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Risk of prolonged opioid use among cancer patients undergoing curative intent radiation therapy for head and neck malignancies

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ABSTRACT

Objective: Patients undergoing radiation treatment (RT) for head and neck malignancies often suffer significant disease- and treatment-related pain requiring opioids for effective management. However, the prevalence and associated risk factors of prolonged opioid use in this population remain poorly characterized. We sought to quantify the rate of prolonged opioid use among opioid naïve patients receiving curative-intent RT for head and neck malignancies and to identify associated risk factors.

Methods: We retrospectively identified patients who had undergone RT for head and neck malignancies at our institution between Jan 2011 and Sept 2017. Our primary endpoint was persistent opioid use 6-months following completion of RT. Patients were included if they were opioid-naïve, underwent curative intent RT, had adequate follow-up, and did not have residual or recurrent disease within our follow-up period. Univariable and multivariable logistic regression was utilized to identify risk factors for prolonged opioid use.

Results: We identified 311 patients meeting our inclusion criteria; 40 (12.9%) continued to use opioids 6-months following RT. Univariable analysis found current smoking, alcohol abuse, RT dose, treatment to the bilateral necks, induction chemotherapy, concurrent chemotherapy, PEG tube, daily milligram morphine equivalents, and adjuvant analgesic medication use to be positively associated with prolonged opioid use; prior surgery was negatively associated with prolonged opioid use. 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) remained statistically significant on multivariable analysis.

Conclusion: The prevalence of prolonged opioid use in previously opioid naïve patients undergoing curative intent head and neck RT was just under 13%. Patients with history of alcohol abuse and those who undergo induction chemotherapy were most at risk.

Introduction

Disease- and treatment-related pain represent a significant problem for patients with cancer, particularly among those with head and neck malignancies wherein the prevalence is reported to be as high as 70% [1]. Opioids remain the mainstay of pharmacologic management for cancer-related pain unresponsive to acetaminophen or non-steroidal anti-inflammatory agents [2,3]. Recently, a dramatic increase in deaths due to opioid overdose in the United States has fueled concern over prescribing practices and the potential for opioid abuse. From 2001 to 2016, the number of opioid-related deaths increased by 345%, from 3.33 to 13.07 deaths per 100,000 of population [4]. This surge has in large part driven by the expanded use of prescription opioids, which has seen an unprecedented 3-fold increase during this time [5,6]. It is widely recognized that many individuals struggling with opioid addiction are first introduced to opioids through their physician with

Abbreviations: RT, Radiation therapy; EMR, Electronic medical record; MMEq, Milligram morphine equivalent

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nearly 4 out of every 5 current heroin users reporting their drug use first beginning with prescription opioids [7].

Cancer patients are not insulated from these risks. A recent study found that among opioid naïve patients with cancer undergoing curative intent surgery, the risk of new persistent opioid use was 10.4% [8]. Persistent opioid use often bears significant negative effects on a patient's quality of life and these consequences become increasingly important as survival for many cancers improves [9]. Effective management of cancer pain therefore requires a balance between the need for adequate analgesia during treatment with the need to minimize prolonged opioid use in the absence of active disease. Multiple organizations have issued statements on how to navigate this delicate balance and preserve access to opioids for patients who need them while mitigating risk across the oncology patient population [3,10].

Given the especially high rates of pain in patients with head and neck cancer, the risk for chronic opioid use following treatment may be considerably higher in this population. In particular, patients undergoing radiation therapy (RT) for head and neck malignancies often suffer significant radiation- and chemotherapy-induced mucositis requiring opioid management to provide adequate analgesia [11–13]. However, the prevalence of prolonged opioid use in this population and its associated risk factors remain poorly characterized. Better knowledge regarding the risk of chronic opioid use is therefore required for radiation oncologists to effectively counsel patients and to manage treatment related morbidity safely.

The objective of the present study was to quantify the rate of prolonged opioid use among opioid naïve patients receiving curative-intent RT for head and neck malignancies and to identify associated risk factors.

Methods

Patient identification

The study design was a retrospective review. We identified opioid naïve patients received curative intent RT between January 1, 2011 and September 1, 2017 through our departmental institutional review board approved head and neck database. Opioid naivety was defined as those patients not chronically receiving opioid analgesic on a daily basis prior to cancer treatment initiation [14]. Allowed primary sites included the oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, sinonasal region, salivary gland, and thyroid; we additionally included those with multiple/overlapping primary sites and those with unknown primaries. We excluded patients who had progressive or residual disease within 6-months of RT completion, required further antineoplastic treatment, had incomplete or missing information, and who received RT with palliative intent. Patients with recent opioid use prior to the start of RT, such as those receiving an opioid prescription in the context of resection or induction chemotherapy, were included so long as they met our definition of opioid naïve.

Data collection

Patient demographic, clinical, and treatment data were abstracted from our departmental radiation oncology and hospital-wide electronic medical record (EMR) systems. Opioid prescription data were collected including dates of opioid prescriptions, the maximum opioid dose prescribed during RT, and the week of RT during which opioids were initiated. Opioid doses were converted to maximum daily milligram morphine equivalent (MMEq) using opioid equianalgesic tables [15]. We additionally documented adjuvant analgesic (i.e. gabapentin, pregabalin, tricyclic antidepressants, or serotonin-norepinephrine reuptake inhibitors) and benzodiazepine use prior to RT.

The primary endpoint was persistent opioid use 6-months following completion of RT. This endpoint was chosen as acute radiation-related toxicities have subsided in the vast majority of patients by this time [16–18]. This endpoint was defined dichotomously and was determined by reviewing follow-up clinic notes and medication orders for ambulatory opioid prescriptions placed through our EMR. In cases where opioid prescriptions were only placed following a period of apparent disuse, an attempt was made to ascertain the reason behind the prescription; those cases that were judged to be unrepresentative of chronic use (e.g. a single opioid prescription following an invasive procedure such as percutaneous endoscopic gastrostomy (PEG) tube removal) were not counted as prolonged opioid use. Additionally, opioid use that occurred following cancer recurrence or further cancer treatment beyond our 6-month endpoint was excluded from consideration. Otherwise, placement of any ambulatory opioid prescription or any report of ongoing opioid use during follow-up visits occurring at least 6-months following completion of RT was sufficient to classify a patient as a persistent opioid user. For our purposes, the terms prolonged opioid use and persistent opioid use are used interchangeably.

All clinical (e.g. stage, primary site, histology), treatment (e.g. RT details, surgical procedures, chemotherapy usage), recurrence, and medication use (e.g. opioid details, adjuvant analgesic use, benzodiazepine use) data were abstracted from the EMR by author WHS, a resident physician in radiation oncology. Demographic information (e.g. medical record numbers, dates of birth, sex) was abstracted by author IL, a research assistant.

Statistical analysis

Descriptive statistics were calculated for all patients. Univariable logistic regression was fit for each covariate and a likelihood ratio test was conducted to compare each univariable model to the null model. Covariates with p-values from likelihood ratio tests < 0.2 were considered as potential predictors and included in multivariable analysis. In multivariable analysis, the models were fit using data with complete information of covariates selected from univariable analysis and the outcome. Stepwise selection with Akaike information criterion (AIC) was conducted to find the best combination of covariates selected from univariable analysis. After choosing the best combination of covariates, we also tested the model with interaction terms. As these did not statistically significantly improve the model on AIC and the likelihood ratio test, we decided not to include interaction terms in the final model.

Results

We identified 311 patients meeting inclusion criteria. Most patients were male (78.1%), had oropharyngeal cancer (58.2%), or had locally advanced (stage IVA-IVB) disease (62.1%). Additional patient and disease characteristics are provided in Table 1. The majority of patients required opioid analgesia during the course of RT (74.3%). Just over half (54%) of patients underwent surgery prior to RT, approximately two-thirds (64%) received concurrent chemotherapy, and about one-quarter (27%) received induction chemotherapy. Treatment characteristics are detailed in Table 2.

Of all 311 patients, 40 (12.9%) had persistent opioid use 6-months following RT completion. Of the 231 patients who required opioids during RT, this percentage was higher (17.3%); conversely, no patient who did not require opioids during RT later required opioids at 6-months following RT completion. Details regarding opioid use in our study population can be found in Table 3. The highest rates of prolonged opioid use were observed in those patients who had a history of alcohol abuse (45.7%) and those who received induction chemotherapy (35.5%).

Odds ratios for univariable analysis with corresponding confidence intervals are shown in Figure 1. In brief, variables significantly associated with increased likelihood of prolonged opioid use included current smoking (as compared to non-smoking) (OR 2.94, CI (95%) 1.16–7.46), history of alcohol abuse (OR 4.36, CI (95%) 2.11–9.01),

Table 1
Patient and Disease Characteristics (n = 311).

Characteristic	Value	%/sd
Age (mean)	58.4	± 12.2
Sex		
Male	243	78.1%
Female	68	21.9%
Married	195	62.7%
Smoking Status		
Never	142	45.7%
Former	130	41.8%
Current	37	11.9%
EtOH Abuse		
None	253	81.4%
Former	27	8.7%
Current	24	7.7%
Primary Site		
Oral Cavity	35	11.3%
Oropharynx	181	58.2%
Larynx/Hypopharynx	25	8.0%
Nasopharynx	23	7.4%
Other[a]	47	15.1%
Stage (AJCC 7th ed)		
I/is	23	7.4%
II	33	10.6%
III	52	16.7%
IVA/IV	178	57.2%
IVB	15	4.8%
Unknown	10	3.2%
Histology		
Squamous Cell Carcinoma	261	83.9%
Other[b]	50	16.1%
Medications Prior to Treatment		
Benzodiazepines	27	8.7%
Adjuvant Analgesics	19	6.1%

Abbreviations: sd = standard deviation; EtOH = Alcohol
[a] Sinonasal, salivary gland, thyroid, unknown primary, or multiple sites.
[b] Nasopharyngeal carcinoma, melanoma, adenocarcinoma, or undifferentiated carcinoma.

Table 2
Treatment Characteristics.

Treatment	Value	%
Surgery	169	54.3%
Neck Dissection[a]		
None	18	10.7%
Unilateral	81	47.9%
Bilateral	70	41.4%
RT Role		
Definitive	151	48.6%
Adjuvant	160	51.4%
RT Fractionation		
Conventional (1.8–2.0 Gy/fx)	277	89.1%
Hypofractionated (> 2.0 Gy/fx)	33	10.6%
Accelerated	1	0.3%
RT Dose (Gy)		
≤60	125	40.2%
60.1–66	63	20.3%
> 66	123	39.5%
Range	(20–70)	
RT Fields		
Primary/Tumor Bed	39	12.5%
Ipsilateral Neck	63	20.3%
Bilateral Necks	209	67.2%
Reirradiation	4	1.3%
Chemotherapy		
Concurrent	198	63.7%
Induction	84	27.0%
PEG Tube	135	43.4%

Abbreviations: Gy = Gray; fx = fraction; PEG = percutaneous endoscopy gastrostomy
[a] Percentages among those undergoing surgery.

Table 3
Details of opioid use in our study population.

Characteristic	Value	%/sd
Persistent Opioid Use at 6-months	40	12.9%
Opioids Prescribed During RT	231	74.3%
Week of RT Opioids Started[a]		
Prior to RT	47	20.3%
Week 1	22	9.5%
Week 2	61	26.4%
Week 3	36	15.6%
Week 4	20	8.7%
Week 5	22	9.5%
Week 6	8	3.5%
Week 7 (or more)	6	2.6%
Unknown	9	3.9%
Maximum Daily MMEq		
Mean	120.5	± 103.9
Median	90	
1st Quartile – 3rd Quartile	54.2–150	

Abbreviations: MMEq = milligram morphine equivalents
[a] Percentage among those prescribed opioids during RT.

increasing RT dose (OR 1.06, CI (95%) 1.00–1.13), treatment to the bilateral necks (OR 8.17, CI (95%) 1.09–61.44), induction chemotherapy (OR 4.12, CI (95%) 2.08–8.17), concurrent chemotherapy (OR 3.70, CI (95%) 1.50–9.11), PEG tube (OR 2.76, CI (95%) 1.38–5.52), maximum daily MMEq prescribed (OR 1.05 (per 10-unit increase), CI (95%) 1.02–1.08), and adjuvant analgesic medication use prior to RT (OR 3.41, CI (95%) 1.21–9.56). Prior surgery was associated with a decreased likelihood of persistent opioid use at 6 months (OR 0.40, CI (95%) 0.20–0.81). On multivariable analysis, only the delivery of induction chemotherapy (OR 2.86, CI (95%) 1.32–6.21) and history of alcohol abuse (OR 3.75, CI (95%) 1.66–8.47) remained significant. Maximum daily MMEq prescribed was marginally significant (OR 1.03 (per 10-unit increase), CI (95%) 0.999–1.06). The results from our final multivariable logistic regression model are shown in Table 4.

Discussion

Our analysis found that just under 13% of opioid naïve patients undergoing curative intent RT for head and neck malignancies demonstrate persistent opioid use 6-months following completion of RT. To our knowledge, only one previously reported study has attempted to quantify the prevalence of persistent opioid use among patients undergoing head and neck RT, albeit in a far a more limited population [19]. While this study reported a much higher rate of continued opioid use 6-months following RT completion (32.9%), its study population included only patients referred for outpatient palliative care consultation. As a result it may have been biased by a highly symptomatic or medically complex study cohort that may not be generalizable to the typical patient presenting for head and neck cancer treatment. We believe our results to be more reflective of the risk for prolonged opioid use faced by typical patients presenting to the head and neck radiation clinic and therefore to be an important addition to the current literature.

Our observed prevalence of prolonged opioid use following head and neck RT (12.9%) is similar in magnitude to that reported for cancer patients undergoing curative intent surgery (10.4%) of other disease sites [8]. The reasons for prolonged opioid use among such patients are likely multifactorial and may relate to treatment-related toxicity, residual disease related pain, opioid-induced hyperalgesia, or psychologic factors. Our analysis identified treatment- and patient-related factors that were predictive of prolonged opioid use.

Intensification of several treatment-related variables (i.e. including radiation dose, field size, and concurrent or induction chemotherapy) was associated with increased risk of prolonged opioid use. The immediate implication is that increased treatment predisposes to more

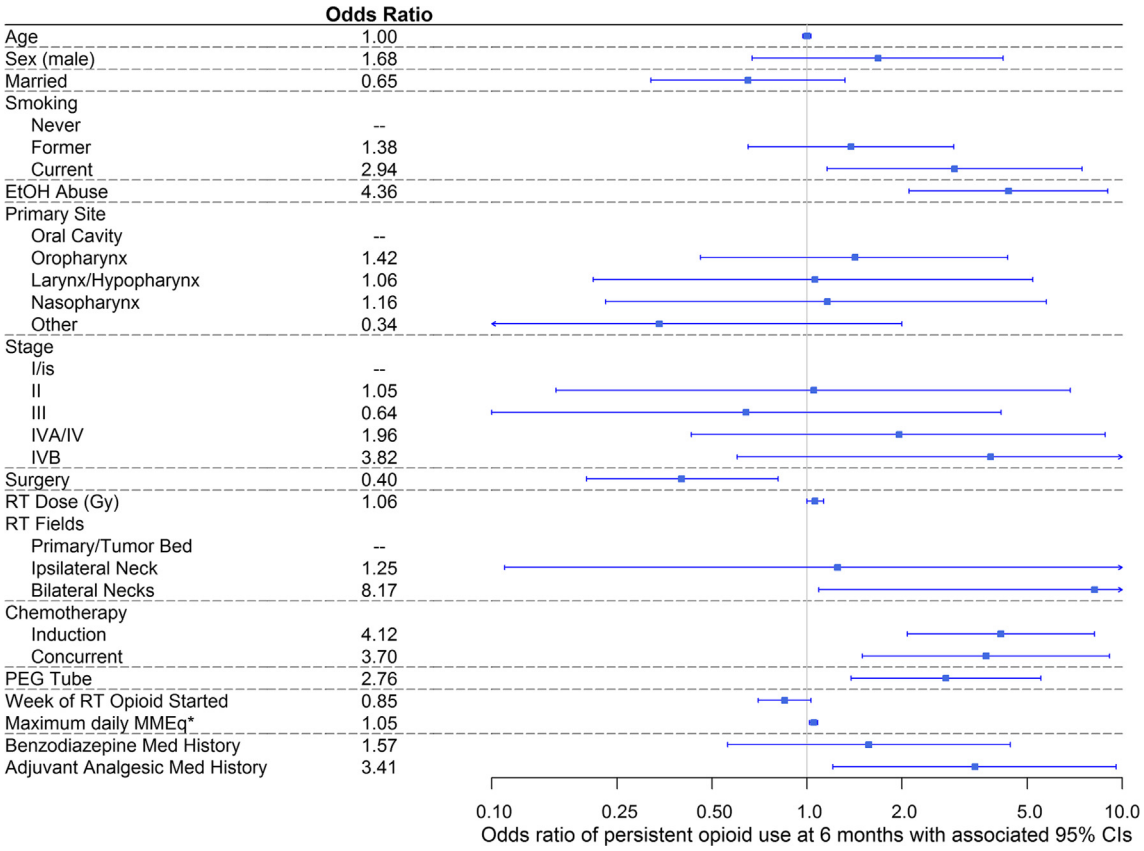

Fig. 1. ***Results of Univariable Analysis***: Odds ratios with corresponding confidence intervals (95%) for covariates tested on univariable logistic regression. Abbreviations: EtOH = alcohol; PEG = percutaneous endoscopic gastrostomy; MMEq = milligrams morphine equivalents; Med = medication. * Per 10 unit increase.

Table 4
Covariate table from final multivariable logistic regression model.

Covariate	OR	CI (95%)	p-value
Induction Chemotherapy	2.86	(1.32, 6.21)	0.008
EtOH Abuse	3.75	(1.66, 8.47)	0.002
Maximum Daily MMEq[a]	1.03	(0.999, 1.06)	0.060

Abbreviations: OR = Odds Ratio; CI = Confidence interval; EtOH = Alcohol; MMEq = milligram morphine equivalents

[a] Per 10-unit increase.

pronounced and prolonged opioid requirements secondary to increased toxicity. While an alternative explanation might hold that such treatment was delivered in response to more advanced cancers carrying higher symptom burden, which in turn were responsible for more prolonged opioid use, this conclusion is not supported by our data. Neither stage nor primary site was significantly associated with prolonged opioid use and all patients remained cancer-free during our follow-up period, arguing against this alternative explanation. Patients receiving induction chemotherapy may additionally have received opioids prior to the start of RT resulting in more protracted opioid exposures thereby increasing their risk of prolonged use. The psychological impact of prolonged treatment time and its effect on chronic opioid use remain unknown. Protracted treatment plans may increase the risk of prolonged opioid use due to a variety of factors beyond treatment related pain and future work in this area is needed.

Conversely, definitive surgery prior to RT was associated with a lower risk of prolonged opioid use in our study population. It is unlikely surgery on its own directly lowered the overall morbidity of cancer treatment and thereby decreased the likelihood of prolonged opioid use. Rather, this association was likely the result of a combination of factors including lower doses of RT required in the adjuvant setting, decreased RT field size in select pathologically lymph node negative patients (i.e. avoidance of bilateral neck RT following negative neck dissection), and obviation of the need for chemotherapy in patients without high risk pathologic risk factors. This conclusion is supported by our analysis, which found the protective effect of surgery to wash out after accounting for confounding factors on multivariable analysis.

The importance of patient-related factors (i.e. current smoking, alcohol abuse, and prior adjuvant analgesic use) is also demonstrated in our data. Among the variables tested, alcohol abuse was the most strongly associated with an increased risk of prolonged opioid abuse. The predictive importance of alcohol abuse in this context has been shown in multiple other studies [19–21]. It has been well established that the endogenous opioid systems play a key role in alcohol addiction through the activation of the mesolimbic dopamine reward pathway via μ- and δ-opioid receptors, providing a putative mechanism for this observation [22]. However, it is not immediately clear to what degree this addiction biology was responsible for prolonged opioid use in our patient population. Our study did not attempt to find distinction between “appropriate” persistent opioid use (e.g. requirement of opioids due to late radiation toxicity) and “inappropriate” opioid use attributable to addictive tendencies. Delineating these differences represents a substantial challenge with the distinction between these realities at times becoming unclear for individual patients.

The identification of risk factors for prolonged opioid use following head and neck RT provides potential guidance to oncologists hoping to minimize these risks. Induction chemotherapy and alcohol abuse were independently associated with an approximately 3-fold and 4-fold increased risk of prolong opioid use, respectively, suggesting these patients to be especially high risk and potentially warranting of targeted intervention. Palliative care has been shown to improve quality of life among patients with advanced cancer and may provide better access to non-opioid based therapies, including both pharmacologic and non-

pharmacologic options [23]. Early palliative care involvement for patients receiving induction chemotherapy or with a history of alcohol abuse may therefore help to lessen these risks. Non-opioid pharmacologic agents have demonstrated efficacy in the management or prevention of radiation induced mucositis and may additionally provide an avenue to limit opioid reliance in high risk patients [24,25]. Such patients may alternatively benefit from routine provision of non-pharmacologic therapy including supportive psychotherapy, cognitive behavioral therapy, or acupuncture [26,27]. It remains to be seen which of these approaches will prove most feasible and effective.

The current study has several important limitations. First, all data was collected retrospectively and was dependent upon review of the electronic records of a single institution. It is therefore possible that some patients received opioid prescriptions from an outside provider and were missed in our analysis; conversely, some patients may have had an opioid prescription placed through our EMR but either did not fill the prescription or did not take the medication. For this reason, thorough review of follow-up notes, including medication reconciliation at follow-up visits, was undertaken to corroborate the findings from EMR medication orders. We believe this combined approach provided for the most accurate assessment of prolonged opioid use available to us. Second, we acknowledge that opioid prescription practices differ across various institutions; the prevalence and risk factors of prolonged opioid use among patients undergoing head and neck RT may likewise be subject to practitioner- and system-specific biases. Similarly, the risk of prolonged opioid use among head and neck cancer patients following RT may differ across populations. Development of rigorous prospective studies outlining preferred treatment approaches with regard to opioid management may help to rectify these deficiencies in the future.

In summary, among opioid naïve patients undergoing curative intent RT for head and neck malignancies just under 13% continued to use opioids 6-months following RT completion. This risk should be discussed with patients at the time of initial consult and should be considered when patients are initiated on opioids during treatment. Among certain high risk populations, this rate was significantly higher. In particular, those patients with a known history of alcohol abuse and those who undergo induction chemotherapy appear to be most at risk. Such patients should be targeted for early intervention such as timely palliative care consultation, increased use of non-opioid based pharmacologic agents, or increased use of non-pharmacologic alternatives to limit symptom burden and reduce the likelihood of prolonged opioid requirements.

Conflicts of interest Statement

None declared.

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