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Chronic Opioid Use Following Surgery for Oral Cavity Cancer

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IMPORTANCE Opioid misuse and overuse has become an epidemic. Chronic opioid use among oral cavity cancer patients after surgery has not been described.

OBJECTIVES To assess the prevalence of chronic opioid use in patients undergoing surgery for oral cavity cancer, and evaluate possible associated clinical factors; and the association between opioid use and survival.

DESIGN, SETTING, AND PARTICIPANTS For this retrospective cohort study of patients undergoing surgery for oral cavity cancer a consecutive sample of 99 patients between January 1, 2011, and September 30, 2016, were identified through the institutional cancer registry from a single academic center.

EXPOSURES Surgery for oral cavity cancer.

MAIN OUTCOMES AND MEASURES Chronic opioid use, defined as more than 90 days from surgery. Factors associated with chronic opioid use were investigated by univariable and multivariable logistic regression. The Kaplan-Meier method and Cox proportional hazards model were used to assess overall survival and disease-free survival.

RESULTS The mean (SD) patient age was 62.6 (14.3) years; 60 patients (60%) were male. Chronic opioid use was observed in 41 patients (41%). On multivariable logistic regression, preoperative opioid use (odds ratio [OR], 5.6; 95% CI, 2.2-14.3), tobacco use (OR, 2.8; 95% CI, 1.0-8.0), and development of persistence, recurrence, or a second primary tumor (OR, 2.8; 95% CI, 1.0-7.4) were associated with chronic opioid use. Among preoperative opioid users, estimated overall survival (hazard ratio [HR], 3.2; 95% CI, 1.4-7.1) was decreased, and chronic opioid use was associated with decreased disease-free survival (HR, 2.7; 95% CI, 1.1-6.6).

CONCLUSIONS AND RELEVANCE In patients undergoing surgery for oral cavity tumors, the prevalence of chronic opioid use was considerable. Preoperative opioid use, tobacco use, and development of persistence, recurrence, or a second primary tumor were associated with chronic opioid use after surgery, and both preoperative and chronic opioid use were associated with decreased survival.

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Chronic pain is a major concern for patients with head and neck cancer (HNC), affecting up to 60% of survivors.[1,2] Despite the need to effectively manage chronic pain, a recent meta-analysis[3] of pain management in patients with cancer concluded that nearly half are not optimally treated. In 2013, the National Comprehensive Cancer Network (NCCN) released its first set of clinical practice guidelines in an effort to improve survivorship of patients with cancer. Pain management was 1 of 8 domains receiving specific attention in these guidelines.[4]

Although health care providers often treat cancer pain with opioid agents, opioid-related overuse and death has become a public health epidemic. In the United States, the age-adjusted death rate from prescription opioid overuse quadrupled between 2000 and 2014, increasing from 1.5 to 5.9 deaths per 100 000.[5] Strikingly, this increase in death rate parallels a 4-fold increase in quantity of drugs dispensed. The economic impact of the increased use of opioids is alarming, as the burden of opioid abuse, misuse, and overdose is estimated to be $78.5 million.[6]

Among patients with cancer, those with HNC are very likely to have pain.[7,8] Patients undergoing treatment for oral cavity cancers often receive multimodality treatment, usually including surgery with or without adjuvant chemotherapy and radiation. To date, there has been no literature on chronic opioid use among patients undergoing surgery for HNC. Furthermore, risk factors for chronic opioid use have not been identified for this population. The purposes of this investigation are to assess the prevalence of chronic opioid use among patients undergoing surgery for oral cavity cancers, identify clinical risk factors for chronic opioid use after surgery, and investigate the relationship between opioid use and survival.

Key Points

Question How prevalent is chronic opioid use after surgery for oral cavity cancer, and are there identifiable clinical risk factors for chronic opioid use?

Findings A cohort study of 99 patients with oral cavity cancer undergoing surgery determined the prevalence of chronic opioid use to be 41%. Preoperative opioid use, prior tobacco use, and development of persistence, recurrence, or a second primary tumor were associated with chronic opioid use, and opioid use was associated with decreased survival.

Meaning Strategies to reduce the likelihood of opioid dependence after oral cavity cancer surgery should consider targeting those patients who are current opioid users, prior tobacco users, and those who develop persistence, recurrence, or a second primary tumor.

Methods

Patient Selection

A retrospective review was performed for all adults (age ≥18 years) with pathologically confirmed carcinoma of the oral cavity treated with surgery at our institution from January 1, 2011, to September 30, 2016. These patients were identified through the institutional cancer registry. Inclusion criteria included patients with a documented opioid prescription and preoperative histology documenting carcinoma or carcinoma in situ. All stages were included, based upon American Joint Commission on Cancer Staging of Head & Neck Cancer (7th edition). Exclusion criteria included patients with primary sites other than oral cavity, patients receiving definitive surgery at another institution, and patients who did not have a prescribed opioid recorded in the medical record.

The study was approved by the institutional review board of the University of California, San Diego. Waivers of consent and HIPAA (Health Insurance Portability and Accountability Act) authorization were provided by the board.

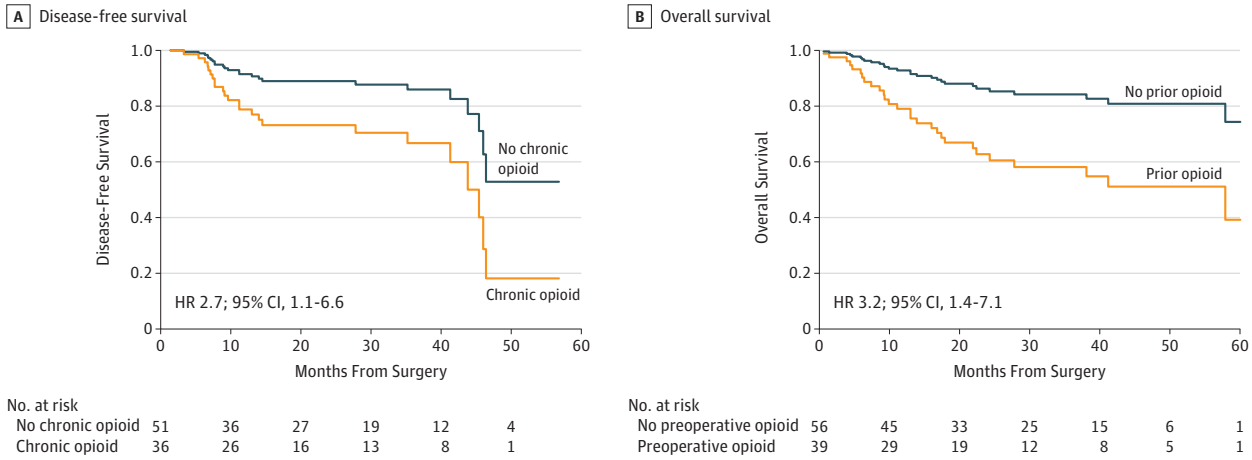
Data Collection

Data extracted from the electronic medical record included patient demographics, past medical history, prior medications, comorbidities, psychiatric illness, prior tobacco use, prior alcohol use, clinical stage, pathologic stage, surgery, neck dissection, adjuvant treatment, maximum inpatient pain rating, maximum pain rating on day of discharge, prescribed daily dose and total amount of opioid upon discharge (in milligrams of oral morphine equivalents), disease status, chronic opioid use, health care provider prescribing opioid at 90 days, and follow-up time. Chronic opioid use was defined in accordance with the postsurgical literature as receiving multiple opioid prescriptions more than 90 days after surgery,[9-11] evidenced by recurring prescriptions in the electronic medical record or in the Controlled Substance Utilization Review and Evaluation System (CURES). The age-adjusted Charlson comorbidity index (CACI) was calculated to assess the 10-year mortality risk for each patient. This scoring system assigns increasing points for age and adds points for comorbid conditions including, but not limited to, myocardial infarction, congestive heart failure, diabetes, cerebrovascular disease, liver disease, and prior cancer.[12,13] Psychiatric illness was defined as having a *Diagnostic and Statistical Manual of Mental Disorders* Axis I disorder or taking a psychiatric medication at the time of surgery. Prior alcohol use was defined according to the definition of drinking above a "low risk" amount by the National Institute on Alcohol Abuse and Alcoholism (>14 drinks/week for men; >7 drinks/week for women).[14]

Statistical Analysis

Descriptive statistics were used to describe the patient population and clinical data. The Jarque-Bera test was used to test continuous variables for normality. The primary outcome variable of interest was chronic opioid use, defined as more than 90 days after surgery. Prestudy sample size calculations were not performed owing to the retrospective nature of this pilot investigation and a lack of prior literature documenting effect sizes related to chronic opioid use after oral cancer surgery. Heterogeneity between chronic opioid users and nonchronic opioid users was tested using Pearson χ^2 test for categorical data, independent *t* test for normally distributed continuous data, and Wilcoxon rank sum test for nonnormally distributed continuous data. Effect size indices, such as

Figure. Estimated Survival by Multivariable Cox Proportional Hazards Regression



A, Estimated disease-free survival stratified by chronic opioid use. Adjusted variables for disease-free survival include CACI, overall stage, postoperative chemotherapy, postoperative radiation, and chronic opioid use. B, Estimated overall survival stratified by preoperative opioid use. Adjusted variables for overall survival include CACI, preoperative opioid use, and overall stage. The Kaplan-Meier method was used to identify the number of patients at risk. Variables were selected based on significance at $P < .10$ on univariable regression analyses with CACI being included a priori. Patients with carcinoma in situ on permanent pathology (n = 4) were dropped from both disease-free survival and overall survival analyses. Patients with persistent disease (n = 8) were dropped from DFS. CACI indicates age-adjusted Charlson comorbidity index.

risk difference in probabilities, Hedges *g* for difference in continuous measures with different sample sizes, the Gardner-Altman approach for nonparametric continuous measures,[15] and odds ratios (ORs) from univariable logistic regression and associated 95% CIs were used to identify factors associated with chronic opioid use. Independent variables included age, sex, CACI, psychiatric history, preoperative opioid use, prior alcohol abuse, prior tobacco use, history of HNC, history of any cancer, clinical T stage, clinical nodal disease at presentation, subsite, pathologic T stage, neck dissection, inpatient pain rated 9 or greater out of 10, discharge opioid dose per day (mg), total discharge opioid dispensed, postoperative radiation therapy, postoperative chemotherapy, disease course (persistence, recurrence, second primary tumor, or disease free), and length of stay. Age, sex, psychiatric history, and substance abuse history were specifically included based upon literature identifying such variables as risk factors for opioid abuse.[16-18] Advanced pathologic T stage was included as a proxy for extent of surgery at the primary site. Subsequently, stepwise multivariable regression analyses were performed with $P < .10$ being required for inclusion.

The Kaplan-Meier method with Cox proportional hazards regression analysis was used for univariable survival analyses of disease-free survival (DFS) and overall survival (OS) based on CACI, preoperative opioid use, pathologic stage, grade, adjuvant chemotherapy, adjuvant radiation, chronic opioid use, and continued smoking (**Figure**). Disease-free survival was calculated from the date of surgery to the date of recurrence, death, or last disease assessment. Patients without a local recurrence were censored at the last disease assessment date. Overall survival was calculated from the date of surgery to the date of death or date last known to be alive. Variables with statistical significance at $P < .10$ were entered into a multivariate Cox proportional hazards regression model, with age-adjusted comorbidities being included a priori.

Statistical analyses were performed using StataIC 14 (Stata, StataCorp LP). All tests were 2-sided and $P < .05$ was considered statistically significant.

Results

A total of 99 patients met the inclusion criteria; 60 (60%) were male and the mean (SD) age was 62.6 (14.3) years (**Table 1**). Twenty-five patients (25%) had a prior psychiatric disorder, and 40 patients (40%) were taking an opioid prior to surgery. Prior alcohol use was observed in 34 patients (34%), and prior tobacco use was observed in 65 patients (66%). The median (interquartile range [IQR]) CACI was 4 (2-5). The mean (SD) follow-up time was 26.0 (17.1) months (range, 0.6-67.5 months).

The primary outcome of chronic opioid use was observed in 41 patients (41%) postoperatively (**Table 2**). The associated diagnosis was listed in 34 chronic opioid users, and in the 28 of 34 of these patients (82%) the reason for chronic opioid therapy was specifically for HNC pain. The most frequent sources of the opioid prescription were HNC treatment providers (20/41 [49%]), followed by primary care and internal medicine (16/41 [39%]). Of the 41 patients who were chronic opioid users after surgery, 27 (66%) were preoperative opioid users, while a quarter of patients (14/59 [24%]) who were not opioid users prior to surgery became chronic opioid users after surgery. Chronic opioid users were nearly 7 times more likely to have been taking opioids preoperatively than nonchronic opioid users. Our data suggest the difference in chronic opioid use was at least as great as 3 times and could be as great as 16 times between preoperative users and nonusers (27/41 [66%]

Table 1. Baseline Characteristics of the Cohort and Relation to Chronic Opioid Use[a]

Characteristic	No. (%)			Effect Index (95% CI)
	Total Sample (n = 99)	Nonchronic Opioid Users (n = 58)	Chronic Opioid Users (n = 41)	
Demographics				
Age, mean (SD) y	62.6 (14.3)	62.8 (15.9)	62.3 (11.9)	0.03
Male	60 (60)	38 (66)	22 (54)	0.6 (0.3-1.4)
Medical history				
CACI, median (IQR)	4 (2 to 5)	4 (2 to 5)	4 (3 to 5)	0 (−1 to 1)
Psychiatric disorder	25 (25)	10 (17)	15 (37)	2.8 (1.1 to 7.0)
Preoperative opioid	40 (40)	13 (22)	27 (66)	6.7 (2.7 to 16.3)
Prior alcohol	34 (34)	16 (28)	18 (44)	2.1 (0.9 to 4.8)
Prior tobacco	65 (66)	32 (55)	33 (80)	3.4 (1.3 to 8.5)
Prior HNC	12 (12)	6 (10)	6 (15)	1.5 (0.4 to 5.0)
Prior any cancer	20 (20)	11 (19)	9 (22)	1.2 (0.5 to 3.2)
Clinical stage				
T1	35 (35)	23 (40)	12 (29)	1 [Reference]
T2	42 (42)	23 (40)	19 (46)	1.6 (0.6 to 4.0)
T3	8 (8)	4 (7)	4 (10)	1.9 (0.4 to 9.0)
T4	14 (14)	8 (14)	6 (15)	1.4 (0.4 to 5.1)
cN+	22 (22)	13 (22)	9 (22)	1.0 (0.4 to 2.6)
Oral subsite				
Oral tongue	39 (39)	24 (41)	15 (37)	1 [Reference]
Lip	9 (9)	5 (9)	4 (10)	1.3 (0.3 to 5.5)
Gingiva	7 (7)	3 (5)	4 (10)	2.1 (0.4 to 10.9)
Floor of mouth	18 (18)	12 (21)	6 (15)	0.8 (0.3 to 2.6)
Buccal mucosa	16 (16)	8 (14)	8 (20)	1.6 (0.5 to 5.2)
Other	10 (10)	6 (10)	4 (10)	1.1 (0.3 to 4.4)

Abbreviations: CACI, age-adjusted Charlson comorbidity index; cN+, clinically positive cervical lymph nodes; HNC, head and neck cancer; IQR, interquartile range.

[a] Unless otherwise indicated, data represent number (percentage) of patients. Instances of column percentages not adding to 100% are due to rounding error. Normally distributed continuous variables are depicted by mean (SD) and nonnormally distributed continuous variables are depicted by median (IQR). Effect indices for categorical variables are presented as odds ratio (95% CI) generated from univariable logistic regression. Effect index for age is presented as Hedges *g* statistic. Effect index for CACI is computed based on the Gardner-Altman approach. The Other category for Oral Subsite includes hard palate, retromolar trigone, and mouth (overlapping or not otherwise specified).

vs 13/58 [22%], respectively; difference, 44%; OR, 6.7; 95% CI, 2.7-16.3). Among tobacco users, chronic opioid use for tobacco users was more than 3 times likely than among nontobacco users and this increase could be as high as 8 times more likely (33/41 [80%] vs 32/58 [55%], respectively; difference, 25%; OR, 3.4; 95% CI, 1.3-8.5) (Table 1).

The clinical stage of the primary ranged from T1 to T4, with the majority presenting as local stage (n = 77 [77%]) vs advanced stage (n = 22 [22%]). The most common subsite was the oral tongue (n = 39 [39%]), followed by floor of mouth (n = 18 [18%]), and buccal mucosa (n = 16 [16%]). Twenty-two patients (22%) presented with clinical nodal disease. Clinical T stage, oral subsite, and clinical nodal disease were not associated with chronic opioid use.

All patients underwent surgical resection of oral cavity tumors. Fifty-three patients (54%) underwent surgery only, whereas 24 patients (24%) received surgery plus adjuvant radiation, 3 patients (3%) received surgery plus chemotherapy, and 19 patients (19%) received adjuvant chemotherapy and radiation (Table 2). The majority of the patients (74 [75%]) had a neck dissection. Sixty-seven (68%) of the patients had disease-free status throughout the follow-up period (ie, no persistence, recurrence, or second primary tumor). Among patients who developed persistence, recurrence, or a second primary tumor, chronic opioid use was nearly 4 times more likely than among patients who did not experience a recurrence, and this difference could be as great as 9 times more likely (20/32 [69%] vs 21/67 [31%], respectively; difference, 38%; OR, 3.7; 95% CI, 1.5-8.8).

On multivariable logistic regression (**Table 3**), preoperative opioid use (OR, 5.6; 95% CI, 2.2-14.3), prior tobacco use (OR, 2.8; 95% CI, 1.0-8.0), and development of persistence, recurrence, or a second primary tumor (OR, 2.8; 95% CI, 1.0-7.4) were all independently associated with chronic opioid use.

Twenty-eight patients (28%) died during the follow-up period. Four patients (4%) with a final pathologic diagnosis of carcinoma in situ were dropped from survival analysis. To calculate DFS, patients with persistent disease after primary treatment (8 [8%]) were dropped from analysis. The Kaplan-Meier method and Cox proportional hazards analysis were implemented to assess OS and DFS. On multivariable survival analysis (**Table 4**), DFS was worse for chronic opioid users (HR, 2.7; 95% CI, 1.1-6.6). On multivariable analysis of OS, CACI (HR, 1.3; 95% CI, 1.0-1.6) and preoperative opioid use were independently associated with worse survival (HR, 3.2; 95% CI, 1.4-7.1).

Discussion

In this study, we found that nearly half of all patients undergoing surgery for oral cavity cancer were using opioids more than 90 days after surgery. Chronic opioid use was strongly associated with a history of opioid use prior to surgery, prior

Table 2. Treatment and Clinical Outcomes[a]

Characteristic	No. (%) Total Sample (n = 99)	Nonchronic Opioid Users (n = 58)	Chronic Opioid Users (n = 41)	Effect Index (95% CI)
Pathologic T stage[b]				
T1	33 (35)	22 (41)	11 (27)	1 [Reference]
T2	27 (29)	12 (22)	16 (39)	2.7 (0.9 to 7.6)
T3	15 (16)	8 (15)	7 (17)	1.8 (0.5 to 6.1)
T4	19 (20)	12 (22)	7 (17)	1.2 (0.4 to 3.8)
Received neck dissection	74 (75)	43 (74)	31 (75)	1.1 (0.4 to 2.7)
Max inpatient pain, median (IQR)	8 (6 to 9)	7 (4 to 8)	8.5 (7 to 10)	2 (1 to 3)
Postdischarge daily opioid dose, mg, median (IQR)	30 (20-45)	30 (30 to 45)	42.5 (20 to 60)	0 (0 to 15)
Total postdischarge opioids dispensed, mg, median (IQR)	225 (150 to 250)	225 (150 to 250)	225 (150 to 275)	0 (0 to 70)
Surgery Only	53 (54)	32 (55)	21 (51)	1 [Reference]
Surgery + XRT	24 (24)	14 (24)	10 (24)	1.1 (0.4 to 2.9)
Surgery + CXRT	19 (19)	9 (15)	10 (24)	1.7 (0.6 to 4.9)
Surgery + chemo	3 (3)	3 (5)	0	Dropped[c]
Adjuvant XRT	43 (43)	23 (40)	20 (49)	1.5 (0.7 to 3.3)
Adjuvant chemo	22 (22)	12 (21)	10 (24)	1.2 (0.5 to 3.2)
Oncologic outcome				
Disease-free	67 (68)	46 (79)	21 (51)	1 [Reference]
Not disease-free	32 (32)	12 (21)	20 (49)	3.7 (1.5 to 8.8)
Locoregional recurrence	18 (18)	7 (12)	11 (27)	3.4 (1.2 to 10.1)
Distal recurrence	2 (2)	0	2 (5)	Dropped[c]
Persistence	8 (8)	4 (7)	4 (7)	2.2 (0.5 to 9.6)
Second primary	4 (4)	1 (2)	3 (7)	6.6 (0.6 to 67.0)
LOS, median (IQR), d	5 (2 to 13)	4 (2 to 12)	5 (3 to 14)	1 (−1 to 3)

Abbreviations: Chemo, chemotherapy; CXRT, chemotherapy and radiation; IQR, interquartile range; LOS, length of stay; XRT, radiation therapy.

[a] Unless otherwise indicated, data represent number (percentage) of patients. Instances of column percentages not adding to 100% are due to rounding error. Normally distributed continuous variables are depicted by mean (SD) and nonnormally distributed continuous variables are depicted by median (IQR). Effect indices for categorical variables are presented as odds ratio (95% CI) generated from univariable logistic regression. Effect indices for pain, dispensed opioids, and LOS were computed based on the Gardner-Altman approach.

[b] Four patients had carcinoma in situ.

[c] Dropped indicates a variable was dropped from logistic regression due to collinearity.

tobacco use, and persistence, recurrence, or a second primary tumor. Of note, nearly a quarter of patients who did not use opioids prior to surgery did develop a chronic use pattern after surgery. We also found an association between opioid use and survival. Preoperative opioid use was associated with decreased OS, and chronic opioid use after surgery was associated with decreased DFS.

Opioid analgesics have become increasingly ubiquitous after surgical procedures[19] and now represent the cornerstone of chronic pain management in patients with cancer. In patients with HNC undergoing chemotherapy, up to 80% take opioids for pain.[20,21] However, the efficacy of opioids in the management of chronic pain has been increasingly questioned.[22,23] A recent systematic review of opioids for chronic pain found no evidence for their effectiveness in improving pain and function. Rather, there was a dose-dependent risk for opioid abuse, myocardial infarction, fractures, and sexual dysfunction.[24] Opioids can also induce paradoxical hyperalgesia in postoperative patients and patients with cancer.[25,26] Additional adverse effects include major depression,[27,28] sleep-disordered breathing,[29,30] cognitive dysfunction,[31,32] and pneumonia.[33] Preoperative opioid use is also associated with longer hospital stays, higher readmission rates, and more than double the postoperative expenditures.[34] Despite these concerns, opioid use has expanded and is now a public health epidemic with staggering medical and financial consequences.[6] As a result, we should seek to question whether current analgesic strategies can be optimized to limit opioid use to patients who need them most, while sparing others from possible adverse effects of long-term use.

The literature is sparse regarding chronic opioid use in patients with HNC, but the prevalence of chronic opioid use in our study is slightly higher than previously reported. A multicenter study[21] of patients with HNC undergoing definitive chemoradiation found that 83% used morphine acutely during therapy, but morphine use fell to 26% after therapy. In our study, however, patients were treated with up-front surgery, and chemotherapy and radiation were given as adjuvant treatments when indicated.

The prevalence of chronic opioid use in our study is higher than that reported across other surgical sites. In a recent cross-sectional study of surgical patients in a large academic center, Jiang et al[11] determined that the prevalence of chronic opioid use at 90 days was 9.2% and highest among orthopedics (23.8%) and neurosurgery (18.7%). The prevalence in otorhinolaryngology was approximately 6.0%. However, the authors did not stratify patients undergoing surgery for cancer vs those treated for benign disease. In a separate population-based study, Clarke et al[10] examined the prevalence of chronic opioid use at 90 days in opioid-naive patients undergoing major elective surgery and assessed the prevalence to be 3.1%. Again, Clarke et al[10] included patients undergoing both

Table 3. Multivariable Logistic Regression of Factors Associated With Chronic Postoperative Opioid Use[a]

Factor Associated With Chronic Postoperative Opioid Use	Odds Ratio (95% CI)
Prior tobacco use	2.8 (1.0-8.0)
Preoperative opioid	5.6 (2.2-14.3)
Persistence, recurrence, or second primary	2.8 (1.0-7.4)

[a] Variables that were significant at $P < .10$ on univariable logistic regression were included in a stepwise multivariable model to generate adjusted odds ratios with corresponding 95% CIs. Adjusted variables include prior tobacco use, preoperative opioid use, and persistence, recurrence, or second primary.

Table 4. Multivariable Cox Proportional Hazards Regression for Estimated Disease-Free and Overall Survival[a]

Characteristic	HR (95% CI) DFS	OS
CACI, per 1-unit increase	1.0 (0.8-1.4)	1.3 (1.0-1.6)
Preoperative opioid use	NA	3.2 (1.4-7.1)
Overall AJCC pathologic stage		
I	1 [Reference]	1 [Reference]
II	2.5 (0.8-8.3)	1.0 (0.3-3.8)
III	1.5 (0.4-5.0)	0.4 (0.1-2.2)
IV	0.9 (0.2-3.4)	2.9 (1.0-8.0)
Postoperative chemotherapy	0.6 (0.1-2.8)	NA
Postoperative radiation	0.4 (0.1-1.2)	NA
Chronic opioid use	2.7 (1.1-6.6)	NA

Abbreviations: AJCC, American Joint Committee on Cancer; CACI, age-adjusted Charlson comorbidity index; DFS, disease-free survival; HR, hazard ratio; NA, not applicable; OS, overall survival.

[a] Variables that were significant at $P < .10$ in the univariable Cox regression were included in the multivariable model to generate adjusted HRs with corresponding 95% CIs. Age-adjusted comorbidity (CACI) was included a priori. Adjusted variables for OS include CACI, preoperative opioid use, and overall stage. Adjusted variables for DFS include CACI, overall stage, postoperative chemotherapy, postoperative radiation, and chronic opioid use. Cells marked NA indicate that the covariable was not retained for the corresponding survival function.

oncologic (ie, radical prostatectomy, lung resections) and nononcologic (ie, coronary artery bypass grafting) procedures. Neither Jiang et al[11] or Clarke et al[10] assessed the association between preoperative opioid use, tobacco, and chronic opioid use.

An association between smoking and opioid use has been documented elsewhere in the literature. A retrospective review[35] of 236 patients receiving patient-controlled analgesia determined that smokers required more opioids than nonsmokers after distal gastrectomy. In addition, a cross-sectional study[36] of 33 960 veterans receiving treatment for chronic pain revealed that smokers were significantly more likely to have received an opioid prescription. Indeed, there may be a mechanistic explanation for stimulation of opioid cravings by nicotine. Functional magnetic resonance imaging studies demonstrated that smoking consistently triggers activation of the μ-opioid receptor neurotransmission in the right anterior cingulate cortex.[37]

Nearly half of opioid prescriptions after 90 days came from an HNC treatment provider. Given that the mechanisms underlying opioid dependence and chronic pain are complex, these patients may be better managed by pain specialists with more expertise in distinguishing neuropathic from nociceptive pain and who may have more experience with alternative analgesics for neuropathic pain, such as tricyclic antidepressants, selective serotonin-norepinephrine reuptake inhibitors, and gabapentinoids.[8,38,39] Chronic opioid use is also highly comorbid with psychiatric illness, which may further complicate pain management strategies.[28] Consequently, HNC treatment providers should consider consulting clinicians with more experience in chronic pain before refilling opioids. At the very least, health care providers should communicate realistic expectations for pain management, specifically that no pain may be an unrealistic goal given the risks of opioid toxic effects.

Several risk factors known to be associated with opioid abuse in the general population were not associated with chronic opioid use in our study. Studies[16,17,40] have shown that younger patients (<50 years of age), patients with alcohol use, and patients with psychiatric illness are significantly more likely to abuse opioids. In our sample, we did observe an association between a history of psychiatric comorbidity and prior alcohol use with chronic opioid use as evidenced by ORs above 1.0, but the wide confidence interval, consistent with the small sample size and limited number of outcome events, as well as the lower bound value below 1.0, prevent us from making definitive conclusions. We also did not observe that patients receiving adjuvant chemotherapy or radiation were significantly more likely to be chronic opioid users, but again failure to detect a difference may be the result of the sample size.

Opioids induce immune deregulation,[41-44] are linked to pneumonia,[33,45] and may even play a mechanistic role in metastases of certain cancers.[46,47] While the lack of high-quality evidence prohibits definitive conclusions regarding opioids and survival at this time, investigations using larger sample sizes may shed light on this relationship in the future. One example of such research may be the use of large-scale, population-based databases such as the Optumlabs Data Warehouse, an insurance claims-linked database containing inpatient and outpatient pharmacy data on 120 million enrollees,[48] to investigate not only survival but also quality-of-life metrics in patients with chronic opioid use as well. In studies with larger sample sizes, effect modification and interaction between variables can be investigated more thoroughly as well.

Limitations

There were several limitations to our study. The primary limitation was a relatively small sample size of patients who developed chronic opioid use. This small number of patients with the outcome of interest reduces the number of independent variables that can be examined in the multivariable models and adds imprecision to all of our estimates. In some cases, this reduced our ability to make definitive conclusions about predictors of chronic opioid use and its effect on survival. A larger cohort would have allowed for more precise determination of factors associated with chronic opioid use and to more soundly

assess the association between opioid use and survival. In addition, during the study period, HNC treatment providers in our system could have given patients a hand-written prescription for opioids without an electronic order. Therefore, the absence of a recorded opioid prescription did not necessarily mean that patients were not prescribed opioids, so some patients who received a hand-written prescription were not captured. An additional limitation was that prescriptions from federal health systems (ie, Veterans Affairs, military hospitals) are unable to be captured by the electronic medical record at our institution and the CURES database, indicating that the prevalence of chronic opioid use in our sample may actually be an underestimate of the true prevalence. The retrospective nature of the study also precluded a more detailed assessment of postoperative pain, such as being nociceptive or neuropathic in character. The interplay between pain character and chronic opioid use therefore went unanalyzed. And finally, the observed associations between chronic opioid use and DFS and OS may be spurious because chronic opioid use was also associated with recurrent or persistent disease.

Conclusions

The prevalence of chronic opioid use in oral cavity patients undergoing surgery is quite high, and preoperative opioid use, prior tobacco use, and development of persistence, recurrence, and second primaries are risk factors. Preoperative opioid users, tobacco users, and patients who develop recurrence or a second primary tumor should receive targeted opioid risk reduction strategies. Additional research is needed to more fully evaluate risk factors for chronic opioid use in patients undergoing surgery for oral cavity cancer.

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