Original Article

# The relationship between palliative radiotherapy and opioid prescribing patterns among patients with metastatic cancer

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**Background:** While randomized trials have established that palliative radiotherapy, especially to bone, can improve qualitative measures of pain, its quantitative relationship to opioid prescribing patterns has remained underexplored. We aimed to identify the association of palliative radiotherapy on opioid prescriptions received among patients with metastatic cancer.

**Methods:** The Virginia Commonwealth University Institutional Review Board approved retrospective analysis extracted prescription data from all adult patients with metastatic cancer who underwent outpatient palliative external beam radiation therapy at Virginia Commonwealth University Health System from 2008–2018. Institutional prescribing data were used to calculate the average opioid oral morphine milligram equivalent (MME) dose 30, 60 and 90 days both before and after radiotherapy. Univariate and bivariate ordinary least squares (OLS) regression models were used to estimate the relationship of MME changes with clinical, radiation-related, and demographic patient factors.

**Results:** A total of 182 patients met inclusion criteria. Overall, patients required higher opioid doses after radiotherapy, with mean MME 30, 60, and 90 days prior to radiotherapy of 24.6, 20.2, and 16.8 mg, respectively; which increased to 62.9, 77.7 and 82.4 mg post-radiation therapy ($P<0.01$). Multivariate OLS models predicting the change of MME 60 days pre- and post-radiation treatment showed that younger age and comorbid depression predicted increased MME after radiotherapy.

**Conclusions:** Patients with metastatic cancer face a relatively high opioid burden, which increases over time, even among those who receive palliative radiation therapy. Patients who are younger and have comorbid depression may have a higher risk of increased opioid burden after radiotherapy.

**Keywords:** Opiate use; palliative radiation; bone metastases; prescription data

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## Introduction

Patients with locally advanced and metastatic cancers often endure a devastating range of symptoms. These advanced disease states cause a shift in the focus of medical care from curative intent to symptom management. Palliative care plays a vital role in symptom management to improve the quality of life in these patients (1). Pain control is a centerpiece of the palliative care plan, especially in advanced/metastatic cancer patients who were found to have a pooled prevalence of pain of 64% upon systematic review (2). Cancer pain results in disabling psychological

distress, thus, recognition and appropriate treatment yield better quality of life (3-5).

Opioids have remained the mainstay of treatment for severe cancer-related pain due to their well-established rapid onset analgesic effects (6,7). However, the ongoing opioid epidemic has shown that opioids carry considerable risk and concerning misuse potential. According to the Centers for Disease Control and Prevention (CDC), rates of drug overdose deaths involving synthetic opioids other than methadone increased by an average of 9% per year from 2017 to 2019 in the United States (8). One integrative review study reported at least 20% of patients with cancer may be at risk of opioid-use disorder (9). Several studies noted an increased risk of nonmedical opioid use among patients with cancer (9-11). The recent dramatic increase in opioid misuse and related deaths has fueled scrutiny over prescribing habits. To that end, use of alternative methods of pain alleviation should be considered whenever possible.

Palliative radiotherapy is one modality that has demonstrated cost-effectiveness and efficacy in managing pain and other cancer-related symptoms (12). Numerous studies have shown significant pain relief following radiotherapy in primary and metastatic disease, especially bone metastases (13-16). Although palliative radiotherapy has proven its success in reducing the qualitative aspect of pain, there is no reported data on how this modality changes opioid prescribing habits. Such an analysis would provide insight into the effectiveness of radiotherapy in reducing the societal opioid burden in patients with cancer who receive palliative radiotherapy. While there have been increasing use of more focused stereotactic radiation for palliative bone metastases over time (17), it is unclear the extent to which these increases have impacted pain control, with results from a recently reported randomized trial reporting similar rates pain control for spinal metastases with stereotactic radiosurgery and more conventional radiotherapy techniques (18).

The aims of this study were to (I) analyze opioid prescribing patterns before and after palliative radiotherapy for metastatic cancer patients; (II) characterize the role of palliative radiotherapy in altering the opioid burden in this patient population; (III) demographically characterize patients that may demonstrate the highest risk of persistent opioid use after palliative radiotherapy. We present this article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-802/rc).

### Highlight box

**Key findings**

- Patients with metastatic cancer receiving palliative radiotherapy required higher opioid doses after radiotherapy.
- Multivariate OLS models pre- and post-radiation treatment showed that younger age and comorbid depression predicted increased opioid doses after radiotherapy.

**What is known and what is new?**

- Palliative radiotherapy is one modality for managing pain and other cancer-related symptoms.
- Patients with metastatic cancer receiving palliative radiotherapy may require higher opioid doses after radiotherapy especially those that are younger or have comorbid depression.

**What is the implication, and what should change now?**

- Opioid use in patients with metastatic cancer receiving palliative radiotherapy who are younger and have comorbid depression should be monitored closely as they may have a higher risk of increased opioid burden after radiotherapy.

## Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This work was approved by the Virginia Commonwealth University Institutional Review Board (No. HM 20014385) and individual consent for this retrospective analysis was waived. Opioid prescription data from all adult patients with metastatic cancer who underwent outpatient external beam radiation therapy at Virginia Commonwealth University Health System from June 2008 to June 2018 was extracted and retrospectively analyzed. We excluded patients with more than 15 treatment fractions, patients treated with brachytherapy or radioactive iodine, and patients receiving stereotactic radiation. Patients receiving whole brain radiation therapy were excluded as well. Incarcerated patients were excluded. Further, patients who expired 6 months or less after radiation therapy were also excluded from this analysis. A 6-month cutoff was employed, as there is concern about the reliability of prescribing data as patients approach the end of life, and where hospice enrollment may be more likely.

Institutional prescribing data were used to calculate average opioid oral morphine milligram equivalent (MME) doses at 30, 60, and 90 days both before and after radiotherapy, based on conversion factors outlined by the CDC (19). Specifically, the average MME was calculated

**Table 1** Baseline descriptive statistics

| Characteristic | Quantity (n=182) |
|---|---|
| Age (years), mean (SD) | 58.1 (11.9) |
| Sex, n (%) | |
| Female | 78 (42.9) |
| Male | 104 (57.1) |
| Race, n (%) | |
| Asian | 1 (0.5) |
| Black or African American | 79 (43.4) |
| White | 95 (52.2) |
| Other | 7 (3.8) |
| Radiation treatment fractions, mean (SD) | 7.9 (4.4) |
| Treatment site, n (%) | |
| Bony | 137 (75.3) |
| Non-bony | 45 (24.7) |
| Alcohol use, n (%) | |
| No | 170 (93.4) |
| Yes | 12 (6.6) |
| Nicotine use, n (%) | |
| No | 121 (66.5) |
| Yes | 61 (33.5) |
| Depression, n (%) | |
| No | 155 (85.2) |
| Yes | 27 (14.8) |
| Anxiety, n (%) | |
| No | 143 (78.6) |
| Yes | 39 (21.4) |
| Diabetes, n (%) | |
| No | 159 (87.4) |
| Yes | 23 (12.6) |
| Back pain, n (%) | |
| No | 97 (53.3) |
| Yes | 85 (46.7) |
| Hypertension, n (%) | |
| No | 105 (57.7) |
| Yes | 77 (42.3) |
| Lung disease, n (%) | |
| No | 138 (75.8) |
| Yes | 44 (24.2) |
| Stroke, n (%) | |
| No | 176 (96.7) |
| Yes | 6 (3.3) |

The sample represents patients with metastatic cancer who received external beam radiation therapy. SD, standard deviation.

between the start date of the palliative radiation therapy and 30, 60 or 90 days prior. Additionally, the average MME was calculated by averaging the MME prescribed during the dates 30, 60 and 90 days after the end of palliative radiation. Prescribing data was included if the medications were written for at least a 14-day supply in an outpatient setting. A broad array of clinical data including patient age, demographic information, cancer site, comorbidities, and treatment site were extracted as well. Treatment sites were classified as either bony sites (e.g., spine, ribs) or soft tissue or primary sites (e.g., lung or head and neck).

A univariate ordinary least squares (OLS) regression model was used to determine the effect of radiotherapy on MME equivalents at the three aforementioned time points before and after radiotherapy. Next, a multivariate OLS regression model was used to control for clinical, radiation-related, and demographic patient factors. P values of <0.05 were considered statistically significant.

## Results

We identified a total of 182 patients who underwent outpatient external beam radiation therapy for metastatic cancer and fit the remaining inclusion criteria. As described in *Table 1*, average patient age was 58.1 years old, with 57.1% being male. The most common primary sites were lung cancer (22%) followed by hematologic cancer (21%). Most patients were treated at a bony site of disease (75.3%), whereas the rest (24.7%) were treated at either a soft tissue or primary site.

The mean MME 30, 60, and 90 days prior to radiotherapy treatment was 24.6, 20.2, and 16.8 mg, respectively (*Table 2*). Thus, there was an increasing quantity of opioid requirements over time leading up the procedure. The mean MME 30, 60, and 90 days post-radiation therapy was 62.9, 77.7, and 82.4 mg, respectively. Patients required higher opioid doses at all time points after radiotherapy (P<0.01). The change in MME remained significant when isolating bony targets, but was not statistically significant when isolating non-bony targets. Furthermore, the increase in MME pre/post radiotherapy in bony sites were not statistically significantly different from the increase in MME requirements pre/post radiotherapy in the non-bony group (*Table 3*).

While focusing on the change in MME intermediate time point of 60 days pre- and post-radiation treatment, the multivariate OLS models showed that younger age was associated with increased MME after radiotherapy (*Table 4*).

**Table 2** MME stratified by treatment site

| Time period | All (N=182) | | | Bony (N=137) | | | Non-bony (N=45) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pre-RT | Post-RT | P value | Pre-RT | Post-RT | P value | Pre-RT | Post-RT | P value |
| 30 days pre- or post-treatment | 24.6 (10.1) | 62.9 (15.2) | <0.01 | 13.9 (3.5) | 61.7 (16.4) | <0.01 | 57.2 (39.3) | 66.6 (36.7) | 0.58 |
| 60 days pre- or post-treatment | 20.2 (10.0) | 77.7 (19.9) | <0.01 | 9.4 (2.9) | 73.8 (19.2) | <0.01 | 53.3 (39.3) | 89.3 (55.8) | 0.09 |
| 90 days pre- or post-treatment | 16.8 (9.3) | 82.4 (21.1) | <0.01 | 6.7 (2.2) | 79.4 (21.1) | <0.01 | 47.5 (36.8) | 91.6 (56.6) | 0.07 |

MME values were reported as mean (SD) with units in mg. MME, morphine milligram equivalents; RT, radiotherapy; SD, standard deviation.

**Table 3** Change in MME before and after radiotherapy bony site *vs.* non-bony site

| MME difference of different periods | All (N=182) | Bony site (N=137) | Non-bony site (N=45) | P value |
|---|---|---|---|---|
| 30 days pre/post | 38.4 (156.1) | 30.7 (131.9) | 3.8 (61.2) | 0.15 |
| 60 days pre/post | 57.4 (190.1) | 42.9 (160.0) | 11.6 (76.3) | 0.39 |
| 90 days pre/post | 65.6 (215.5) | 49.2 (180.7) | 14.2 (86.7) | 0.44 |

MME difference values were reported as mean (SD) with units in mg. MME, morphine milligram equivalents; SD, standard deviation.

**Table 4** Multivariate ordinary least squares regression model—MME change from 60 days before to 60 days after radiotherapy

| Variable | Change in MME (mg) | Standard error | *t* | P value | 95% confidence interval |
|---|---|---|---|---|---|
| Age at diagnosis | –4.017704 | 1.20415 | –3.34 | 0.001 | –6.394918, –1.640489 |
| Male | 48.07325 | 27.24591 | 1.76 | 0.079 | –5.715216, 101.8617 |
| Non-white | –25.1718 | 27.81629 | –0.9 | 0.367 | –80.0863, 29.74271 |
| Bony treatment site | –9.690225 | 32.34186 | –0.3 | 0.765 | –73.53905, 54.1586 |
| # of radiation treatments | –2.869134 | 3.230482 | –0.89 | 0.376 | –9.246704, 3.508436 |
| Alcohol use | 42.16042 | 55.30244 | 0.76 | 0.447 | –67.01684, 151.3377 |
| Opioid use disorder | –77.76414 | 92.9725 | –0.84 | 0.404 | –261.3091, 105.7808 |
| Depression | 114.1027 | 41.26519 | 2.77 | 0.006 | 32.6376, 195.5679 |
| Anxiety | 64.19301 | 36.59271 | 1.75 | 0.081 | –8.047781, 136.4338 |
| Back pain | 35.86603 | 28.36271 | 1.26 | 0.208 | –20.12721, 91.85928 |
| Diabetes | –51.0504 | 42.46567 | –1.2 | 0.231 | –134.8855, 32.78471 |
| Hypertension | 9.875613 | 29.98099 | 0.33 | 0.742 | –49.31242, 69.06364 |
| Stroke | 1.692542 | 76.42149 | 0.02 | 0.982 | –149.1776, 152.5627 |

Change in MME was reported as a function of isolated patient demographic/comorbidity data. MME, morphine milligram equivalents.

The head and neck cancer site was associated with increased MME use after radiotherapy in comparison to other treatment sites. Finally, comorbid depression was also associated with substantially increased opioid burden post-radiotherapy.

## Discussion

This study examined opioid dose prescriptions pre- and post-palliative radiotherapy in metastatic cancer patients. The opioid burden of patients with metastatic cancer

receiving palliative radiation therapy increased over time. Younger age, head and neck primary cancer site, and comorbid anxiety and back pain were all associated with increased opioid MME requirements. To our knowledge, no other study has established a relationship between exact quantitative changes in opioid prescribing patterns before and after palliative radiotherapy.

One of the largest correlations noted in the multivariate analysis was that between depression and subsequent opioid use. While depression is common in cancer patients and survivors (20), there is a complex relationship between depression, chronic pain and opioid use (21) which is large and applies to the non-oncologic patient cohort as well. Additionally, increasing age is associated with lower rates of opioid prescription. Part of this reason may be a perceived poorer tolerance of opioid to older individuals to opioid pain medications, or alternatively different patient or family preferences among analgesics among older individuals. Likewise, male patients showed a trend toward increased opioid prescription rate after radiation therapy compared to females.

Palliative radiotherapy has been shown to be an effective avenue for pain relief in metastatic cancer patients (22-24). Pin *et al.*, were able to quantify a rate of complete or partial pain relief in 49% to 88% of patients one month after treatment and from 60% to 74% after three months (22). Paradoxically, prior literature consistently shows that radiotherapy yielded a decrease in qualitative pain, but the present study shows an increase in opioid burden in this patient population. A possible explanation for this observation are the looser prescribing guidelines in this population set forth by the CDC in this population. Thus, higher prescription rates at later time points may not necessarily be due to an increased pain burden, but rather, out of an abundance of caution and ease of access. Metastases, specifically to bone, are associated with a poor prognosis with median survival rates constrained to just a few months (1). Though this study excluded patients who expired within the first six months after radiotherapy, concern about long-term opioid use disorder is likely not at the forefront of prescription decision making. Rather, maintenance of quality of life is a priority. One way to prioritize quality of life is to make opioids accessible for moderate to severe cancer pain, as outlined by the World Health Organization's most recent recommendations (21,25). However, if the primary goal of a medical provider is to reduce opioid use in metastatic cancer patients, then palliative radiotherapy may not be the optimal route to reach that goal and other options should be considered as well. Next, the results identify certain characteristics that are associated with risk of increased opioid burden which could elucidate expectations of pain and opioid requirements for certain cancers.

This study was limited by lack of data in certain aspects. It would have been beneficial to have data on the specific indication for palliative radiotherapy (pure pain control/reduce analgesic burden/maintain skeletal stability) in each case, and stratify accordingly. A major limitation is that the present study uses opioid prescription data rather than fill data, which entertains the possibility that physicians are prescribing these high MMEs out of an abundance of caution, but patients may not be filling them. Similarly, opioid prescription data was not available from providers outside of our institution, resulting in a possible underestimation of opioid dose. Another limitation is that it is not possible to differentiate between opioid prescriptions due to cancer pain or non-cancer pain. Additionally, it is unknown the extent to which radiation therapy alleviated the pain, in that it is unclear whether any increased pain burden was secondary to the treated site, or other sites outside the radiated field. Studies with access to clinical or radiographic data may be able to ascertain these differences. Also, a deeper analysis into opioid prescription data correlated with median survival post-radiotherapy may uncover an important relationship in this discussion; the exclusion of some patients toward the end of life, as was done in this study, may partially obfuscate this relationship. Lastly, it must be noted the patients in this study were all from a single urban academic institution. Providers at other institutions may have different pain management protocols/preferences and patient populations may differ, thus this study may only be generalizable to other academic institutions of similar size, patient populations, geography, and prescribing habits.

## Conclusions

This study provides a novel perspective on palliative radiotherapy through the lens of opioid prescription data. This study identifies that patients with metastatic cancer receiving palliative radiotherapy required higher opioid doses after radiotherapy. Patients of younger age and with comorbid depression may be at the highest risk for increased opioid doses after radiotherapy. Therefore, opioid use in patients with metastatic cancer receiving palliative radiotherapy who are younger and have comorbid depression should be monitored closely as they may have a

 

higher risk of increased opioid burden after radiotherapy.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-802/rc

*Data Sharing Statement:* Available at https://apm.amegroups.com/article/view/10.21037/apm-22-802/dss

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-802/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This work was approved by the Virginia Commonwealth University Institutional Review Board (No. HM 20014385) and individual consent for this retrospective analysis was waived.



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