Model**			
	Significant		Theoretical		Significant		Theoretical	
Characteristic	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value

Intercept	-0.07 (-1.92, 1.79)	0.9430	10.01 (-0.50, 20.52)	0.0620	-1.72 (-3.61, 0.17)	0.0750	-2.13 (-13.29, 9.02)	0.7076
Average OME Per Day	--	--	--	--	**0.01 (0.01, 0.01)**	**<0.0001**	**0.01 (0.01, 0.01)**	**<0.0001**
Baseline Opioid Prescription	**72.59 (66.43, 78.75)**	**<0.0001**	**70.54 (64.23, 76.84)**	**<0.0001**	**72.59 (66.43, 78.76)**	**<0.0001**	**70.64 (64.34, 76.93)**	**<0.0001**
Age at Diagnosis			**-0.15 (-0.30, 00-.00)**	**0.0430**			-0.15 (-0.30, 0.00)	0.0530
Gender (Male)			-0.43 (-5.62, 4.76)	0.8710			0.31 (-4.89, 5.51)	0.9058
Race (African American)			-1.84 (-5.15, 1.48)	0.2780			-1.85 (-5.16, 1.46)	0.2726
Insurance (Public)			**5.64 (2.11, 9.18)**	**0.0020**			**5.39 (1.86, 8.92)**	**0.0028**
Cancer Type								
Breast			-4.03 (-10.74, 2.68)	0.2390			6.09 (-1.56, 13.75)	0.1185
Colorectal			0.56 (-7.26, 8.38)	0.8890			**9.81 (0.84, 18.77)**	**0.0321**
Female Genital			4.15 (-5.35, 13.65)	0.3920			**13.78 (3.23, 24.34)**	**0.0105**
Head and Neck			0.02 (-8.04, 8.07)	0.9970			**9.43 (0.82, 18.04)**	**0.0319**
Lung			-1.88 (-10.16, 6.39)	0.6560			7.80 (-1.14, 16.73)	0.0871
Prostate			-4.35 (-12.33, 3.63)	0.2850			4.99 (-3.48, 13.46)	0.2484
Other			-0.48 (-7.84, 6.88)	0.8980			**14.00 (6.02, 21.99)**	**0.0006**
Comorbid Condition								
Anxiety	**9.70 (4.42, 14.98)**	**<0.0001**	**8.48 (3.14, 13.83)**	**0.0020**	**9.70 (4.42, 14.99)**	**0.0003**	**8.50 (3.17, 13.84)**	**0.0018**
Back Pain	**6.94 (1.89, 11.99)**	**0.0070**	**6.78 (1.70, 11.86)**	**0.0090**	**6.94 (1.89, 11.99)**	**0.0071**	**6.50 (1.43, 11.57)**	**0.0120**
Depression	**13.45 (7.24, 19.67)**	**<0.0001**	**13.49 (7.26, 19.71)**	**<0.0001**	**13.45 (7.23, 19.67)**	**<0.0001**	**13.72 (7.50, 19.94)**	**<0.0001**
Diabetes			**-7.18 (-12.22, -2.14)**	**0.0050**			**-7.02 (-12.05, -1.99)**	**0.0062**
Hypertension	**-4.79 (-8.07, -1.52)**	**0.0040**	-3.20 (-6.84, 0.43)	0.0840	**-4.79 (-8.07, -1.51)**	**0.0042**	-3.03 (-6.66, 0.61)	0.1025
Substance Use								
Alcohol Use	**15.40 (5.91, 24.89)**	**0.0010**	**12.90 (3.12, 22.67)**	**0.0100**	**15.40 (5.90, 24.89)**	**0.0015**	**14.12 (4.34, 23.90)**	**0.0047**
Nicotine Use			3.58 (-1.34, 8.50)	0.1530			3.66 (-1.23, 8.55)	0.1424
Other Drug Use	**41.67 (31.43, 51.91)**	**<0.0001**	**38.10 (27.54, 48.67)**	**<0.0001**	**41.67 (31.43, 51.92)**	**<0.0001**	**37.66 (27.10, 48.22)**	**<0.0001**

95% CI: 95% Confidence Interval; Bold indicates statistical significance, p-value <0.05;
3CS: 3-year Cancer Survivors

Sensitivity Analysis 4: Lived Without Recurrence, Metastatic Disease, or Death for at Least 1 Year (1CS)

The fourth sensitivity analysis allowed for an additional two years of data that included patients surviving at least one year following diagnosis (1CS). 1CS had similar demographics to those in the base case and in the 3CS group (Table 4.4). Estimates in the 1CS models followed similar trends to as the 3CS models, with some characteristics having estimates slightly larger in magnitude (Table 4.10). Notably, this was the first group to have statistically significant estimates of higher OMEs for males compared to females.

Table 4.10: Panel Data and Mixed Linear Models of OME Over Time in Cancer (1yr)

	Panel Data Model				**Mixed Linear Model**			
	Significant		**Theoretical**		**Significant**		**Theoretical**	
Characteristic	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
Intercept	7.63 (-0.05, 15.32)	0.0520	**16.22 (5.85, 26.59)**	**0.0020**	5.22 (-2.48, 12.92)	0.1837	3.82 (-6.79, 14.42)	0.4806
Average OME Per Day	--	--	--	--	**0.01 (0.01, 0.02)**	**<0.0001**	**0.01 (0.01, 0.02)**	**<0.0001**
Baseline Opioid Prescription	**72.21 (66.21, 78.21)**	**<0.0001**	**71.66 (65.63, 77.70)**	**<0.0001**	**72.21 (66.21, 78.21)**	**<0.0001**	**71.88 (65.85, 77.90)**	**<0.0001**
Age at Diagnosis	**-0.14 (-0.26, -0.01)**	**0.0300**	**-0.25 (-0.40, -0.11)**	**0.0010**	**-0.14 (-0.26, -0.01)**	**0.0297**	**-0.24 (-0.39, -0.09)**	**0.0017**
Gender (Male)	**4.34 (1.04, 7.65)**	**0.0100**	**4.97 (0.16, 9.77)**	**0.0430**	**4.34 (1.04, 7.65)**	**0.0100**	**5.39 (0.59, 10.19)**	**0.0279**
Race (African American)			-1.95 (-5.31, 1.41)	0.2560			-1.94 (-5.30, 1.41)	0.2560
Insurance (Public)			**6.20 (2.64, 9.77)**	**0.0010**			**5.89 (2.32, 9.45)**	**0.0012**
Cancer Type								
Breast			-4.48 (-10.81, 1.86)	0.1660			4.69 (-1.91, 11.28)	0.1635
Colorectal			-2.33 (-10.01, 5.34)	0.5510			4.88 (-3.32, 13.08)	0.2434
Female Genital			7.11 (-2.25, 16.47)	0.1370			**14.59 (4.75, 24.44)**	**0.0037**
Head and Neck			-2.75 (-10.58, 5.09)	0.4920			5.93 (-1.99, 13.85)	0.1422
Lung			-3.77 (-10.91, 3.37)	0.3010			5.07 (-2.23, 12.37)	0.1736
Prostate			**-9.55 (-17.41, -1.68)**	**0.0170**			-0.88 (-8.81, 7.05)	0.8287

Other			-1.68 (-8.61, 5.25)	0.6340			**13.53 (6.39, 20.67)**	**0.0002**
Comorbid Condition								
Anxiety	**7.03 (1.60, 12.45)**	**0.0110**	**5.94 (0.50, 11.39)**	**0.0320**	**7.03 (1.60, 12.45)**	**0.0111**	**6.01 (0.58, 11.45)**	**0.0301**
Back Pain	**11.70 (6.57, 16.83)**	**<0.0001**	**11.44 (6.30, 16.58)**	**<0.0001**	**11.70 (6.57, 16.83)**	**<0.0001**	**10.95 (5.81, 16.09)**	**<0.0001**
Depression	**9.62 (3.27, 15.96)**	**0.0030**	**9.87 (3.51, 16.22)**	**0.0020**	**9.62 (3.27, 15.97)**	**0.0030**	**9.86 (3.52, 16.20)**	**0.0023**
Diabetes			**-5.69 (-10.68, -0.69)**	**0.0260**			**-5.52 (-10.51, -0.53)**	**0.0303**
Hypertension	**-5.69 (-9.06, -2.31)**	**0.0010**	**-4.25 (-7.93, -0.57)**	**0.0240**	**-5.69 (-9.06, -2.31)**	**0.0010**	**-4.08 (-7.76, -0.41)**	**0.0296**
Substance Use								
Alcohol Use	**14.83 (5.31, 24.36)**	**0.0020**	**14.16 (4.59, 23.73)**	**0.0040**	**14.83 (5.30, 24.37)**	**0.0023**	**15.17 (5.60, 24.74)**	**0.0019**
Nicotine Use	**5.83 (1.04, 10.63)**	**0.0170**	**5.08 (0.19, 9.97)**	**0.0420**	**5.83 (1.04, 10.63)**	**0.0171**	**5.18 (0.32, 10.05)**	**0.0369**
Other Drug Use	**29.42 (19.36, 39.36)**	**<0.0001**	**28.52 (18.44, 38.61)**	**<0.0001**	**29.42 (19.35, 39.48)**	**<0.0001**	**28.66 (18.59, 38.73)**	**<0.0001**

95% CI: 95% Confidence Interval; Bold indicates statistical significance, p-value <0.05

Predictions of estimated average daily OME following radiation from the mixed linear models of each subgroup were calculated and presented in Table 4.11.

Table 4.11: Prediction of Average Daily OME in Cancer Survivors Following Radiation

OME (95% CI)					
Group	**Estimate**	**90 days**	**180 days**	**270 days**	**360days**
5CS	0.0091 (0.0069, 0.0113)	1.64 (1.25, 2.03)	2.46 (1.88, 3.04)	3.27 (2.50, 4.05)	4.09 (3.13, 5.06)
Subgroups					
5CS VCC	0.0195 (0.0084, 0.0305)	3.50 (1.51, 5.50)	5.25 (2.27, 8.24)	7.01 (3.03, 10.99)	8.76 (3.78, 13.74)
5CS No NOU	0.0643 (0.0494, 0.0793)	11.58 (8.89, 14.27)	17.37 (13.33, 21.41)	23.16 (17.78, 28.54)	28.95 (22.22, 35.68)
3CS	0.0102 (0.0079, 0.0125)	1.83 (1.42, 2.24)	2.75 (2.14, 3.36)	3.67 (2.85, 4.49)	4.59 (3.56, 5.61)
1CS	0.0149 (0.0123, 0.0175)	2.68 (2.21, 3.15)	4.02 (3.32, 4.72)	5.36 (4.42, 6.30)	6.70 (5.53, 7.87)

OME: Oral Morphine Equivalent; 95% CI: 95% Confidence Interval; 5CS: 5-Year Cancer Survivors; 3CS: 3-Year Cancer Survivors; 1CS: 1-Year Cancer Survivors

Discussion

This is the first study to evaluate opioid doses utilized following radiation in cancer survivors. From this study, we can see that many cancer survivors do not utilize opioids long term before or after radiation. However, sustained doses of opioids are used for those that took opioids to manage cancer and treatment related pain, particularly for patients with baseline (pre-radiation) opioid prescriptions with measurable OMEs. This study determined that for patients with baseline opioid prescriptions, average OME dose was 62.8-73.3 higher over the course of the study than patients without baseline opioid prescriptions from both models used.

While there are no opioid prescribing guidelines specifically for patients with cancer or those that have undergone cancer treatment, there are guidelines for opioid dosing in non-cancer pain. The 2016 chronic opioid prescribing guidelines for non-cancer pain (where cancer pain is explicitly excluded) recommend avoiding daily OME doses greater than 90 and for prescribers to use caution with daily OME doses greater than 50.[20] In this study, we saw prescribed OME on average around the recommendation of non-cancer pain, but with large variations far above the recommended limit. For those with baseline opioid prescriptions across all models, average OME doses over time fell within non-cancer pain recommendations. This suggests that while pain guidelines explicitly exclude cancer pain, prescribers may have followed non-cancer prescribing recommendations when prescribing for cancer patients.

In this study, we found that factors contributing to higher average OMEs over time were dependent on demographics rather than cancer related clinical characteristics. Our results have shown that public insurance, comorbid conditions, and substance use resulted in higher OMEs over time, controlling for other factors. We did not find that cancer related clinical factors, especially additional treatments such as chemotherapy or surgery, were associated

with opioid dose. We only observed OME dose associations with cancer type in some models (5CS MLM [increased dose with colorectal, female genital, and head and neck cancers]; 3CS MLM[increased dose with colorectal, female genital, head and neck cancers]; 1CS PDM [decreased dose with prostate cancer] and MLM [increased dose with colorectal, female genital, head and neck cancers]) This is in contrast to what we showed in Chapter 3 where initiation of long-term opioid use was associated with cancer type and treatment. This suggests that opioid dose, but not use, is patient specific regardless of their cancer diagnosis or treatment regimen. This may be the reason why diabetes and hypertension were not shown to be associated with NPOU in Chapter 3, but shown in this study to be associated with lower average OMEs over time. Patients with these chronic conditions may be receiving closer and more regular primary care management, resulting in high provider attention and management of prescription medications including opioids.

While age at diagnosis was not a factor that was statistically significant across all cases and models, the direction of the association was consistent with prior chapters of increasing age being associated with lower opioid use. As suggested in Chapter 3, patients of younger age may have more aggressive disease or are given a more aggressive treatment strategy to prolong life resulting in a higher opioid requirement. Additionally, physicians may be more cautious in opioid dose prescribing for patients of increasing age due to concerns related to opioids including sedation, fall risk, and risk of side effects including opioid induced constipation.

From the subgroup analyses of this study, removing no known opioid prescriptions resulted in higher doses across characteristics and models, suggesting that our base case estimates are conservative estimates of opioid dose use in cancer survivors. Notably anxiety and other drug use estimates double when potentially unknown OMEs are removed. The

effects of these two characteristics may be underestimated in the base case model and therefore should be screened for in cancer survivors using opioids long-term for risk of high dose use. Subgroup analysis including patients that survived less than one and three years after cancer diagnosis resulted in similar estimates across characteristics and models supporting the robustness of our results. However, as patients had lower survival, there were slight increases in opioid doses which may be related to the severity of disease. Notably in patients that only survived one year following cancer diagnosis, males were significantly associated with higher opioid doses over time controlling for other factors. This finding echoes what was seen in Chapter 2 and could be a real effect that is undetected due to insufficient power in the base case model.

Subgroup analysis of patients with VCC resulted in statistically significant associations with race. Patients with VCC of African American race had lower estimates of OME doses over time, controlling for other factors. This corresponds with the results from Chapter 2. While not statistically significant, the direction of the race estimate is also seen in the base case. This could be due to the capture of all prescriptions in patients with VCC or inherent differences between patients in the base case and patients that utilize VCC. Inherent differences between the VCC group and the base case are underscored by the lack of significant associations related to comorbid conditions and substance use in patients with VCC. While differences exist between the 5CS and VCC groups, the findings of the VCC subgroup reinforce the baseline opioid prescription finding. Additionally, the differences between the groups were all in the same direction: VCC patients being sicker, and therefore, may serve as a high end extreme.

Predicting average OME dose following radiation from the MLM of various groups suggests that undergoing cancer radiation therapy results in at least some long-term opioid dose use. When patients not suspected of using opioid prescriptions are included in the model,

predicted opioid dose use is relatively small overall. However, when patients with no known OMEs are removed, predicted OME doses following radiation therapy are about three times higher. Therefore, predicted doses of the base case are likely conservative estimates of long-term opioid dose.

Limitations

This study had several limitations. First, this study only included patients at a single, urban, academic institution. Providers here may have different pain management practices or preferences that may not be nationally representative. Thus, the results of this study may only be generalizable to other academic institutions of similar size, patient population, and geography.

Our analyses utilized prescription data rather than fill data. This raises the possibility of patients not filling prescriptions. Also, our analysis does not include opioid prescriptions written by doctors outside of the institution. This could have resulted in underestimation of opioid use overall and opioid dose. Additionally, 38.7% of patients had prescriptions that were missing variables necessary to calculate OME to fall within their pre-determined opioid use classification (NPOU, COU, NOU, POU). To the best of our ability, we verified prescription use over time and did not include patients with missing OME prescriptions that resulted in OME use contrary to opioid use classification. In order to address missing prescriptions that would have resulted in different opioid utilization classifications, we conducted two subgroup analyses: first, with VCC patients for which we have all prescription data and second, removing patients with no known opioid prescriptions. Second, the NOU group is the group with the highest likelihood of having missed prescriptions (written outside the institution) since we could not capture any prescriptions for those patients, in other categories we have at least some prescription information and some confidence in the accuracy of their prescriptions. Average

OME over time with presence of OME at baseline and OME per day were higher for both subgroups (patients with VCC and excluding NOU patients) than the base case. From the VCC subgroup, being of African American race resulted in statistically significant lower OME doses.

We could not differentiate the indication of opioid prescription to be due to cancer or non-cancer pain. Opioid prescriptions due to cancer pain would be, in theory, easier to discontinue than those for non-cancer pain because curative intent therapy would remove or reduce the underlying inciting malignancy. Lastly, this study can only be generalized to patients with cancer that receive radiation, as all of the patients in the study received radiation.

Conclusion

In conclusion, we determined that on average, cancer survivors that undergo radiation and have a baseline opioid prescription use about 68 OMEs more per day than those that do not, controlling for other factors. Patients with public insurance, anxiety and depression, and substance use are associated with higher average OMEs over time. Conversely, patients with diabetes and hypertension are associated with lower average OMEs over time. Controlling for other factors, we predict that patients that undergo radiation for their cancer will use, on average, 4.1 OMEs (2.7mg of oxycodone 5CS) per day including NOU, or 29.0 OMEs (19.3mg of oxycodone) per day for No NOU one year after the end of radiation. These findings warrant evidence-based recommendations and guidelines for opioid use and discontinuation in cancer survivors receiving radiation to prevent misuse and opioid related deaths.

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CHAPTER 5: TIME TO DISCONTINUATION OF OPIOIDS IN PATIENTS WITH CANCER AFTER CURATIVE INTENT RADIATION

Abstract

Background: There is growing awareness of long-term opioid use after curative intent radiotherapy in cancer survivors as the number of patients surviving cancer increases. Patients receiving curative intent radiotherapy should be able to discontinue opioids soon after treatment, although this has not been studied. Objective: Examine the time patients with cancer receiving curative intent radiation (CIR) remain on opioids after curative intent treatment and examine associated factors to help identify patients that may have difficulty weaning off opioid regimens. Methods: Electronic medical record clinical and opioid prescription data of cancer survivors from a single academic institution between January 1, 2008 and December 31, 2018 was utilized. Kaplan Meier survival models were used to estimate time to discontinuation (TTD) of opioids after end of radiation therapy. Stepwise Cox proportional hazards models were employed to identify factors associated with time until opioid discontinuation. Results: For cancer survivors receiving opioid prescriptions following radiation, median TTD of opioids was 16.8 months (95% CI: 13.1-19.1 months) following the end of radiation. Median TTD of opioids was shorter for patients without opioid exposure prior to therapy (NPOU; 13.0 months, 95% CI: 10.0-17.3 months) compared to patients with opioid exposure prior to therapy (COU; 21.4 months, 95% CI: 17.5-28.8 months) (p-value = 0.0004). Factors associated with shorter TTD included: new persistent opioid use (NPOU; no opioid exposure prior to radiation) compared to chronic opioid use (COU; opioid exposure prior to radiation) (HR: 1.35, 95% CI: 1.07-1.71) and head and neck cancers (HR: 1.60, 95% CI: 1.01-2.53) in comparison to breast cancer. Conversely, additional surgery (HR: 0.68, 95% CI: 0.50-0.91), death after more than five years of diagnosis (HR: 0.55, 95% CI: 0.34-0.91), as well as

alcohol (HR: 0.63, 95% CI: 0.42-0.95) and nicotine (HR: 0.78, 95% CI: 0.62-0.98) use were associated with longer TTD of opioids. Discussion: Cancer survivors continue receiving opioid prescriptions for almost a year and a half after completion of CIR. Patients receiving additional surgery and those with alcohol and nicotine use are at higher risk. Patients with NPOU and head and neck cancers have shorter TTD. Conclusion: Evidence based guidelines for clinical management of opioid use in cancer survivors after CIR are warranted due to high numbers of patients that continue to use opioids long after CIR.

Background

Five-year survival from cancer has increased from less than 50% in the 1970s to a mean of 69.6% in 2011 (with a large range based on cancer site).[1,2] This increase in survival has led to an increase in both the aggregate number of cancer survivors and also the duration of time patients spend in the survivorship period. Pain management is an important consideration for patients with cancer, as malignancies can lead to significant pain in addition to pain resulting from invasive surgery, chemotherapy, and radiation. Opioids are a cornerstone of pain management for cancer patients.[3–5] Curative intent therapy (treatment to cure) with surgery and/or radiation subjects patients to burdensome acute and delayed treatment-related pain, but in theory, removes underlying painful malignancies and associated morbidity long-term. Pain in cancer survivors that have undergone curative intent therapy is poorly characterized and there is little to no consensus on the therapeutic framework of treating pain for these patients.[6] As more patients are surviving cancer, continued opioid use after curative intent therapy is of greater concern.

A goal of curative intent therapy is to remove the underlying cause of pain so that pain management with opioids is no longer needed. However, discontinuing opioids in patients with

chronic pain can be quite difficult. A study of non-cancer chronic pain patients found that 65-67% of patients receiving chronic opioids remained on treatment after five years.[7] Another study utilizing a national representative database (Truven Health Marketscan) of non-cancer patients found that 43-87% of patients continue opioids beyond two years, and more troubling, "drug abuse and overdose rates increased with longer use."[8] Additionally, from a combined cohort study and meta-analysis published in 2020, cancer-related pain and opioid requirements (including high-dose opioids) are associated with poor survival in patients with cancer.[9] Therefore, decreasing cancer pain burden and ultimately, discontinuation of opioids, while potentially difficult, should be an essential part of cancer survivor care.

Discontinuation of opioids following curative intent treatment has not been studied well. A study of non-cancer patients using chronic opioids receiving non-orthopedic surgery matched to non-surgical chronic opioid users found that surgery was associated with a 34% likelihood of discontinuation of opioids after one year.[10] Oxycodone use, higher opioid dose, COPD, and dementia were associated with reduced odds of discontinuation. One study investigating opioid discontinuation in patients with oropharyngeal cancer from the Surveillance, Epidemiology and End Results (SEER)–Medicare database reported median time on opioids of 3 weeks (95% confidence interval, 3.00-4.00) and mean of 7.37 (SE: 0.31) weeks censoring at 6 months after treatment.[11]

Radiotherapy has a role in pain mitigation and is used in the palliative setting as a non-invasive adjunctive treatment to complement opioid therapy and minimize opioid dependence.[12] Approximately 50% of cancer patients will receive radiation therapy as a component of their treatment.[13] Patients receiving curative intent radiotherapy should be able to discontinue opioids after treatment, although this has not been studied. Understanding the duration that patients with cancer remain on opioids after curative intent radiation (CIR) and

the patient factors associated with time to discontinuation (TTD) may assist in identifying patients that have difficulty weaning off opioid regimens. The objective of this study is to describe opioid use by TTD in the months following radiation and factors associated with length of TTD (Table 5.1 – Specific Aim 3d).

Table 5.1: Methods for Specific Aim 3

Specific Aim 3		
In cancer survivors who received curative intent radiation therapy for their malignancy, examine new persistent and continued chronic opioid use and 30-day average daily OME dose after radiation therapy		Method
3d	Describe opioid use by time to discontinuation in the months following radiation	Kaplan-Meier Survival & Cox Proportional Hazard Models

Methods

Data Source, Patient Identification, and Patient Covariates

We utilized electronic medical record data from cancer survivors who received radiotherapy for any indication at Virginia Commonwealth University Massey Cancer Center between January 1, 2008 and December 31, 2018. Patients 18 years of age or older with any cancer type and stage receiving radiation with or without any additional treatment modalities (i.e. surgery, chemotherapy) were included. We only included patients that classified as cancer survivors, defined as the absence of metastatic disease or recurrence within 5 years of diagnosis. Prisoners were excluded. Relevant covariates potentially associated with continued opioid use after radiation included cancer type, stage, treatment type, comorbid conditions, germane social history (nicotine use), and demographic information (age, race, and insurance status and type – including Virginia Coordinated Care [VCC], the institution sponsored health insurance for indigent patients for which all medical records should be). Patients with prescribed opioid medications were included if prescriptions were written for the outpatient setting, written after the radiation therapy end date, and written for at least a 14-day supply.

Patients receiving opioid prescriptions were followed for 36 months following end of radiation. There were 872 patients that met these criteria.

Opioid Discontinuation

Patients were followed from the end date of radiation to the last day of available prescribed opioids (last day-supply prescribed based on date prescribed and calculated total day-supply). Patients were censored if (1) the maximum encounter date documented from the electronic medical record fell before the last day of the last prescribed opioid, (2) the date of death fell before the last day of the last prescribed opioid, or (3) the study period ended before the last day of the last prescribed opioid.

Statistical Analysis

Descriptive statistics including means, medians, standard deviations, and interquartile ranges were calculated for patient clinical and sociodemographic characteristics. One-way ANOVA was conducted for continuous variables against opioid exposure status. Chi-squared tests were used on categorical variables with Fisher's exact test used when expected cell counts were less than 5. P-values of <0.05 were considered statistically significant. Table 5.1 describes the methods associated with Specific Aim 3. Kaplan Meier survival models were used to estimate TTD of opioids after the end of radiation therapy. Subsequently, Cox proportional hazards models were conducted with the SAS stepwise selection process using criterion of p<=0.05 to select and retain significant variables. Categorical variables for comorbid conditions and substance used were coded as "1"= yes, presence of comorbid condition or substance use or "0"=no, with "0" being the reference group. Reference groups for other categorical variables were as noted in the results table. A final model was built with relevant clinical factors and significant factors from the stepwise model to determine

associations with time until opioid discontinuation. Statistical analyses were conducted using Stata v15.1 and SAS v9.4 (SAS Institute, Cary, NC).

Subgroup Analyses

To determine if prior use of chronic opioid medications was associated with discontinuation, patients were grouped by opioid exposure prior to radiation therapy by previously described methods (Chapter 3).[14,15] Patients were initially stratified by opioid exposure as opioid naïve (ON) or opioid exposed (OE). They were then categorized as: New Persistent Opioid User (NPOU: ON prior to radiation, but continued use after radiation) or Chronic Opioid User (COU: OE prior to radiation and continued use after radiation) (Table 5.2).[14,16] Lastly, in order to determine if differences existed due to potentially missed opioid prescriptions written outside of the institution and thus not captured, we conducted a subgroup analysis for patients with VCC for which we had full prescription data.

Table 5.2: Summary of Patient Groups by Opioid Exposure

Group		Abbreviation	Definition
Pre-Radiation Treatment			
	Opioid Naïve	ON	No known prescribed opioids greater than or equal to 30 days before treatment
	Opioid Exposed	OE	Known opioids prescribed greater than or equal to 30 days before treatment
Pre- and Post-Radiation Treatment			
	Chronic Opioid User	COU	Prescribed at least one opioid prescription 30 days before treatment (OE) and at least one opioid prescription 30 days after treatment
	New Persistent Opioid User	NPOU	Previously ON who was prescribed at least one opioid prescription 30 after treatment

Results

The majority of patients in this study were white (52.2%) and female (62.6%). The high proportion of females may be due to the high proportion of breast cancers (32.5%) in the sample. The majority of patients had additional chemotherapy (59.5%) or surgery (57.9%).

However, the majority of patients did not have comorbid conditions or use alcohol or nicotine (Table 5.3).

Overall, median TTD of opioids for all patients was 16.8 months/1.4 years (95% CI: 13.6-19.1 months, Figure 5.1). Factors associated with shorter TTD of opioids included: NPOU compared to COU (HR: 1.35, 95% CI: 1.07-1.71) and head and neck cancer (HR: 1.60, 95%CI: 1.01-2.53) when compared to breast cancer (Table 5.4). Conversely, additional surgery (HR: 0.68, 95% CI: 0.50-0.91), death more than five years after diagnosis (HR: 0.55, 95% CI: 0.34-0.91), as well as alcohol (HR: 0.63, 95% CI: 0.42-0.95) and nicotine (HR: 0.78, 95% CI: 0.62-0.98) use were associated with longer TTD.

Table 5.3: Demographics of 5CS Overall and by Opioid Exposure

Characteristic	Overall (n = 872)			COU (n = 227, 26%)	NPOU (n = 645, 74%)	P-value
	Mean (Std)	Median (IQR)		Mean (Std)	Mean (Std)	
Age	56.4 (12.2)	57 (15)		55.5 (11.8)	56.7 (12.4)	0.2076
	N	%		N (%)	N (%)	
Gender						0.0270*
Female	546	62.6		156 (68.7)	390 (60.5)	
Male	326	37.4		71 (31.3)	255 (39.5)	
Race						0.0124*
African American	378	43.4		111 (48.9)	267 (41.4)	
Other	39	4.5		15 (6.6)	24 (3.7)	
White	455	52.2		101 (44.5)	354 (54.9)	
Insurance Type						0.1326
Commercial	265	30.4		64 (28.2)	201 (31.2)	
VCC	89	10.2		34 (15.0)	55 (8.5)	
Insurance, Not Specified	79	9.1		18 (7.9)	61 (9.5)	
Medicaid	86	9.9		28 (12.3)	58 (9.0)	
Medicare	250	28.7		57 (25.1)	193 (30.0)	
Military	7	0.8		2 (0.9)	5 (0.8)	
Self-Pay	87	10.0		22 (9.7)	65 (10.1)	
Unknown	9	1.0		2 (0.9)	7 (1.1)	
Cancer Type						<0.0001*
Breast	283	32.5		103 (45.4)	180 (27.9)	
Colorectal	78	8.9		11 (4.8)	67 (10.4)	
Female Genital	60	6.9		5 (2.2)	55 (8.5)	
Gastrointestinal	34	3.9		12 (5.8)	22 (3.4)	
Head and Neck	126	14.4		24 (10.6)	102 (11.7)	
Lung and Bronchus	96	11.0		18 (7.9)	78 (12.1)	

Other	151	17.3		36 (15.9)	115 (13.2)	
Prostate	44	5.0		18 (7.9)	26 (4.0)	
Clinical Stage						0.0018*
0	33	3.82		9 (4.0)	24 (3.8)	
1	189	21.9		52 (23.0)	137 (21.5)	
2	222	25.7		80 (35.4)	142 (22.3)	
3	198	22.9		38 (16.8)	160 (25.1)	
Unknown	230	26.4		48 (21.1)	182 (28.2)	
Death 5 Years or More After Diagnosis						
Yes	37	4.2		11 (4.8)	26 (4.3)	0.6000
No	835	95.8		216 (95.2)	619 (95.7)	
Recurrence 5 Years or More After Diagnosis						
Yes	3	0.3		0 (0)	3 (0.5)	0.3030
No	869	99.7		227 (100.0)	642 (99.5)	
Additional Chemotherapy						0.3370
Chemotherapy +	519	59.5		129 (56.8)	390 (60.5)	
Chemotherapy -	353	40.5		98 (43.2)	255 (39.5)	
Additional Surgery						0.0061*
Surgery +	505	57.9		149 (65.6)	356 (55.2)	
Surgery -	367	42.1		78 (34.4)	289 (44.8)	
Additional Immunotherapy						0.5200
Immunotherapy +	43	4.9		13 (5.7)	30 (4.7)	
Immunotherapy -	829	95.1		214 (9.4)	615 (95.3)	
Comorbid Conditions						
Anxiety +	192	22.0		74 (32.6)	118 (18.3)	<0.0001*
Anxiety -	680	78.0		153 (67.4)	527 (81.7)	
Arthritis +	180	20.6		83 (36.6)	97 (15.0)	<0.0001*
Arthritis -	692	79.4		144 (63.4)	548 (85.0)	
Back Pain +	236	27.1		96 (42.3)	140 (21.7)	<0.0001*
Back Pain -	636	72.9		131 (57.7)	505 (78.3)	
Depression +	147	16.8		63 (27.8)	84 (13.0)	<0.0001*
Depression -	725	83.1		164 (72.3)	561 (87.0)	
Hypertension +	423	48.5		138 (60.8)	285 (44.2)	<0.0001*
Hypertension -	449	51.5		89 (39.2)	360 (55.8)	
Lung Disease +	241	27.6		76 (33.5)	165 (25.6)	0.0222*
Lung Disease -	631	72.4		151 (66.5)	480 (74.4)	
Substance Use						
Alcohol Use +	64	7.3		31 (13.7)	33 (5.1)	<0.0001*
Alcohol Use -	808	92.7		196 (86.3)	612 (95.9)	
Nicotine Use +	295	33.8		109 (48.0)	186 (28.8)	<0.0001*
Nicotine Use -	577	66.2		118 (52.0)	459 (71.2)	

n = 872. Chi Squared test used unless stated; * denotes statistical significance with p-value < 0.05; Std: Standard Deviation; IQR: Interquartile Range; 5CS: 5-Year Cancer Survivors; COU: Chronic Opioid User; NPOU: New Persistent Opioid User; VCC: Virginia Coordinated Care

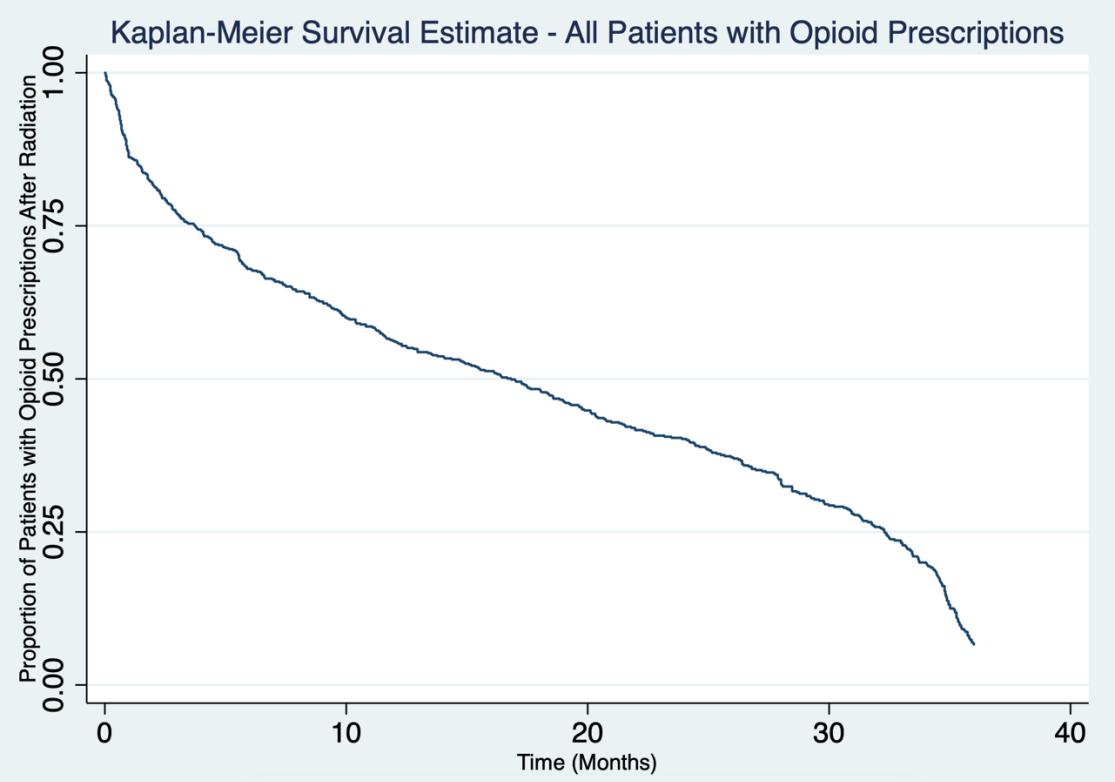

Figure 5.1: TTD of Opioid Prescriptions in 5CS Following Radiation

Table 5.4: Cox Proportional Hazard Model Results of TTD of Opioids in 5CS

	Stepwise	Stepwise + Theoretical
Covariates (n=872)	HR (95% CI)	
Age	**1.01 (1.01, 1.02)**	**1.02 (1.00, 1.03)**
Race		
African American	1.01 (0.82, 1.24)	0.95 (0.76, 1.18)
Other	**1.76 (1.15, 2.70)**	**1.58 (1.01, 2.48)**
White	Reference	
Gender		
Male		0.81 (0.60, 1.09)
Female		Reference
Insurance Type		
Commercial	Reference	
VCC		1.10 (0.79, 1.53)
Insurance, Not Specified		**1.71 (1.18, 2.47)**
Medicaid		0.94 (0.63, 1.41)
Medicare		0.97 (0.71, 1.33)
Military		2.11 (0.64, 6.93)
Self-Pay		1.15 (0.82, 1.62)
Opioid Exposure		
NPOU (ON prior to radiation)	**1.38 (1.11 ,1.72)**	**1.35 (1.07, 1.71)**
COU (OE prior to radiation)	Reference	
Cancer Type		
Breast	Reference	

Colorectal	1.22 (0.87, 1.73)	1.08 (0.71, 1.64)
Female Genital	0.77 (0.48, 1.24)	0.68 (0.40, 1.14)
GI	1.03 (0.62, 1.70)	0.99 (0.55, 1.76)
Head and Neck	**1.44 (1.01, 2.06)**	**1.60 (1.01, 2.53)**
Lung and Bronchus	**0.52 (0.35, 0.77)**	0.53 (0.33, 0.87)
Other	0.90 (0.59, 1.39)	0.91 (0.55, 1.50)
Prostate	0.80 (0.46, 1.38)	1.47 (0.69, 3.13)
Clinical Stage		
0	Reference	
1		0.94 (0.58, 1.53)
2		0.77 (0.45, 1.32)
3		1.04 (0.59, 1.84)
Additional Chemotherapy		1.24 (0.92, 1.66)
Additional Surgery		**0.68 (0.50, 0.91)**
Additional Immunotherapy		1.39 (0.82, 2.36)
Death 5 Years or More After Diagnosis	**0.57 (0.36, 0.91)**	**0.55 (0.34, 0.91)**
Recurrence 5 Years or More After Diagnosis		0.55 (0.13, 2.32)
Comorbid conditions		
Anxiety		0.93 (0.73, 1.19)
Arthritis		0.89 (0.68, 1.17)
Back Pain		0.91 (0.73, 1.14)
Lung Disease		0.97 (0.77, 1.23)
Substance Use		
Alcohol Use	**0.55 (0.37, 0.81)**	**0.63 (0.42, 0.95)**
Nicotine Use		**0.78 (0.62, 0.98)**

Bold denotes statistical significance ; NPOU: New Persistent Opioid User; ON: Opioid Naïve; OE: Opioid Exposed; COU: Chronic Opioid User; HR: Hazard Ratio; 95% CI: 95% Confidence Interval; VCC: Virginia Coordinated Care

Subgroup Analyses

Opioid Exposure Status

The majority of patients continuing opioid use after radiation were classified as NPOU (74%). Bivariate analysis with opioid exposure status revealed significantly more females (and breast cancers) and patients of African American race in the COU group than in the NPOU group (Table 5.3). In the NPOU group, there were more patients with head and neck (laryngeal and oropharyngeal) cancers and patients using Medicare. Conversely, in the COU group, there were more comorbid diseases and patients using VCC or Medicaid. There was a statistically significant difference in median TTD of opioids when patients were grouped by opioid

exposure status. Patients' median TTD was 13.0 months/1.1 years (95% CI: 10.0-17.3 months) for patients with NPOU compared to 21.4 months/1.8 years (95% CI: 17.5-28.8 months) for patients with COU (p-value = 0.0004, Figure 5.2).

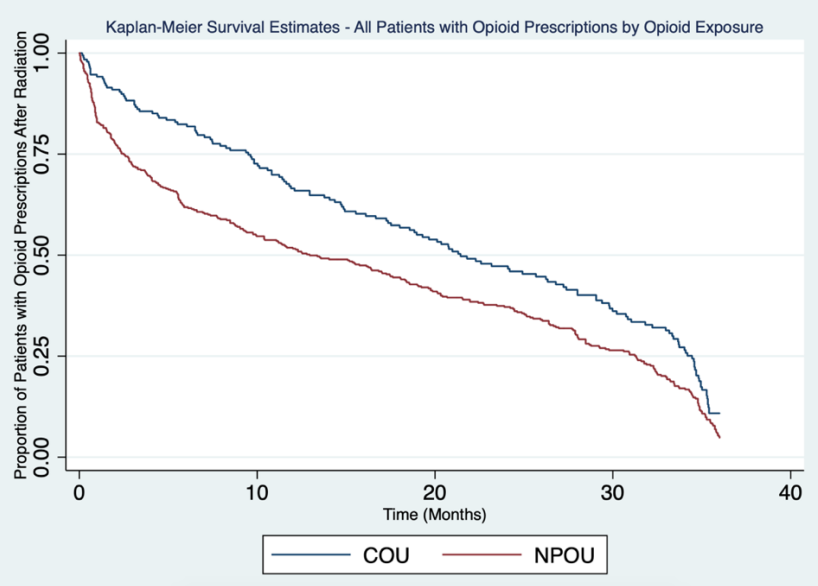

Figure 5.2: TTD of Opioid Prescriptions in 5CS Following Radiation by Opioid Exposure Group (TTD: Time to Discontinuation; 5CS: 5-Year Cancer Survivors; COU: Chronic Opioid User, NPOU: New Persistent Opioid User)

Patients with VCC Only

Similar to the results obtained on the entire sample, the majority of VCC patients were classified as NPOU (61.8%), female (71.9%) (with high proportion of patients with breast cancer: 43.8%), and having additional chemotherapy (55.9%) or surgery (70.8%) (Table 5.5). In contrast to the entire sample, patients with VCC were slightly younger, most patients with VCC were Black or African American (56.2%), had comorbid hypertension (58.4%), and less than half of the patients used nicotine (49.4%). There was a higher proportion of breast cancers in the COU group and higher proportion of colorectal cancers in the NPOU compared to the full sample. Additionally, there were higher proportions of anxiety and nicotine use in the NPOU group for patients with VCC.

Patients with VCC had a median TTD of opioids of 27.2 months (2.3 years; 95% CI: 12.8-31.3 months, Figure 5.3). No variables were found to be associated with discontinuation of opioids from the Cox proportional hazard model stepwise building (Table 5.6). However, from the theoretical model, female genital cancers (HR: 8.54, 95% CI: 2.09-34.92) when compared to breast cancer and comorbid back pain (HR: 2.03, 95% CI: 1.12-3.69) were associated with shorter TTD of opioids.

Like the entire sample, bivariate analysis with opioid exposure status showed that there were more patients with breast cancer and patients of African American race in the COU group than in the NPOU group. There were less male and white patients, and more head and neck cancers in the NPOU group than the COU group. There were more comorbid diseases in the COU group, except for anxiety (Table 5.5). Unlike the entire sample, there was no statistically significant difference in discontinuation of opioids for patients based on opioid exposure status (NPOU: 28.5 months/2.4 years, 95% CI: 12.5-32.4 months; COU: 27.2 months/2.3 years, 95% CI: 7.5-31.8 months; p-value 0. 6651; Figure 5.4).

Table 5.5: Demographics for 5CS with VCC: Overall and by Opioid Exposure

	Overall (n = 89)		COU (n = 34, 38.2%)	NPOU (n = 55, 61.8%)	P-value
	Mean (Std)	Median (IQR)	Mean (Std)	Mean (Std)	
Age	52.2 (11.4)	52 (14)	55.1 (9.3)	50.5 (12.2)	0.0652
	N	%	N (%)	N (%)	
Gender					0.7893
Female	64	71.9	25 (73.5)	39 (70.9)	
Male	25	28.1	9 (26.5)	16 (29.1)	
Race					0.0519†
African American	50	56.2	22 (64.7)	28 (50.9)	
Other	8	9.0	5 (14.7)	3 (5.5)	
White	31	34.8	7 (20.6)	24 (43.6)	
Cancer Type					<0.0001*†
Breast	39	43.8	22 (64.7)	17 (30.9)	
Female Genital	19	21.4	1 (2.9)	18 (32.7)	
Gastrointestinal	6	6.7	1 (2.9)	5 (9.1)	
Head and Neck	5	5.6	1 (2.9)	4 (7.3)	
Lung and Bronchus	5	5.6	1 (2.9)	4 (7.3)	

Other	8	9.0	2 (5.6)	6 (10.9)	
Prostate	7	7.9	6 (17.7)	1 (7.9)	
Clinical Stage					0.2902
0	3	3.4	1 (2.9)	2 (3.6)	
1	21	23.6	8 (23.5)	13 (23.6)	
2	27	30.3	14 (41.2)	13 (23.6)	
3	18	20.2	7 (20.6)	11 (20.0)	
Unknown	20	22.5	4 (11.8)	16 (29.1)	
Death 5 Years or More After Diagnosis					
Yes	5	5.6	3 (8.8)	2 (3.6)	0.3660†
No	84	94.4	31 (91.2)	53 (96.4)	
Recurrence 5 Years or More After Diagnosis					
Yes	0	0	0 (0)	0 (0)	--
No	34	100	34 (100)	55 (100)	
Additional Chemotherapy					0.7017
Chemotherapy +	52	58.4	19 (55.9)	33 (60.0)	
Chemotherapy -	37	41.6	15 (44.1)	22 (40.0)	
Additional Surgery					0.1595
Surgery +	63	70.8	27 (79.4)	36 (65.5)	
Surgery -	26	29.2	7 (20.6)	19 (34.6)	
Additional Immunotherapy					0.4210†
Immunotherapy +	7	7.9	4 (11.8)	3 (5.5)	
Immunotherapy -	82	92.1	30 (88.2)	52 (94.5)	
Comorbid Conditions					
Anxiety +	23	25.8	8 (23.5)	15 (27.3)	0.6951
Anxiety -	66	74.2	26 (76.5)	40 (72.7)	
Arthritis +	22	24.7	13 (38.3)	9 (16.4)	0.0201*
Arthritis -	67	75.3	21 (61.8)	46 (83.6)	
Back Pain +	33	37.1	16 (47.1)	17 (30.9)	0.1254
Back Pain -	56	62.9	18 (52.9)	38 (69.1)	
Depression +	10	11.2	5 (14.7)	5 (9.1)	0.4151
Depression -	79	88.8	29 (85.3)	50 (90.9)	
Hypertension +	52	58.4	22 (64.7)	30 (54.6)	0.3447
Hypertension -	37	41.6	12 (35.3)	25 (45.5)	
Lung Disease +	26	29.2	11 (32.4)	15 (27.3)	0.6086
Lung Disease -	63	70.8	23 (67.7)	40 (72.7)	
Substance Use					
Alcohol Use +	4	4.5	3 (8.8)	1 (1.8)	0.1540†
Alcohol Use -	85	95.5	31 (91.2)	54 (98.2)	
Nicotine Use +	44	49.4	18 (52.9)	26 (47.3)	0.6033
Nicotine Use -	45	50.6	16 (47.1)	29 (52.7)	

n = 89. Chi Squared test used unless stated; †: Fisher's Exact Test; * denotes statistical significance $p < 0.05$; 5CS: 5-Year Cancer Survivors; VCC: Virginia Coordinated Care; Std: Standard Deviation; IQR: Interquartile Range; COU: Chronic Opioid User; NPOU: New Persistent Opioid User

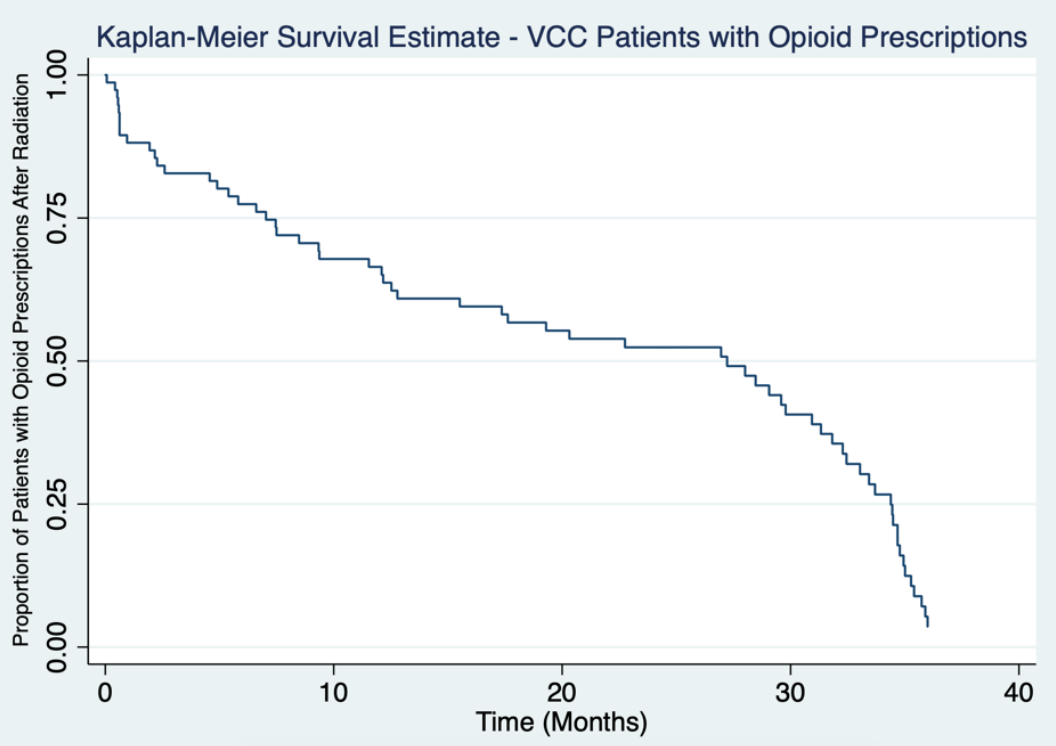

Figure 5.3: TTD of Opioid Prescriptions in 5CS with VCC by Opioid Exposure Group (TTD: Time to Discontinuation; 5CS: 5-Year Cancer Survivors; VCC: Virginia Coordinated Care)

Table 5.6: Cox Proportional Hazard Model Results of TTD of Opioids in 5CS with VCC Following Radiation

	Theoretical
Covariates	HR (95% CI)
Age	**1.04 (1.01, 1.08)**
Race	
African American	0.94 (0.44, 2.00)
Other	0.82 (0.25, 2.64)
White	Reference
Gender	
Male	0.43 (0.13, 1.41)
Female	Reference
Opioid Exposure	
NPOU	0.86 (0.39, 1.89)
COU	Reference
Cancer Type	
Breast	Reference
Female Genital	**8.54 (2.09, 34.92)**
Gastrointestinal	2.17 (0.48, 9.78)
Head and Neck	7.88 (0.97, 63.88)
Lung and Bronchus	1.16 (0.16, 8.66)
Other	**38.50 (3.80, 390.48)**

Prostate	5.27 (0.52, 53.22)
Clinical Stage	
0	Reference
1	0.52 (0.11, 2.54)
2	1.46 (0.23, 9.30)
3	1.98 (0.27, 14.50)
Unknown	**0.12 (0.02, 0.92)**
Additional Chemotherapy	1.17 (0.40, 3.48)
Additional Surgery	2.01 (0.66, 6.07)
Additional Immunotherapy	2.09 (0.66, 6.64)
Death 5 Years or More After Diagnosis	0.58 (0.15, 2.30)
Comorbid conditions	
Anxiety	0.73 (0.32, 1.66)
Arthritis	1.08 (0.51, 2.30)
Back Pain	**2.03 (1.12, 3.69)**
Depression	1.44 (0.48, 4.34)
Substance Use	
Alcohol Use	2.52 (0.64, 9.94)
Nicotine Use	0.78 (0.38, 1.59)

n = 89; **Bold denotes statistical significance**; 5CS: TTD: Time to Discontinuation; 5-Year Cancer Survivor; NPOU: New Persistent Opioid User; COU: Chronic Opioid User; VCC: Virginia Coordinated Care; HR: Hazard Ratio; 95% CI: 95% Confidence Interval

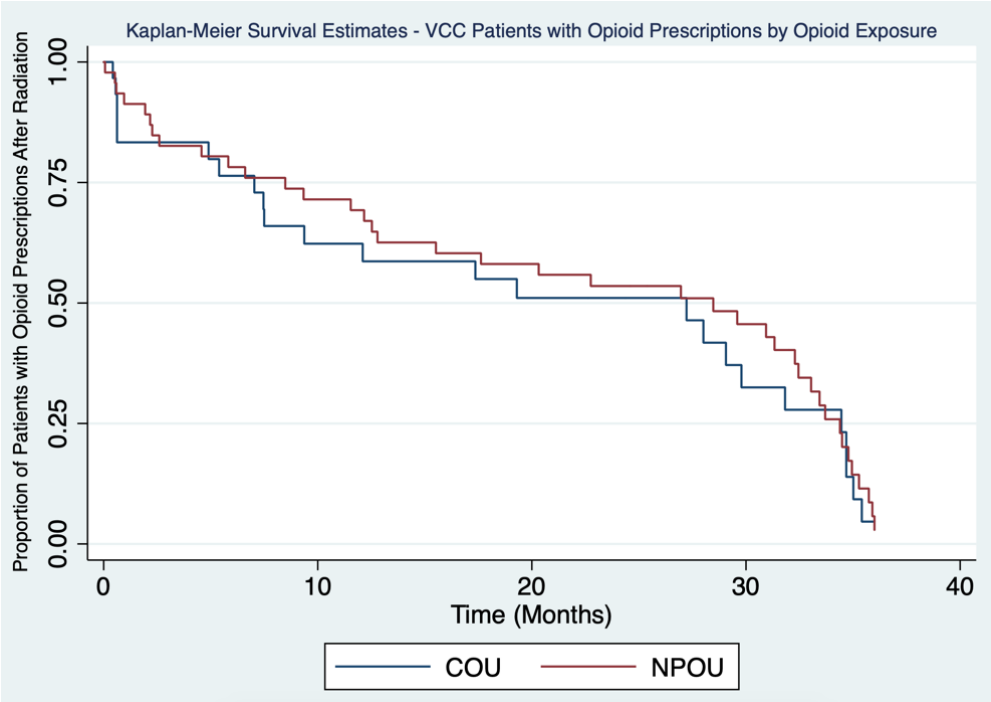

Figure 5.4: TTD of Opioid Prescriptions in 5CS with VCC Following Radiation by Opioid Exposure Group (TTD: Time to Discontinuation; 5CS: 5-Year Cancer Survivors; COU: Chronic Opioid User, NPOU: New Persistent Opioid User, VCC: Virginia Coordinated Care)

Discussion

This is the first study to show that cancer survivors receiving opioid prescriptions after completion of CIR continue opioid use for months-to-years after the end of treatment. Discontinuation of opioids in these patients should be an essential part of cancer survivor care in order to prevent poor outcomes associated with continued opioid use.[9] Continued use of opioids in non-cancer patients has resulted in "drug abuse and overdose rates [which] increased with longer use" and may be the case for patients with cancer.[8] Therefore, decreasing opioid utilization in patients with cancer that received curative intent radiotherapy should be prioritized soon after completion of treatment.

Our study identifies potentially modifiable patient factors (alcohol and nicotine use) that are associated with increased TTD of opioid therapy following CIR. Knowledge of patient use of alcohol and nicotine should alert prescribers to the need for substance use management. Such knowledge is also helpful for future public health initiatives in order to target interventions towards patient populations at-risk for prolonged opioid use after radiation therapy.

It was not surprising to observe that patients with alcohol and nicotine use had longer times to discontinuation of opioids. Current smoking has been shown to be associated with increased odds of opioid use disorder and higher daily opioid doses among males.[17] Additionally, studies have shown that almost one third of patients on chronic opioid therapy concurrently use alcohol and sedatives.[18] Therefore, substance use management should be considered for these patients at high risk for continued use, abuse, and misuse.[19]

A notable finding was that patients with head and neck experienced earlier discontinuation of opioids following curative intent radiotherapy. Head and neck cancers are notoriously caustic. As a result, as discussed in Chapter 3, we found an increased risk of developing NPOU for patients with these cancers. While patients with head and neck cancers

may have increased opioid utilization following radiotherapy (due to caustic disease and treatment symptoms such as dysphagia and odynophagia), they may have an easier time discontinuing opioids. This could be because they are more likely to have no prior use of opioids before treatment which was also highly associated with shorter TTD. Associated early discontinuation with NPOU also suggests that those with longer term opioid exposure may have more difficulty in discontinuing. Supporting this, we found that prior opioid exposure before initiation of radiotherapy leads to approximately a 2/3 additional year of opioid prescription utilization following radiotherapy treatment completion. This could be due to increased dependence on opioids or the presence of painful comorbid conditions that persist during and after cancer treatment.

It was not surprising to find that surgery was associated with longer time to opioid discontinuation. A previous study found that patients with cancer continued filling prescriptions with daily doses similar to chronic opioid users one year after curative intent surgery.[14] As suggested from Chapter 2, invasive surgery may be able to limit opioid dose requirement due to physical removal of the tumor pain source, but not opioid treatment duration time. Additionally, the finding that older patients have shorter times to discontinuation is somewhat expected. As patients age, concerns with opioid side effects, such as sedation, risk of falls, constipation, respiratory depression, and overdose, increase. This finding is consistent with the result from Chapter 3 that there is a decrease in risk of developing NPOU as patients age.

The purpose of the VCC subgroup analysis was to assess the robustness of our results. Unfortunately, we were unable to replicate overall TTD or difference in discontinuation of opioids by opioid exposure group for patients with VCC. This may have been due to low VCC sample size, incomplete capture of prescriptions in the full sample, or because the VCC subgroup was inherently different from the full sample. We suspect the latter to be true from

comparing patient demographics. There were 12.2 percentage points less patients with NPOU and 15.6 percentage points more patients with nicotine use in the VCC subgroup than in the entire sample. Both of these characteristics were associated with discontinuation time. NPOU was associated with shorter TTD while nicotine use was associated with longer TTD. Therefore, patients in the VCC subgroup, may be at higher risk for long-term opioid use following CIR because all VCC patients were indigent and because the VCC group included a higher proportion of COU and nicotine use, both of which are associated with longer TTD. This suggests that the TTD determined in patients with VCC may be on the long end of the range of opioid treatment duration following CIR.

Limitations

There are several limitations to this study. First, due to its cross-sectional nature, we pooled data over ten years. We have shown that the mean opioid dose prescribed decreased over time (Chapter 2; especially in later parts of this study) and it could be that those that had exposure to higher opioid doses from the first half of the study may have had a more difficult time discontinuing opioids or were transitioned to methadone. Additionally, we did not assess the type of medication used. Patients that were on methadone may not be eligible to discontinue due to maintenance therapy for opioid dependence. We also did not investigate differences between long- and short-acting opioid formulations.

Second, we utilized prescriptions ordered. These may not have necessarily been filled. If prescriptions were not filled, TTD was overestimated. Conversely, if patients were not adherent to medications as prescribed and had gaps between fills, TTD would be underestimated. It is also possible that opioid prescriptions written outside of the institution after CIR were missed and we potentially underestimated TTD. We attempted to assess this with a subgroup analysis of VCC patients with known prescriptions However, patients in this

group were different from the entire sample and, as a result, may be at higher risk for slower discontinuation of opioids.

Lastly, it would have been ideal to conduct a sensitivity analysis with patients that survived only 1 or 3 years beyond diagnosis (1-year cancer survivors [1CS]; 3-year cancer survivors [3CS]). However, the median TTD of opioids for the patients in this study was 1.4 and 2.3 years following end of radiation for the total sample and VCC sample, respectively. Including a sensitivity analysis of patients with survival less than the median TTD (1CS) could artificially shorten TTD. Including a sensitivity analysis of 3CS could artificially shorten TTD as with 1CS, or lengthen TTD, if 3CS continue opioids until end of life (beyond end of study period 36 months).

Conclusion

Cancer survivors receiving opioid prescriptions after completion of CIR continue opioid use for a median of almost one and a half years after the end of treatment. Therefore, decreasing opioid utilization in patients with cancer after curative intent radiotherapy should be prioritized. Evidence-based guidelines for clinical management of opioid use in cancer survivors after CIR is warranted to prevent poor outcomes associated with long-term opioid use. Our results indicate that patients that receive surgery or use alcohol or nicotine are more likely to have longer times to discontinuation of opioids and should be prioritized for opioid management after CIR.

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CHAPTER 6: DISCUSSION

Summary of Findings

This dissertation focused on four specific issues related to opioid utilization in cancer survivors that received curative intent radiation (CIR). The first study examined longitudinal 30-day average daily oral morphine equivalent (OME) doses at a single institution in cancer survivors who received CIR that survived at least 5 years without death or recurrence of disease (5CS) over the course of a decade. It also described differences in 30-day average daily OME dose by various groups. The second study examined opioid use patterns (new persistent opioid use [NPOU] or chronic opioid use [COU]) in 5CS over the same time period and assessed factors associated with opioid use. The third study examined opioid doses in 5CS before and after CIR as well as factors associated with opioid dose. The final study examined time to discontinuation (TTD) of opioids following CIR in 5CS. Major findings are summarized in Table 6.1.

Based on our analysis, there was an increase in 30-day average daily OME dose prescribing from late 2009 to 2012, which decreased after 2012. We saw that men, those of white compared to black race, those with public insurance, and patients with additional chemotherapy or no additional surgery appeared to be prescribed higher 30-day average daily OME doses between 2008 and 2018. Additionally, 5CS at this institution were generally prescribed higher rates of opioid prescriptions per patient and 30-day average daily OME doses than in the general American, non-cancer public. Trends of opioid prescribing in the last decade for 5CS receiving CIR were similar to previously reported trends in patients without cancer and outside of the United States, but with higher per patient prescriptions and 30-day average daily OME dose quantities.

From our analysis of 5CS receiving CIR, roughly one in five opioid naïve (ON) 5CS developed new persistent opioid use (NPOU) and more than half of patients with opioid exposure prior to radiation continued opioid use (COU). Certain cancer types (including head and neck cancer), stage 3 disease, and additional chemotherapy conferred increased odds of NPOU. Sociodemographic factors that conferred increased risk of NPOU included African American race, certain insurance types, and comorbid conditions including: arthritis, back pain, depression, lung disease, other opioid use, and nicotine use. Indigent provided health insurance, anxiety, back pain, hypertension, and nicotine use were significantly associated with increased odds of COU after radiation.

Our findings suggest that 5CS with opioid prescriptions prior to radiation have, on average, prescriptions with sustained doses of 68.2 - 68.3 OMEs per day higher that those that do not have opioid prescriptions prior to radiation. We found that most 5CS do not utilize opioids long-term before or after CIR. However, those with public insurance and comorbid conditions of anxiety, depression, and other drug use are associated with higher average OMEs. Conversely, 5CS with diabetes and hypertension are associated with lower average OMEs. From our results, we predict that 5CS that undergo CIR for their cancer will use at least some level of opioids, on average 4.1 OMEs per day, one year after end of radiation regardless of opioid use before CIR.

Our analysis revealed that 5CS with opioid prescriptions following CIR continue receiving opioid prescriptions for almost a year and a half (16.8 months) after completion of CIR. Median TTD of opioids was shorter for patients without opioid exposure prior to therapy (NPOU; 13.0 months) compared to patients with opioid exposure prior to therapy (COU; 21.4 months). Factors associated with shorter TTD included NPOU and head and neck cancers.

Conversely, additional surgery, death more than five years after diagnosis, as well as alcohol and nicotine use were associated with longer TTD of opioids.

Overall, presence of comorbidities, substance use, and indigent or public insurance were associated with greater opioid burden, use, dose and length of time of opioid use. Specific Aim 4 of this dissertation was to explicitly describe health disparities including gender, race, and insurance status associated with opioid utilization in 5CS (Table 6.2). This study identified socioeconomic and health differences in patients receiving CIR that result in increased opioid use, odds of NPOU and COU, opioid dose, and longer TTD of opioids (Table 6.3).

Just as health disparities exist in cancer and opioid prescribing independently, we were able to show that significant health disparities exist in opioid use and development of NPOU and COU across models in this study. African American patients were at 38% increased estimated odds of developing NPOU. Those of lower socioeconomic status (requiring indigent, charity insurance - VCC) were at 60% and 2.39 increased estimated odds of developing NPOU and COU, respectively. Additionally, those using Medicaid had 2.08 greater odds of developing NPOU. The results of higher opioid prescription use in low income insurance types following radiation therapy may be due to the fact that patients in disadvantaged sociodemographic positions have poorer outcomes. Our observations were reinforced with a subgroup analysis of 5CS with VCC. From our studies, we observed that patients with lower presumed income (based on use of Medicaid or institution charity care VCC) carry greater odds of developing NPOU or COU. Additionally, higher disease burden in indigent patients resulted in odds ratios showing significant associations with NPOU of much higher magnitudes. 5CS with VCC of African American race had lower estimates of OME doses over time, controlling for other factors. This corresponds with the descriptive results from Chapter 2 showing that those of

white race were prescribed higher doses of opioids. It has been well established that white patients receive greater access to opioid analgesics than African Americans, despite similar pain levels in non-cancer pain.[1–8] While these practices have protected African American patients from increased hospitalizations, African Americans have not had pain adequately treated.[9,10] Even in patients with cancer, African American patients are more likely not to receive adequate guideline recommended pain treatment, and more likely to receive analgesics with toxic metabolites.[11,12] This study adds to the collection of work on racial disparities in analgesic treatment, specifically in cancer survivors.

Health disparities in cancer survivors were echoed in this study with chronic conditions and substance use, which are highly prevalent in lower socioeconomic patient populations and may confer poorer outcomes. In this study, 5CS with comorbid conditions including anxiety, arthritis, back pain, depression, hypertension, and lung disease were at higher risk for higher average OME, longer TTD of discontinuation of opioids, and at greater odds of developing NPOU or COU.

Table 6.1: Summary of Findings

Chapter	2	3	4	5
Study	1	2	3	4
Title	Longitudinal Opioid Prescription Use in Patients with Cancer Receiving Radiotherapy from 2008 to 2018 at a Single Cancer Center	Incidence and Associated Risks of New Persistent and Continued Opioid Use in Cancer Survivors After Curative Intent Radiation	Prescribed Opioid Doses in Cancer Survivors Pre and Post Curative Intent Radiation	Time to Discontinuation of Chronic Opioids in Cancer Survivors After Curative Intent Radiation
Objective	Describe longitudinal trends in 5CS who received CIR	Calculate incidence of and examine factors associated with NPOU and COU in 5CS who received CIR	Determine OME doses in 5CS who received CIR and factors associated with opioid dose burden	Determine TTD of opioids in months and factors associated with length of TTD in 5CS following CIR
Method	Descriptive time series	Incidence and binomial logistic regression	Panel data model and mixed linear model	Kaplan-Meier survival and Cox proportional hazard models
Outcomes	Descriptive 30-day average daily OME dose longitudinal trends	NPOU and COU incidence OR of factors associated with NPOU and COU	Average OME dose after end of radiation Predicted OME dose 1 year following CIR	TTD of opioids following CIR HR of factors associated with TTD
Major Findings	30-day average daily OME dose prescribing increased from late 2009 to 2012, and decreased after 2012 Factors with apparent higher 30-day average daily OME doses: • Men • White race • Chemotherapy • No surgery	19.7% ON 5CS developed NPOU 54.8% OE 5CS COU Factors associated with increased risk of NPOU: • Head & neck cancers • Stage 3 disease • Chemotherapy • African American race • Anxiety • Arthritis • Back Pain • Depression • Lung disease • Other Opioid use • Nicotine use Factors associated with increased risk of COU: • VCC • Anxiety • Back pain • Hypertension • Nicotine use	OE 5CS have 68.2 (PDM) – 68.3 (MLM) OMEs prescribed higher than ON over time Factors associated with higher average OMEs over time: • Public insurance • Anxiety • Depression • Other drug use Factors associated with lower average OMEs over time: • Diabetes • Hypertension 5CS are predicted to have 4.1 daily OMEs prescribed 1 year after CIR	5CS median TTD of opioids 16.8 months (95% CI: 13.1-19.1) following end of radiation NPOU median TTD: 13.0 months COU median TTD: 21.4 months Factors associated with shorter TTD: • NPOU • Head & neck cancers Factors associated with longer TTD: • Surgery • Death after >5 years of diagnosis • Alcohol use • Nicotine use

Table 6.2: Specific Aim 4

Specific Aim 4: In cancer survivors who received curative intent radiation therapy for their malignancy, examine health disparities that may exist in sex, race, and socioeconomic status in patients with new persistent and continued chronic opioid use

Table 6.3: Summary of Health Disparities

	Gender	Race	Insurance	Comorbid Conditions
Overall Opioid Use	Descriptively higher OME: • Men	Descriptively higher OME: • White Higher average OME: • White with VCC	Descriptively higher OME: • Public insurance Higher average OME: • Public insurance	Higher average OME: • Anxiety • Depression • Other drug use Associated with longer TTD of opioids: • Alcohol use • Nicotine use
NPOU		Associated with NPOU: • African American	Associated with NPOU: • Indigent insurance • Public insurance	Associated with NPOU: • Arthritis • Back pain • Depression • Lung disease • Other Opioid use • Nicotine use
COU			Associated with COU: • Indigent insurance	Associated with COU: • Anxiety • Back pain • Hypertension • Nicotine use

Implications

As cancer therapies continue to improve and patients with cancer continue to live longer, opioid use considerations should be of greater concern for survivorship care. Our results have demonstrated substantial opioid use in cancer survivors and, as mentioned earlier, there are no evidence-based recommendations for treating cancer pain. There may be justifiable instances for CS where long term opioid use may be necessary for chronic pain. However, evidence-based recommendations and guidelines are warranted to prevent potential misuse and deaths due to high numbers of patients that continue to use opioids long after CIR,

risk of NPOU, COU, and high OMEs utilized. Findings from these studies should serve as a baseline for identifying patients with cancer that are at greatest risk of opioid use after CIR. Opioids are necessary for pain management of cancer and cancer therapies. However, once patients that have undergone caustic cancer therapies have attained remission or no evidence of disease, they must be safely weaned off or transitioned to substance use treatment to prevent potential poor outcomes such as overdose and death. Assessment of factors associated with greater and long term use of opioids can help identify patients that may be good candidates for substance use treatment. Lastly, our findings provided real-world evidence of opioid use in cancer survivors.

Limitations

There are several limitations to our studies. First, this study only included patients at a single, urban, academic institution. Due to access to only institutional medical records, it is possible that outside information may have been missed. For example, access to the Virginia Prescription Monitoring Program (PMP) was not permitted, and therefore, access to additional opioid prescriptions written by doctors outside of the VCU Health medical network was not available. Providers at our health system may have different pain management practices or preferences that may not be nationally representative. Thus, the results of this study may only be generalizable to other academic institutions of similar size, patient population, and geography. Additionally, the results from our analysis can only be generalized to patients with cancer that receive CIR.

Second, we pooled data over ten years. We have shown that the mean opioid dose prescribed was different over time (Chapter 2; especially in later parts of this study). It could be that those that had exposure to higher opioid doses from the first half of the study may have

been at higher risk for NPOU and COU, had a more difficult time discontinuing opioids at a later time, or were transitioned to maintenance methadone. We did not find significant differences between types of medications in our results, but we did not investigate differences between long- and short-acting opioid formulations.

Third, this study utilized prescribing data rather than fill data. There exists the possibility of patients not filling prescriptions, or missing prescriptions due to lack of access to opioid prescriptions written by doctors outside of the institution. Therefore, missed prescriptions could have resulted in underestimation of opioid use if patients received outside opioid prescriptions. Conversely, if prescriptions were not filled by the patient, opioid use could have been overestimated. In order to address this, we conducted the subgroup analysis with VCC patients for which we have all prescribing data. However, patients in this group were sicker than the entire sample with a higher proportion of comorbidities and, as a result, may be at higher risk for higher opioid use.

A prescription specific limitation was that there was a large amount of missing prescription data information necessary to calculate accurate daily OME doses. In order to accurately calculate a daily OME dose, a medication name, medication strength, tablet or quantity amount (number of doses), daily frequency, and the OME conversion factor were needed. Due to the inherent limitations of documentation of the prescriptions from the electronic medical record, 59.6% of prescriptions were missing at least one component of the OME dose calculation. This could have resulted in underestimation of opioid use. The authors considered imputing missing data to address this issue, however, it was ultimately decided that imputation was not necessarily needed due to the large sample size of available prescriptions for which all data was available to calculate 30-day average daily OME dose. Patients were retained in our sample while prescriptions with missing data were dropped. This likely resulted

in underestimations of opioid dose in our sample, suggesting our dose estimates are conservative.

Another prescription limitation was due to the inherent flexibility that prescribers often use when writing prescriptions for patients, particularly for “as needed” (i.e. PRN) dosing. Ranges were often provided in prescriptions for dose and frequency (i.e. 1-2 tablets every 4-6 hours per day). Therefore, daily OME doses were calculated based on patients using the highest possible dose at the greatest frequency for the ranges given in a prescription. As a result, it is possible that 30-day average daily OME doses may be overestimated. However, minimum daily OME doses were also calculated for all prescriptions and differences in results were negligible.

Lastly, we could not differentiate whether the indication for an opioid prescription was for cancer or non-cancer pain. Opioid prescriptions due to cancer pain would be, in theory, easier to discontinue than those for non-cancer pain after CIR from decreasing or eliminating the source of the underlying cancer pain.

Future Directions

This study assessed opioid utilization in cancer survivors. Future research should examine the association of palliative radiotherapy with opioid burden among patients in the last 6 months of life. While we observed that almost one-fifth of patients develop NPOU, there may be a lower incidence of NPOU in cancer survivors receiving radiation due to the potential of radiation alleviating some cancer pain. Additionally, we saw that 5CS utilize high doses of opioids, which decreased over time, but were still significantly higher for those with a baseline opioid prescription. Addressing opioid trends in the palliative radiotherapy space may indicate a lower opioid dose requirement.

This study specifically excluded inpatient and acutely prescribed opioids. Examining the association of inpatient opioid administration with long-term opioid utilization in these patients should be explored. We also did not assess prevalence of opioid use disorder (OUD) in our patients. As patients are surviving longer after CIR, risk of OUD should be assessed and guidelines for transitioning patients to substance use treatment should be recommended. Further, there is a significant need to assess opioid related outcomes in cancer survivors. Lastly, our study did not assess health-related quality of life or costs associated with opioid use for these patients.

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VITA

Elena Valerie Fernández was born on May 30, 1990 in Framingham, Massachusetts and is a Mexican and American citizen. She graduated from James Madison High School, Vienna, Virginia in 2008. She received her Bachelor of Science in Biochemistry from the University of Mary Washington, Fredericksburg, Virginia in 2012 and subsequently worked at the National Cancer Institute, Bethesda, Maryland for two years. She received a Doctor of Pharmacy from Virginia Commonwealth University, Richmond, Virginia in 2018. She received two fellowships from the American Foundation for Pharmaceutical Education, the Pre-Doctoral Fellowship in Health Outcome Disparities and Nellie Wakeman Fellowship in partnership with Kappa Epsilon Fraternity, to complete this dissertation.