Advances in Radiation Oncology (2022) 7, 100833

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Opioid Use in Patients With Cervical Cancer at Two Urban Medical Centers

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Received September 13, 2021; accepted October 6, 2021

Abstract

Purpose: Patients with cervical cancer are at high risk for opioid use. This study aimed to characterize opioid prescribing patterns at 2 urban hospitals.

Methods and Materials: Data from patients with cervical cancer treated with curative intent from 2011 to 2018 were retrospectively collected. Women with unrelated chronic opioid use before diagnosis, persistent/recurrent disease at 3 months after initiation of treatment, or initiation of opioids >6 months after treatment were excluded. Demographics, disease characteristics, treatment, and outpatient prescription practices were collected. Endpoints included duration of opioid use ≥6 and ≥12 months.

Results: There were 106 women included, of whom 83% received definitive radiation. Most patients (n = 91, 85.8%) received outpatient opioids. Most common timing of prescriptions were before cancer therapy (35.9%), postprocedure (26.4%), and during radiation therapy (17.0%). Median duration was 3 (interquartile range, 1-11) months; 35.2% of these patients received opioids ≥6 months and 22% received opioids ≥12 months. Greater International Federation of Gynaecology and Obstetrics (FIGO) stage, recurrent/residual disease, initiation of opioids before treatment, history of depression or anxiety, and use of gabapentin or steroids were associated with long-term opioid use.

Conclusions: Most patients were prescribed outpatient opioids, many of whom used opioids for 12 months. Improvement in provider communication and education, increased posttreatment monitoring, and further evaluation of nonopioid therapies are needed in this patient population to reduce long-term opioid use.

Sources of support: This project was funded in part by NIH CTSA UL1 TR000430. Funding was used to collect data through REDCap, a secure, web-based application designed to support data capture for research studies Informed consent was obtained from all individual participants included in the study.

Disclosures: none.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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https://doi.org/10.1016/j.adro.2021.100833

Introduction

Opioids are mainstays in cancer pain treatment based upon recommendations of the American Society of Clinical Oncology, National Comprehensive Cancer Network, and World Health Organization.[1-3] Unfortunately, one recent metanalysis estimated that moderate-severe pain is present in 38% of all patients with cancer and pain management for these patients has been complicated by the ongoing opioid epidemic in the United States.[4] Policy statements from oncology societies reflect this dilemma, cautioning against unmanaged pain but advocating for increased stewardship.[5,6] Such complex dynamics require clinical data to best guide practice, yet several Cochrane reviews comparing the efficacy of several opioid and nonopioid modalities have shown minimal benefits in outcomes, noting bias or limitations, such as unknown reasons for prescribing, low-quality data surrounding comparative efficacy, minimal data regarding length of prescriptions, and unknown frequency of adverse effects such as opioid dependence.[7-10] Another systematic review noted the extreme heterogeneity in reporting of adverse opioid side effects in this population with a need for further insight into adverse event rates in opioid use for cancer-related pain.[11] The absence of definitive data showing clear efficacy for opioid monotherapy compared with nonopioid or multimodal pain management, as well as unknowns regarding prescribing characteristics and long-term use, is troubling for practitioners treating a vulnerable population at high risk for chronic pain.

Cervical cancer remains the second largest cause of cancer death for female patients <40 years old, often with poor prognosis on diagnosis and prevalence of pain as a predominant symptom as high as 96% in patients with advanced cervical cancer.[7] Not only are patients with cervical cancer at higher risk of chronic pain relative to other patients with cancer, but long-term survivors also often struggle with pain years after diagnosis and one study even demonstrates higher rates of opioid use in this group compared with other cancer survivors.[7-10,12,13] The pain secondary to cervical cancer treatment is particularly complex given the combination of potential interventions (surgery, chemotherapy, and radiation) and can be somatic, visceral, neuropathic, or a combination of these.[14] Cervical cancer may also carry a higher risk of persistent opioid use secondary to anatomic location; a large retrospective study found that patients with primary malignancies originating from the lower abdomen had an odds ratio of 2.43 for opioid use at time of death.[15] Several drugs that are cornerstones in cervical cancer chemotherapy regimens, such as the platinum analogs and taxanes, as well as radiation therapy to the pelvis, are among the primary risk factors of neuropathic pain and chronic pelvic pain respectively.[14] Patients with cervical cancer also face unique comorbidities that make treating their pain particularly difficult, such as chronic bowel symptoms and fistulae, that may be exacerbated by opioid use.[7,9]

For these reasons, it is imperative to understand opioid use patterns in patients with cervical cancer, use of alternative and adjunctive therapies for these patients, as well as prescribing trends between physicians. Only one other study has reported on opioid use and its risk factors in patients with cervical cancer, noting that nearly 40% of cervical cancer survivors reported persistent use 6 months after the completion of treatment.[16] Our study aims to contribute further data regarding rates of persistent opioid use and risk factors by reporting trends around opioid and nonopioid prescription patterns.

Methods and Materials

Clinical and demographic data for patients treated with curative intent for cervical cancer at 2 urban academic institutions from 2011 to 2018 were retrospectively collected. All patients were treated by a multidisciplinary team including gynecologic and radiation oncologists. Clinical data was abstracted using institutional electronic medical records. The study was approved by both institutional review boards.

Only patients who were opioid-naïve before their cervical cancer diagnoses were included in this study. Those with chronic opioid use unrelated to cancer were excluded. Women who were started on opioids >6 months after treatment for reasons other than treatment or cancer-related pain were excluded as well. Lastly, women with persistent or recurrent disease at 3 months after initiation of treatment were also excluded. "Outpatient opioid" use was defined as any outpatient opioid prescription, including postprocedural medications. "Any opioid use" was defined as receiving opioids as an inpatient or as an outpatient; opioids administered solely during or immediately after procedures (including postoperative and postbrachytherapy) were not included in this tabulation. Duration of opioid use was tabulated by counting months of written prescriptions for any opioid analgesic available in the electronic medical record and verified with provider notes. Gaps in prescriptions greater >2 months were not counted toward the tabulation of total duration of outpatient opioid use. Duration of opioid treatment was verified with the state Prescription Drug Monitoring Program (PDMP) when available to confirm accuracy of the medical chart. Demographic information, disease characteristics, treatment type, and outpatient medication prescription practices were collected.

All data was stored via REDCap data capture, a secure web-based application designed to support data capture for research studies.[17,18] Endpoints examined were opioid

Table 1 Patient characteristics

Characteristic	N = 106
Age at diagnosis, y	
≤60	79 (74.5)
>60	27 (25.5)
Race	
White	31 (29.3)
Black/African-American	50 (47.2)
Other	25 (23.6)
Marital status	
Single/divorced/widowed	69 (65.1)
Married	33 (31,1)
Unknown	4 (3.7)
Median body mass index (kg/m^2)	29.3 (interquartile range, 24.0-35.3)
Smoking status	
Current/prior	50 (47.2)
Never	56 (52.8)
Alcohol use	
None	64 (60.4)
<3 drinks/wk	34 (32.1)
≥3 drinks/wk	8 (7.5)
Recreational drug use	
None	91 (85.9)
Current or prior	15 (14.1)
History of depression/anxiety	27 (25.5)
History of "other" psychiatric disorder	6 (5.7)
FIGO stage	
Stage I	38 (35.9)
Stage II	34 (32.1)
Stage III	29 (27.4)
Stage IV	4 (3.8)
Recurrent	1 (0.9)
Radiation therapy intent	
Definitive	88 (83.0)
Adjuvant	18 (17.0)
Brachytherapy applicator type	
Tandem and ovoid	59 (55.7)
Interstitial	24 (22.6)
No brachytherapy or N/A	23 (21.7)

Abbreviation: FIGO = International Federation of Gynaecology and Obstetrics.

use ≥6 months and opioid use ≥12 months. Logistic regression, χ^2d, Cramér's V, and Wilcoxon rank-sum were used to assess strength of association between clinical or demographic variables with endpoints. Univariate analysis and multivariable models were carried out using logistic regression and multinomial logistic regression. Variables with P value > 0.1 on univariate logistic regression were included in the multivariable model. Linear regression was used to determine whether there was association between duration of use and variables. Statistical analysis was conducted using Stata v14.0 (StataCorp LP, College Station, TX).

Results

Patient characteristics

From 2011 to 2018, 106 women receiving curative intent treatment for cervical cancer were identified (Table 1). Median follow-up was 27 (interquartile range [IQR], 14-37) months from time of diagnosis. Median age was 49.5 (IQR 40-60). The majority of women were treated with definitive radiation therapy (83%). Ninety-three women (87.7%) received opioids at some point during their treatment or follow-up course (not including opioids administered during procedures), and 91 women (85.9%) received at least one outpatient opioid prescription. Of the 91 women who received an outpatient opioid prescription, 35.2% used opioids for ≥6 months and 22.0% used opioids for ≥12 months. Most patients (73.4%) received prescriptions for other, nonopioid medications to manage pain, including gabapentin (9.4%), topical lidocaine (24.5%), nonsteroidal anti-inflammatory drugs (51.9%), steroids (16.0%), acetaminophen (31.1%), and dicyclomine (<1%).

Opioid prescription characteristics

Opioid prescription details are described in Table 2. In women who were prescribed outpatient opioids, median duration of opioid use was 3 months (IQR, 1-10 months). The most commonly prescribed opioid was hydrocodone-acetaminophen (71.4%).

Opioid use analysis

Tables 3 and 4 describe the univariate and multivariable analyses of variables associated with duration of use ≥6 months and ≥12 months. On univariate analysis, ≥6 months of opioid use was associated with the use of gabapentin, the use of steroids, International Federation of Gynaecology and Obstetrics (FIGO) stage, pretreatment opioid use (compared with no opioids pretreatment), and recurrence; ≥12 months was associated with pretreatment opioid use, FIGO stage, and anxiety and depression (all $P < .05$). In a multivariable model including race, FIGO stage, anxiety/depression, use of other pain medications, recurrence, and pretreatment use of opioids, only recurrence and pretreatment use remained associated with ≥6 months of opioid use. FIGO stage, pretreatment use and anxiety/depression were significantly associated with >12 months of opioid use.

Among those receiving outpatient opioid prescriptions, longer duration of use was associated with pretreatment receipt of opioids (coefficient 5.98; 95% confidence interval [CI], 0.27-11.7; $P = .04$) compared with no

Table 2 Opioid prescription characteristics

Timing of initial prescription (inpatient or outpatient)	N = 106 (%)
Before initiation of therapy	38 (35.9)
Routine postprocedure pain	28 (26.4)
During RT	18 (17.0)
<3 mo after completion of RT	1 (0.9)
>6 mo after completion of RT	7 (6.6
No opioids prescribed	13 (12.3)
Unknown	1 (0.9)
Reason for initial prescription (for patients receiving outpatient prescriptions)	N = 91 (%)
Cancer pain	30 (33.0)
Routine postprocedure pain	27 (29.7)
Dysuria	1 (1.1)
Abdominal pain	5 (5.5)
Pelvic insufficiency fracture	1 (1.1)
Pelvic pain not otherwise specified	3 (3.3)
Other, unknown, or not otherwise specified	24 (26.3)
First prescriber (for patients receiving outpatient prescriptions)	N = 91 (%)
Gynecologic oncology	56 (61.5)
Radiation oncology	4 (4.4)
Medical oncology	2 (2.2)
ER/urgent care	4 (4.4)
Other/unknown	25 (27.5)
Type of outpatient opioid first prescribed	N = 91 (%)
Hydrocodone/acetaminophen	65 (71.4)
Oxycodone/acetaminophen	8 (8.8)
Oxycodone	1 (1.1)
Morphine	2 (2.2)
Tramadol	8 (8.8)
Other	7 (7.7)

Abbreviations: ER = emergency room; RT = radiation therapy.

opioids pretreatment. Higher FIGO stage (as a continuous variable) also trended toward association with longer duration of opioid use (coefficient 2.66; 95% CI, −0.28 to 5.6; P = .08). Receipt of routine postoperative prescriptions was associated with shorter durations of opioid use (coefficient −9.26; 95% CI, −15.8 to −2.69; P <.01) compared with those who received opioids pretreatment.

Discussion

We sought to explore clinical and demographic factors associated with outpatient opioid prescriptions, reasons for initiation of opioids, and use of other adjunctive medications in women with cervical cancer who require radiation. In our population, >80% of women received at least one outpatient opioid prescription, most commonly by gynecologic oncologists (61.5%), and the majority of patients received their initial prescriptions just before or during their treatment course. Most concerning was that 35.2% of patients prescribed opioids continued receiving opioid prescriptions for ≥6 months, and that 22.0% received them for ≥12 months.

Our analysis is consistent with previous findings that suggest depression and anxiety are positively correlated with persistent opioid use.[16] Another study demonstrated that long-term opioid use had a greater association with developing treatment-refractory depression; it was the duration of opioid use, rather than its prescription dose or strength, that was more closely associated with treatment-resistant depression.[19] This is significant, given the complicated relationship between depression and pain and the fact that patients with cervical cancer in particular are noted to have a high prevalence of anxiety and depression (30%-50%).[20] Physiologically, depression is linked to long-term inflammatory responses and overlapping genetic predispositions to chronic pain, but lack of function and mobility secondary to pain also increases the risk for depression.[21,22] Indeed, definitive radiation for cervical cancer is also itself associated with high rates of posttraumatic stress disorder during the months after treatment.[23]

Our findings did not demonstrate a significant association between tobacco, alcohol, or recreational drug use and persistent opioid use. A variety of reasons may account for this discrepancy, including physician and patient inaccuracies in self-reporting and physician prescribing bias based on prior substance use history. In a randomized controlled trial of patients with advanced cancer with a history of alcohol use disorders, palliative specialists were able to adequately control patients' pain through alternative modalities without increasing opioid dosages, demonstrating that appropriate multimodality management can lead to successful results.[24] In another publication, the same group of researchers reported undocumented substance abuse may be highly prevalent in patients with cancer. In this study, only 13% of those having a previously documented record of substance use disorder actually screened positive in a hospital wide screen for alcohol abuse.[24,25] These patients were more likely to be on opioids at time of screening and continue opioid use at follow-up with 50% higher morphine equivalent doses on average relative to other patients with cancer.[24] Therefore, careful elucidation of alcohol or other drug use history would be beneficial in optimizing opioid management. Notably, many patients who reported recreational drug use in this study specifically noted marijuana use. Given conflicting and limited data regarding the efficacy of cannabis use for symptom management in this patient population, it is difficult to determine the nature its relationship with opioid use and requires further exploration.[26-28] Additionally, those with substance abuse may have more limited follow-up and thus there could be selection bias in identifying those who had persistent opioid use.

Additional research is also warranted regarding nonopioid medications, which are an important adjunct to opioids.[3,29] Our study found that there was a positive association between use of alternative nonopioid prescriptions and long-term opioid use, with statistically significant associations between long-term opioid use and gabapentin and steroid prescriptions. The increased use of such modalities

Table 3 Univariate analysis for opioid use ≥6 months and ≥12 months

	Opioid use ≥6 mo		Opioid use ≥12 mo	
Variable	**Odds ratio (95% CI)**	***P***	**Odds ratio (95% CI)**	***P***
Age, y	0.98 (0.95-1.01)	.34	0.98 (0.95-1.02)	.41
Body mass index				
<30 kg/m^2	Ref.	-	Ref.	-
≥30 kg/m^2	1.44 (0.61-3.4)	.41	1.9 (0.70-5.31)	.20
Race				
White	Ref.	-	Ref.	-
Black	1.16 (0.44-3.07)	.77	0.58 (0.19-1.70)	.32
Other	0.26 (0.06-1.09)	.07*	0.22 (0.04-1.17)	.08*
FIGO (continuous)	1.62 (1.01-2.60)	.04†	2.00 (1.15-3.47)	.01†
Postoperative vs definitive radiation	0.37 (0.10-1.40)	.14	0.45 (0.09-2.18)	.32
Brachytherapy				
Tandem and ovoid	Ref.	-	Ref.	-
Interstitial	0.63 (0.22-1.8)	.40	0.42 (0.11-1.63)	.21
None	0.52 (0.16-1.67)	.27	0.74 (0.21-2.63)	.64
Alcohol use				
None	Ref.	-	Ref.	-
<3x/wk	1.62 (0.64-4.12)	.31	1.30 (0.44-3.82)	.63
≥3 × /wk	2.29 (0.42-12.5)	.34	2.04 (0.33-12.6)	.44
Drug use	0.62 (0.18-2.14)	.45	0.87 (0.22-3.43)	.84
Current/past vs none				
Smoking	1.51 (0.63-3.61)	.35	1.12 (0.41-3.04)	.82
Current/past vs none				
Married	0.98 (0.39-2.50)	.97	0.92 (0.31-2.70)	.87
Depression/anxiety	2.12 (0.82-5.46)	.12	3.73 (1.31-10.6)	.01†
Other pain medications	2.57 (0.85-7.70)	.09*	2.38 (0.63-8.99)	.20
Gabapentin	5.22 (1.25-21.9)	.02†	2.71 (0.68-10.7)	.16
Lidocaine	2.57 (0.95-6.96)	.06*	2.19 (0.74-6.51)	.16
Nonsteroid antiinflammatory drugs	1.85 (0.76-4.50)	.18	1.61 (0.58-4.52)	.36
Steroids	11.2 (2.86-43.8)	<.01†	4.24 (1.31-13.8)	.02†
Acetaminophen	1.48 (0.60-3.69)	.40	1.20 (0.42-3.42)	.73
Pretreatment opioids	5.47 (2.14-14.0)	<.001†	5.09 (1.73-15.0)	<.01†
Recurrence	3.39 (1.30-8.84)	.01†	2.12 (0.74-6.04)	.16

Abbreviations: CI = confidence interval; FIGO = International Federation of Gynaecology and Obstetrics.
* $P < .1$.
† $P < .05$.

Table 4 Multivariable models for opioid use ≥6 months and ≥12 months

	Opioid use ≥6 mo		Opioid use ≥12 mo	
Variable	**Hazard ratio (95% CI)**	***P***	**Hazard ratio (95% CI)**	***P***
Race				
White	Ref.	-	Ref.	-
Black	3.41 (0.86-13.5)	0.08	1.00 (0.26-3.77)	1.0
Other	0.35 (0.06-2.02)	0.24	0.32 (0.05-2.02)	0.2
FIGO stage	1.79 (0.95-3.34)	0.07*	2.11 (1.10-4.10)	0.03†
Depression/anxiety	1.92 (0.58-6.30)	0.28	4.02 (1.16-13.9)	0.03†
Other pain medications	3.83 (0.97-15.2)	0.06*	3.29 (0.68-15.8)	0.14
Recurrence	4.72 (1.32-16.90)	0.02†	1.71 (0.48-6.01)	0.41
Pretreatment opioids	9.07 (2.67-30.8)	<0.001†	4.93 (1.44-16.9)	0.01†

Abbreviations: CI = confidence interval; FIGO = International Federation of Gynaecology and Obstetrics.
* $P < .1$.
† $P < .05$.

in those receiving long courses of opioid therapy suggest that other forms of pain, such as neuropathic or inflammatory etiologies, are suspected to play a role in these patients and that opioid therapy alone is likely insufficient. Patients with cervical cancer are at particularly high risk for multiple pathophysiological causes of pain and evidence suggests a benefit from multimodal management.[14] Gabapentin has a well-defined role in other chronic neuropathies as well as some reported efficacy in cancer/treatment related pain.[30] Data surrounding the use of steroids for cancer-related pain in oncology patients are conflicting. Although steroids have long been demonstrated to significantly relieve cancer-related fatigue, anorexia, and cachexia, a recent systematic review also suggests they may offer moderate control of cancer-related pain.[31-33] There may also be a greater role for steroids in relieving discomfort related specifically to radiation-induced inflammation.[34] Steroids may also be a more feasible alternative than high dose nonsteroidal anti-inflammatory drugs for cervical cancer patients, given the renal toxicity of cisplatin and potential for underlying renal compromise due to tumor-associated hydronephrosis.

Unsurprisingly, patients with recurrent or residual disease were more likely to be prescribed longer course of opioids; this is likely also related to our findings that those with higher initial FIGO stage and pretreatment pain requiring opioids were also more likely to require long-term opioid therapy. Extensive locoregional disease is more likely to be symptomatic, with patients requiring more invasive therapies such as interstitial implants, and also more likely to be associated with recurrence compared with earlier stages of disease. In this study, pretreatment pain requiring opioids was a risk factor for long-term opioid use independent of recurrence; thus, these patients should be monitored carefully after treatment for appropriate management and tapering.

A systemic issue that was noted in analyzing initial prescribers of opioid therapy include the substantial proportion (26.3%) of initial opioid prescribers who were unknown or not recorded in the medical record. Appropriate opioid prescribing is difficult if prescribers are unaware of one another. In this study a substantial proportion (26.3%) of initial opioid prescribers were unknown or not recorded in the medical chart. Although many initial prescribers may have been from outside hospital emergency departments or providers, this reveals a systemic challenge in physician communication between hospital systems and specialties. Programs such as the PDMP are crucial in filling the gap in communication and its use should continue to be encouraged in our nation's segmented health care system. Notably, it was outside the scope of this study to determine the appropriateness of initial opioid prescriptions, which may or may not be modifiable.

There are several limitations to our study. First is the inherent nature of retrospective chart review, which is reliant on accurate records and patient-reported history of anxiety/depression and alcohol use. PDMP records were not available for all patients to verify the medical record; however, the medical record was generally accurate in patients from whom this data was available. The study analyzed patients treated at 2 academic centers within a single urban city; thus, our findings may not be generalizable to other populations or geographic locations. Additional detailed information regarding prescriber management of opioid prescriptions would be helpful, as well as the involvement of supportive or palliative care practitioners, pelvic floor therapy, or physical medicine and rehabilitation specialists in symptom management.

Strengths of our study include findings regarding the use and duration of opioid therapy in patients with locally advanced cervical cancer, including that a large proportion of women continue to use opioids for >6 to 12 months. We also report on nonopioid medications frequently used to manage posttreatment pain, as well as the timing of and reasons for opioid prescribing. Increased participation in existing systemic modalities of reporting opioid prescriptions, such as the PDMP, along with effective interprovider communication is needed. Appropriate opioid stewardship should be promoted especially for patients with prior history of anxiety or depression while remaining cognizant of these populations' poorer health outcomes, higher risk of chronic pain, and effect of cancer treatment on underlying psychiatric disorders. Future directions also include additional research and provider education regarding application and efficacy of nonopioid medications and multidisciplinary care that includes specialists in psychiatry, palliative care, physical therapy, and addiction medicine.

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