Short- and Long-term Opioid Use in Patients with Oral and Oropharynx Cancer

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Abstract

Objective. Opioid use and abuse is a national health care crisis, yet opioids remain the cornerstone of pain management in cancer. We sought to determine the risk of acute and chronic opioid use with head and neck squamous cell cancer (HNSCC) treatment.

Study Design. Retrospective population-based study.

Setting. Surveillance, Epidemiology and End Results (SEER)–Medicare database from 2008 to 2011.

Subjects and Methods. In total, 976 nondistant metastatic oral cavity and oropharynx patients undergoing cancer-directed treatment enrolled in Medicare were included. Opiate use was the primary end point. Univariate and multivariable logistic analyses were completed to determine risk factors.

Results. Of the patients, 811 (83.1%) received an opioid prescription during the treatment period, and 150 patients (15.4%) had continued opioid prescriptions at 3 months and 68 (7.0%) at 6 months. Opioid use during treatment was associated with prescriptions prior to treatment (odds ratio [OR], 3.28; 95% confidence interval [CI], 2.11-5.12) and was least likely to be associated with radiation treatment alone (OR, 0.35; 95% CI, 0.18-0.68). Risk factors for continued opioid use at both 3 and 6 months included tobacco use (OR, 2.23; 95% CI, 1.05-4.71 and OR, 3.84; 95% CI, 1.44-10.24) and opioids prescribed prior to treatment (OR, 3.84; 95% CI, 2.45-5.91 and OR, 3.56; 95% CI, 1.95-6.50). Oxycodone prescribed as the first opioid was the least likely to lead to ongoing use at 3 and 6 months (OR, 0.33; 95% CI, 0.17-0.62 and OR, 0.26; 95% CI, 0.10-0.67).

Conclusion. Patients with oral/oropharyngeal cancer are at a very high risk for receiving opioids as part of symptom management during treatment, and a significant portion continues use at 3 and 6 months after treatment completion.

Keywords

head and neck squamous cell cancer, oral cavity cancer, oropharyngeal cancer, opioid, opiate, pain, SEER, Medicare

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The opioid crisis is a national health emergency. The Centers for Disease Control and Prevention (CDC) estimates that opioid addiction and overdose claimed more than 70,000 lives in 2017 and has resulted in an estimated annual economic cost of $78.5 billion.1-4 Opioid therapy is the cornerstone of management of severe chronic pain in patients with cancer, putting these patients at a greater risk of addiction.

More than 60,000 patients are diagnosed with head and neck squamous cell cancer (HNSCC) in the United States annually, with nearly 90% of them having no distant metastases at diagnosis.5 To achieve a cure, rigorous multimodal treatment regimens are employed, including surgery, radiation, and chemotherapy.6-8 These therapies have severe, painful toxicities that can result in altered or delayed treatment and occasionally hospitalization.9-12 To improve symptom management and compliance with treatment, pain

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management is a critical factor with opioid medications as a common and effective intervention. There is significant concern, however, that prolonged use could lead to misuse or dependence.

Recent studies have reported that 10.4% of patients undergoing curative-intent cancer surgery had new persistent opioid use at 1 year, and cancer survivors had opioid prescribing rates 1.22 times higher than age-matched controls. Opioid use in nondistant metastatic HNSCC has not been evaluated outside of 2 single-institution studies, each with fewer than 100 patients. These studies reported persistent opioid use in over 40% of their patients at 3 months. We performed a retrospective cohort study using population-based data to estimate the number of patients with stage I to IVB nondistant metastatic HNSCC undergoing cancer-directed treatment who received opioid prescriptions during treatment and continued use at 3 and 6 months.

Methods

Data Source

We used data from the linked Surveillance, Epidemiology and End Results (SEER)–Medicare database. The SEER program collects information from population-based cancer registries that currently cover approximately 28% of the US population. The data include information on patient demographics, tumor characteristics at diagnosis, first course of treatment, and overall and cancer-specific mortality based on linkage to mortality data from the National Center for Health Statistics. The SEER-Medicare database links SEER patients to Medicare enrollment and claims data. Medicare claims provide information on health care services, procedures, diagnoses, socioeconomic measures, and payments for beneficiaries enrolled in fee-for-service Medicare. This project was reviewed by our local institutional review board (COMIRB) and deemed to be exempt due to the deidentified status of the data.

Sample Selection

We selected patients whose first and only cancer was a squamous cell carcinoma (third edition of the International Classification of Diseases for Oncology [ICD-O-3] morphology codes 8050-8089; squamous cell neoplasms) of the oral cavity and oropharynx ([ICD-O-3] topography codes C00-C14) diagnosed from 2008 through 2011 (N = 13,521) (see Supplemental Figure S1, available in the online version of the article). Laryngeal cancers were not included in this study as they are categorized separately under “thoracic cancers” in SEER-Medicare, which we did not have timely access to. We limited the analysis to American Joint Committee on Cancer, Sixth Edition (AJCC) TNM stage I to IVB nondistant metastatic tumors (N = 10,523). Patients with more than 1 primary tumor, missing month of diagnosis, or with a diagnosis identified at death were excluded (n = 31). Patients had to be at least 66 years of age at diagnosis and continuously enrolled in fee-for-service (FFS) Medicare Part A and Part B with paid claims during the 12-month observation period (n = 3466). To study opioid use, we restricted the study to Medicare beneficiaries who were also enrolled in Medicare Part D, the voluntary prescription drug coverage program. Of the patients with FFS Medicare Part A and Part B, 47.73% (n = 1650) were also enrolled in Part D for 12 months prior to and 12 months following the month of diagnosis (or until death). This left 1641 patients with complete claims data to examine prior health status, treatment, opioid use, and outcomes of interest.

We used Current Procedural Terminology (CPT), Healthcare Common Procedure Coding Systems (HCPCS), and International Classification of Diseases, Ninth Revision ([ICD-9] codes reported on Medicare Provider Analysis and Review (MEDPAR), Outpatient, National Claims History (NCH) Physician/Supplier, and Durable Medical Equipment (DME) claims to identify patients undergoing treatment regimens of interest (see Supplemental Table S1, available in the online version of the article). We required that the first date of treatment be within 6 months of diagnosis, that treatment last no more than 6 months, and that no additional treatments be initiated in the 12 weeks following the end of treatment (n = 1232). We further limited the sample to patients who had at least 6 months of survival after the end of treatment to avoid including patients receiving palliative care. We excluded patients with atypical treatment indicated in their claims, with no census tract information, and with an unknown N-stage, for an analytic sample of 976.

Outcomes

We used National Drug Codes (NDC) and generic names to identify opioids reported in Part D prescription drug claims and defined the time on opioids based on the prescription fill dates and the number of days supply dispensed. We included codeine, fentanyl, hydrocodone, hydromorphone, meperidine hydrochloride, morphine, nalbuphine, oxycodone, and tramadol. The primary outcome was any initial opioid use, measured as opioid use any time between the start of treatment and 3 months after the end of treatment. In addition, we examined continued opioid use at 3 months and 6 months from the end of treatment. Opioid use was considered continuous if the time between the last day of one opioid prescription and the first day of the next opioid prescription was less than 30 days based on definitions from prior literature.

Control Variables

We used SEER data to obtain patients’ age at diagnosis, race, sex, marital status, geographic region, and population density (metropolitan, nonmetropolitan), as well as primary tumor site and AJCC T and N categories. We used Medicare claims to identify the type of treatment facility and type of treatment, defined as surgery alone, radiation therapy (RT) alone, chemoradiation (CRT), surgery and RT, or surgery and CRT. Using Part D claims, we determined characteristics of the opioid prescriptions in the initial use period: first opioid prescribed, high doses of opioids (>100 mg morphine equivalent), and long-acting opioids. Claims from the year prior to diagnosis were used...
to calculate the Charlson Comorbidity Index (CCI) values to address overall health and identify a history of opioid, tobacco, alcohol, or other substance use prior to the start of treatment (see Supplemental Table S2, available in the online version of the article).

**Statistical Analysis**

We compared our final patient population to the entire cohort of nondistant metastatic oral cavity and oropharynx patients and to those over age 65 who did not have all 3 parts of Medicare to determine the generalizability of our data. We also performed sensitivity analyses to determine whether less stringent inclusion criteria would affect these findings.

The primary outcome measures were initial opioid use, continued opioid use at 3 months, and continued opioid use at 6 months. We used \( \chi^2 \) tests to assess univariate associations with categorical characteristics and conducted logistic regression to assess multivariable associations.

Survival analysis using the Kaplan-Meier method was conducted to assess univariate differences in the length of time on opioids following the end of treatment. Discontinued opioid use was considered the event of interest and was defined as either no additional opioid prescriptions or a more than 30-day break between prescriptions. Patients with continued opioid use for more than 26 weeks (approximately 6 months) were censored at the 27th week. All analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina), and significance was evaluated at \( P < .05 \).

**Results**

In total, 976 patients with stage I to IVB oral cavity and oropharynx cancer undergoing cancer-directed treatment were included in this study. Compared to the entire cohort (\( N = 10,523 \)) of stage I to IVB oral cavity and oropharynx patients, our patients were older, had a higher percentage of females, were more likely to have oral cavity cancer, had slightly different geographic locations, and had lower T and N tumor stages (see Supplemental Table S3, available in the online version of the article). When comparing to a narrowed cohort of patients > 65 years old (\( n = 5761 \)), our patients continued to have a higher percentage of females, different geographic regions, and lower T and N tumor stages (see Supplemental Table S4, available in the online version of the article). We performed sensitivity analyses that included removing our criteria of Medicare exclusions, treatment requirements, survival of 6 months, and 12 months of prior claims coverage. All of these increased the similarity of our cohort to the general population.

Of the total 976 patients included, 811 (83.1\%) received an opioid prescription between the start of cancer-directed treatment and 3 months after its completion. A total of 150 patients (15.4\%) had continuous opioid prescriptions through 3 months after treatment and 68 patients (7.0\%) through 6 months after treatment. The median and mean time on opioids were 3 and 7.37 weeks, respectively (Figure 1).

**Figure 1.** Continued opioid use over time for all patients receiving any opioid prescriptions during oral and oropharyngeal cancer treatment (censored at 6 months). Median time on opioids was 3 weeks (95\% confidence interval, 3.00-4.00). The mean (SE) time on opioids was 7.37 (0.31) weeks censoring at 6 months.

**Table 1** compares patients who received opioids during their HNSCC treatment vs those who did not in univariate analysis. Patients in the opioid group were more likely to be younger and unmarried. Opioid users were more likely to have higher nodal stages, oropharyngeal cancer, and multimodality treatment. They were also more likely to have received opioids in the months preceding treatment.

In multivariable logistic regression, the only variables that were significantly associated with opioid use during cancer treatment were treatment type and prior opioid use (see Supplemental Table S5, available in the online version of the article). Patients who received radiation alone were significantly less likely to receive opioids compared to the other treatment modalities (odds ratio [OR], 0.35; 95\% confidence interval [CI], 0.18-0.68; overall \( P < .001 \)). Patients who received opioids prior to initiating treatment were 3.3 times more likely to also receive opioids during treatment (OR, 3.28; 95\% CI, 2.11-5.12).

**Long-term Opioid Use**

**Table 2** compares those who received opioid prescriptions during cancer treatment and discontinued opioid use within 3 months with those who had continuous opioid use through 3 or 6 months. Patients who continued opioid use at 3 months were significantly more likely to be younger, unmarried, and in lower income groups. They had higher tumor T and nodal N stages, had higher CCIs, and were more likely to have reported tobacco and alcohol use than those who discontinued opioids. They were more likely to have opioid use prior to treatment, initial use of hydrocodone or "other" opioids (fentanyl, hydromorphone, meperidine hydrochloride, morphine, nalbuphine, and tramadol), and receipt of long-acting and high-dose (>100 mg morphine equivalent/d) opioids. Compared to those who discontinued opioid use by 6 months, those who continued were also younger, unmarried, and with history of tobacco and
### Table 1. Characteristics of Patients Who Received Opioids vs Nonopioid Users.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonopioid Users (n = 165), No. (%)</th>
<th>Opioid Users (n = 811), No. (%)</th>
<th>Univariate P Valueb</th>
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<td>232 (28.6)</td>
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<td>70 to 74</td>
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<td>Oropharynx</td>
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<tr>
<td>Other</td>
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<td></td>
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<td>45 (27.3)</td>
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<td>All others</td>
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<td>&gt; 65 (&gt; 39.4)</td>
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<td></td>
<td><strong>&lt;.0001</strong></td>
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<td>Surgery + CRT</td>
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<tr>
<td>&lt; 11 (&lt; 6.7)</td>
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<tr>
<td>Surgery + RT</td>
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<td>126 (15.5)</td>
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<tr>
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<td>474 (58.4)</td>
<td><strong>&lt;.0001</strong></td>
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**Abbreviations:** CRT, chemotherapy and radiation; RT, radiation.

*a* Analyzed but not included in the table due to nonsignificance include year of diagnosis, geographic location, teaching vs nonteaching hospital, education level, and percent below poverty level.

*b* Boldface values represent statistically significant estimates based on a P value threshold of .05 on the univariate analysis.
<table>
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<th>Characteristic</th>
<th>Discontinued by 3 Months (n = 661), No. (%)</th>
<th>Continued at 3 Months (n = 150), No. (%)</th>
<th>Continued at 6 Months(^b) (n = 68)</th>
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<td>249 (37.7)</td>
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<td>Nodal stage(^c)</td>
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<td>379 (57.3)</td>
<td>65 (43.3)</td>
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<td>23 (33.8)</td>
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<td>2 or more</td>
<td>160 (24.2)</td>
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<td>Median income quartile</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All others</td>
<td>505 (76.4)</td>
<td>98 (65.3)</td>
<td>46 (67.6)</td>
</tr>
<tr>
<td>Lowest quartile</td>
<td>156 (23.6)</td>
<td>52 (34.7)</td>
<td>22 (32.3)</td>
</tr>
<tr>
<td>% below poverty quartile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All others</td>
<td>508 (76.8)</td>
<td>98 (65.3)</td>
<td>45 (66.2)</td>
</tr>
<tr>
<td>Highest quartile</td>
<td>153 (23.1)</td>
<td>52 (34.7)</td>
<td>23 (33.8)</td>
</tr>
<tr>
<td>Treatment type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery alone</td>
<td>237 (35.8)</td>
<td>29 (19.3)</td>
<td>15 (22.1)</td>
</tr>
<tr>
<td>Surgery + CRT</td>
<td>103 (15.6)</td>
<td>25 (16.7)</td>
<td>&lt;11 (&lt;16.2)</td>
</tr>
<tr>
<td>Surgery + RT</td>
<td>103 (15.6)</td>
<td>23 (15.3)</td>
<td>15 (22.1)</td>
</tr>
<tr>
<td>CRT</td>
<td>179 (27.1)</td>
<td>58 (38.7)</td>
<td>&gt;18 (&gt;26.5)</td>
</tr>
<tr>
<td>RT alone</td>
<td>39 (5.9)</td>
<td>15 (10.0)</td>
<td>&lt;11 (&lt;16.2)</td>
</tr>
<tr>
<td>Prior opioid use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>423 (64.0)</td>
<td>51 (34.0)</td>
<td>21 (30.9)</td>
</tr>
<tr>
<td>Yes</td>
<td>238 (36.0)</td>
<td>99 (66.0)</td>
<td>47 (69.1)</td>
</tr>
<tr>
<td>History of tobacco use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>582 (88.1)</td>
<td>113 (75.3)</td>
<td>51 (75.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>79 (12.0)</td>
<td>37 (24.7)</td>
<td>17 (25.0)</td>
</tr>
</tbody>
</table>

(continued)
alcohol use. They were more likely to have prior opioid use, to have long-acting and high-dose opioid use, and to have been prescribed hydrocodone or “other” opioids as their initial opioid.

In adjusted logistic regression (Table 3), older patients (aged 70-74 years and 75 years and older) were significantly less likely to remain on opioids at 3 months following treatment (OR, 0.70; 95% CI, 0.42-1.17 and OR, 0.39; 95% CI, 0.23-0.67, respectively; overall $P = .0052$). Patients with higher T tumor stages (T3-T4) were more likely to continue opioids at 3 months (OR, 2.64; 95% CI, 1.48-4.71; $P = .0036$). Persistent opioid use at 6 months was associated less often with female sex (OR, 0.47; 95% CI, 0.24-0.91; $P = .0246$) and more often in nonmarried patients compared to married/partnered patients (OR, 2.22; 95% CI, 1.19-4.14; $P = .0117$). Tobacco use was associated with continued opioid use at both 3 and 6 months posttreatment (OR, 2.23; 95% CI, 1.06-4.71; $P = .0357$ and OR, 3.84; 95% CI, 1.44-10.24; $P = .0073$, respectively).

At 3 months, patients with opioids prescribed prior to treatment were 3.8 (95% CI, 2.45-5.91; $P < .0001$) times more likely to remain on opioids, and those who received long-acting opioids were 3.0 (95% CI, 1.95-6.50; $P < .001$) times more likely to. Compared to patients who initially started on hydrocodone, those who started on oxycodone (OR, 0.33; 95% CI, 0.17-0.62; $P = .0077$) were less likely to have continued opioid use at 3 months. Prior opioid use was also associated with continued use at 6 months (OR, 3.56; 95% CI, 1.95-6.50; $P < .0001$), as was initial high-dose (>100 mg morphine equivalent/d) opioid use (OR, 2.82; 95% CI, 1.41-5.65; $P = .0035$). At 6 months, compared to initial hydrocodone use, initial oxycodone use was still less likely to be associated with continued use (OR, 0.26; 95% CI, 0.10-0.67; $P = .0049$). Figure 2 shows Kaplan-Meier curves for risk factors associated with persistent opioid use at both 3 and 6 months.

**Discussion**

In the largest study to date of opioid use in oral cavity and oropharyngeal HNSCC, over 80% of patients receiving cancer-directed treatment received at least 1 opioid prescription. Approximately 15% remained on opioids at 3 months and 7% at 6 months. Receipt of opioids prior to starting treatment increased the risk of receiving them during treatment while radiation alone decreased the risk compared to multimodality regiments. Long-term use was consistently associated with tobacco use, prior opioid use, and type of opioid use.

The percentage of patients who receive opioids during nondistant metastatic oral cavity and oropharyngeal HNSCC treatment nationally has not been previously reported. This study demonstrates that most of these patients receive opioids as part of their pain regimen. The 7% of patients who remain on opioids chronically is comparable to 10.4% of postoperative patients with breast, melanoma, colorectal, hepato-pancreato-biliary, gastric, and thoracic cancers in another recent study and to a reported 3% to 9% of non-cancer surgical patients. Interestingly, this number is lower than 2 prior small single-institution studies evaluating patients with HNSCC. One found that 41% of patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Discontinued by 3 Months (n = 661), No. (%)</th>
<th>Continued at 3 Months (n = 150), No. (%)</th>
<th>Continued at 6 Months ($^a$) (n = 68), No. (%)</th>
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</thead>
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<tr>
<td>History of alcohol or other substance use</td>
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<td>No</td>
<td>597 (90.3)</td>
<td>119 (79.3)</td>
<td>55 (80.9)</td>
</tr>
<tr>
<td>Yes</td>
<td>64 (9.7)</td>
<td>31 (20.7)</td>
<td>13 (19.1)</td>
</tr>
<tr>
<td>First opioid prescribed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>82 (12.4)</td>
<td>12 (8.0)</td>
<td>&lt;11 (&lt;16.2)</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>376 (56.9)</td>
<td>95 (63.3)</td>
<td>&gt;34 (&gt;50.0)</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>155 (23.4)</td>
<td>22 (14.7)</td>
<td>&lt;11 (&lt;16.2)</td>
</tr>
<tr>
<td>Other opioid</td>
<td>48 (7.3)</td>
<td>21 (14.0)</td>
<td>14 (20.6)</td>
</tr>
<tr>
<td>Any initial high-dose use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>533 (80.6)</td>
<td>91 (60.7)</td>
<td>35 (51.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>128 (19.4)</td>
<td>59 (39.3)</td>
<td>33 (48.5)</td>
</tr>
<tr>
<td>Any initial long-acting opioids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>550 (83.2)</td>
<td>88 (58.7)</td>
<td>39 (57.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>111 (16.8)</td>
<td>62 (41.3)</td>
<td>29 (42.6)</td>
</tr>
</tbody>
</table>

Abbreviations: CRT, chemotherapy and radiation; RT, radiation.

$^a$Patients in the 6-month group are also included in the 3-month group.

$^b$Boldface values represent statistically significant estimates of opioid continuers vs noncontinuers based on a $P$ value threshold of .05 on the univariate analysis for each variable. Analyzed but not included in the table due to nonsignificance include year of diagnosis, geographic location, teaching vs nonteaching hospital, and education level.

undergoing surgery for oral cavity cancer remained on opioids 90 days after surgery, although they did not exclude patients with persistent or recurrent disease or account for the fact that many may have been still undergoing adjuvant therapy at 90 days. Another evaluated 70 patients receiving chemotherapy and radiation with 63% continuing opioids at 3 months and 33% at 6 months. Sample heterogeneity in terms of disease presentation and behavioral

| Table 3. Multivariable Logistic Regression Models for Continuous Opioid Use at 3 and 6 Months. a |
|--------------------------------------------------|---------------------------------|---------------------------------|
| Model Variables                                  | Opioid Use at 3 Months (n = 150) | Opioid Use at 6 Months (n = 68) |
| Age (ref. 66 to 69), y                            |                                 |                                 |
| 70 to 74                                         | 0.70 (0.42-1.17)                | 0.76 (0.39-1.51)                |
| 75 and older                                     | 0.39 (0.23-0.67)                | 0.48 (0.23-0.98)                |
| Sex (ref. male)                                  |                                 | 0.47 (0.24-0.91)                |
| Female                                           | 0.83 (0.52-1.33)                |                                 |
| Race/ethnicity (ref. white/non-Hispanic)         |                                 |                                 |
| Other                                            | 1.08 (0.63-1.85)                | 1.26 (0.61-2.61)                |
| Marital status (ref. married)                    |                                 |                                 |
| Nonmarried                                       | 1.42 (0.91-2.20)                | 2.22 (1.19-4.14)                |
| Patient location (ref. metropolitan)             |                                 |                                 |
| Nonmetropolitan                                  | 0.89 (0.50-1.58)                | 0.91 (0.41-1.96)                |
| Primary site (ref. oral cavity)                  |                                 |                                 |
| Oropharynx                                        | 1.46 (0.83-2.58)                | 0.74 (0.34-1.61)                |
| Other                                            | 0.80 (0.36-1.76)                | 0.56 (0.18-1.72)                |
| Tumor size stage (ref. T1)                       |                                 |                                 |
| T2                                               | 1.56 (0.89-2.74)                | 1.31 (0.62-2.76)                |
| T3-4, unknown                                    | 2.64 (1.48-4.71)                | 1.58 (0.73-3.42)                |
| Nodal stage (ref. N0)                            |                                 |                                 |
| N1                                               | 1.96 (1.05-3.68)                | 1.42 (0.60-3.39)                |
| N2-3                                             | 1.08 (0.61-1.94)                | 1.43 (0.63-2.34)                |
| Comorbidity index (ref. 0)                       |                                 |                                 |
| 1                                                | 1.31 (0.79-2.19)                | 1.85 (0.94-3.63)                |
| 2 or more                                        | 1.39 (0.83-2.31)                | 1.14 (0.56-2.34)                |
| Median income level (ref. all others)            |                                 |                                 |
| Lowest quartile                                  | 1.04 (0.53-2.03)                | 0.90 (0.37-2.22)                |
| Treatment type (ref. surgery alone)              |                                 |                                 |
| Surgery + CRT                                    | 0.69 (0.30-1.58)                | 0.57 (0.17-1.86)                |
| Surgery + RT                                     | 0.97 (0.47-2.00)                | 1.38 (3.42-0.49)                |
| CRT                                              | 0.69 (0.30-1.56)                | 0.64 (0.20-2.05)                |
| RT alone                                         | 1.86 (0.75-4.61)                | 1.16 (0.32-4.24)                |
| Prior opioid use (ref. no)                       |                                 |                                 |
| Yes                                              | 3.80 (2.45-5.91)                | 3.56 (1.95-6.50)                |
| History of tobacco use (ref. no)                 |                                 |                                 |
| Yes                                              | 2.23 (1.05-4.71)                | 3.84 (1.44-10.24)               |
| History of alcohol/substance abuse (ref. no)     |                                 |                                 |
| Yes                                              | 0.71 (0.32-1.60)                | 0.37 (0.12-1.12)                |
| First opioid prescribed (ref. hydrocodone)       |                                 |                                 |
| Codeine                                           | 0.74 (0.34-1.59)                | 0.32 (0.08-1.21)                |
| Oxycodone                                         | 0.33 (0.17-0.62)                | 0.26 (0.10-0.67)                |
| Other opioid                                      | 0.89 (0.45-1.77)                | 1.70 (0.75-3.86)                |
| Initial high-dose opioid use (ref. no)            |                                 |                                 |
| Yes                                              | 1.37 (0.80-2.35)                | 2.82 (1.41-5.65)                |
| Initial long-acting opioid use (ref. no)          |                                 |                                 |
| Yes                                              | 3.00 (1.70-5.31)                | 1.83 (0.87-3.85)                |

Abbreviations: CI, confidence interval; CRT, chemotherapy and radiation; OR, odds ratio; ref., reference variable; RT, radiation.

Boldface values represent statistically significant overall estimates based on a P value threshold of .05 on the multivariable analysis. Analyzed but not included in the table due to nonsignificance include year of diagnosis, geographic location, teaching vs nonteaching hospital, education level, and percent below poverty.
practices likely explains the differences. This latter study had a very high percentage of patients who screened positive for alcoholism (30%), which was found to be a significant predictor for chronic opioid use and may have contributed to their high ongoing use.\textsuperscript{17}

We found that patients receiving radiation alone were significantly less likely to receive opioids compared to those receiving surgery. Multimodal treatment including surgery combined with radiation and chemotherapy had a positive trend toward receiving any opioids compared to single-modality treatments. This is likely attributable to the majority of patients with HNSCC reporting perioperative pain.\textsuperscript{23} Radiation alone results in pain-inducing side effects such as mucositis and odynophagia,\textsuperscript{9,10} but the addition of chemotherapy can increase these adverse effects by as much as 40%, resulting in increased pain management requirements.\textsuperscript{7,10} Importantly, the treatment modality association did not carry over to long-term opioid use, suggesting that modifying treatment regimens may not change this risk.

Short- and long-term opioid use were associated with opioid use prior to treatment start. This is similar to findings from the postoperative oral cavity cancer study.\textsuperscript{18} It is not possible to know if these patients were on opioids initially due to cancer-related pain vs other chronic pain, although this would be important to elucidate in future studies. The type of opioid initially used to treat pain was also significantly associated with the risk of chronic opioids, with hydrocodone and other opioids (fentanyl, hydromorphone, meperidine hydrochloride, morphine, nalbuphine, and tramadol) having the highest risk. There are minimal data on this risk in patients with cancer, but in noncancer patients, tramadol and short-acting opioids other than hydrocodone and oxycodone increase the probability of long-term use.\textsuperscript{24} Use of long-acting opioid medications was a risk factor for ongoing use at 3 months while high daily doses of opioids (>100 mg morphine equivalent) were a risk factor for persistent use at 6 months, both of which have been identified in studies for non-cancer-related pain.\textsuperscript{25,26}

Tobacco use, a known risk factor for HNSCC, was underreported in our study, with only 14% of patients coded as tobacco users, but was still a significant predictor of chronic opioid use. Tobacco use has been associated with worse HNSCC-related outcomes and increased toxicity with treatment, including more fibrosis, edema, and dysphagia.\textsuperscript{27} Prior studies have reported tobacco use as a risk factor for acute and chronic opioid use in cancer and noncancer patients.\textsuperscript{18,28,29} The other demographic factors of young age, male sex, and nonmarried status found to have variable...

\textbf{Figure 2.} Continued opioid use over time across significant risk factors. Tobacco use (A), opioid use prior to the start of treatment (B), and type of initial opioid prescribed (C) were all significantly associated with continued opioid use at 3 and 6 months.
association at 3 and 6 months have all also been identified as potential risk factors for chronic opioid use.\textsuperscript{25,26,29,30}

Pain control plays an important role in patient comfort and treatment compliance, which can affect survival and treatment efficacy,\textsuperscript{11,12} but opioids can also cause significant side effects and complications that may jeopardize health outcomes. Opioid use has been associated with worse physical symptoms (constipation, insomnia, lack of energy, anorexia, etc) and lower quality of life measures in cancer and noncancer patients.\textsuperscript{30,31} Preclinical studies have demonstrated potential opioid-mediated cancer cell progression,\textsuperscript{32-36} and opioid use has been associated with decreased disease-free and overall survival in some patients with cancer.\textsuperscript{18,37,38}

These concerns persist with the added issues of dependence, addiction, depression, and overdose in chronic opioid users.\textsuperscript{12,39} Nonopioid alternative agents and treatments including acetaminophen, nonsteroidal anti-inflammatory drugs, gabapentin, tricyclic antidepressants, physical therapy, and acupuncture have been evaluated in small series to manage HNSCC treatment-related toxicity with mixed effects.\textsuperscript{40-44} Further research and use of these and other opioid-sparing medications and treatments will be critical to reduce acute and chronic opioid use in patients with curative HNSCC.

There are limits to our study inherent to a retrospective SEER-Medicare analysis. Our study patient selection criteria were stringent to ensure the quality of our data, decreasing our total numbers and the generalizability to the excluded population. We felt that this was necessary for appropriate covariate adjustment and valid models to strengthen our findings. The database available to us did not include the laryngeal subset. Overall, our patients are comparable to the elderly population with patient and opioid prescribing patterns as demonstrated potential opioid-mediated cancer cell progression,\textsuperscript{12-36} and opioid use at 3 and 6 months remains high relative to the general population with patient and opioid prescribing patterns as significant risk factors. These findings underline the importance of monitoring high-risk patients, evaluating the types of opioid medications prescribed, and finding alternative pain management regimens that can decrease short- and long-term opioid use.

Author Contributions

Jessica D. McDermott, first author, designed the study, wrote and edited the manuscript, approved final version to be published, agrees to be accountable for all aspects; Megan Eguchi, study concept design, database filtering and statistical analysis, drafting, revising, and reviewing final manuscript, approved final version, agrees to be accountable for all work; William A. Stokes, database construction, study design, critically revised work for intellectual content, approved final version, agrees to be accountable for all aspects of work; Arya Amini, database construction, study design, revision of work for intellectual content, approved final version of manuscript, agrees to be accountable for all aspects of work; Mohammad Hararah, database construction, study design, editing of the manuscript, approved final version, agrees to be accountable for all aspects of the work; Ding Ding, database construction, study design, editing of the manuscript, approved final version, agrees to be accountable for all aspects of the work; Allison Valentine, database design, filtering and statistical analysis, interpretation of data, drafted part of manuscript, approved final manuscript version, agrees to be accountable for all aspects of work; Cathy J. Bradley, mentored the project, helped with study design, revised final draft, approved final draft, agrees to be accountable for all aspects of the work; Sana D. Karam, mentored the project, helped with study design, drafted and manuscript and revised final draft, approved final draft, agrees to be accountable for all aspects of the work.

Disclosures

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Supplemental Material

Additional supporting information is available in the online version of the article.

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