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The impact of intraoperative opioid use on survival after oral cancer surgery

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ABSTRACT

Objectives: To investigate the impact of opioid use on cancer recurrence after oral cancer surgery. We hypothesized that the amount of opioids administered during oral cancer surgery is an independent predictor of recurrence free survival (RFS) and overall survival (OS).

Methods: After Institutional Review Board approval, we collected demographic, tumor related, intraoperative and survival data of patients who had oral cancer surgery. Multivariable Cox proportional hazards models were used to determine the impact of important covariates on RFS and OS.

Results: 268 patients were included. After adjusting for significant covariates, the amount of opioids administered during surgery was not an independent predictor of RFS (HR: 1.27 [CI 95%, 0.838–1.924], p = 0.26). However, we observed an association between opioid consumption and shorter OS (HR = 1.77, [CI 95% = 0.995–3.149]. p = 0.05).

Conclusions: High requirements of opioids during surgery increase the risk of recurrence and mortality by 27% and 77%, although the association is not statically significant.

Introduction

In the year 2012, there was an estimate of 300,400 new cases of oral cavity cancer and 145,400 deaths from the disease worldwide [1]. In the United States, by the end of 2017, there will be an estimate of 32,670 new cases, and 6,650 patients are expected to die from the disease [2]. Squamous cell carcinoma (SCC) is the most common histology, comprising 90% of oral cancer cases [3]. The treatment of early stage oral cancers (stage I and II) usually requires surgery or radiation therapy (RT). Whereas, advanced disease (stage III and IV) typically needs a combination of treatments including surgery and RT with or without chemotherapy. The prognosis of patients with advanced oral cancers is dismal. For instance, the 5-year relative survival rate is 51% in SEER registries [4].

One of the predictive factors for tumor recurrence and survival after oral cancer surgery is the presence of minimal residual disease (MRD). Positive surgical margins, cervical metastases, extranodal extension (ENE) and perineural invasion are all associated with MRD, and are independent predictors of recurrence [5]. It has been speculated that the MRD can grow during the perioperative period because of inflammation, immunosuppression and increased angiogenesis [6]. Thus, extensive research has been conducted to identify perioperative factors that can exaggerate the inflammatory response, suppress the innate immunity and increase angiogenesis.

Opioids are widely used for intraoperative and postoperative analgesia in oral cancer surgery [7]. It has been hypothesized that opioids can stimulate tumor growth by acting directly on mu opioid receptors (MOR) located in cancer cells, by increasing angiogenesis or by inducing immunosuppression [8]. Additionally, several investigations have reported a negative association between the amount of opioids administered during surgery, the expression of MOR, and the recurrence-free or overall survival of patients with non-small cell lung cancer, laryngeal and esophageal cancers [9–11].

It has been reported that opiates might increase the risk of oral cavity cancers and reduced survival [12,13]. Furthermore, Oral SCC cells can produce endogenous opioids and mediate antinociception [14]. Therefore, it is possible to speculate that exogenous opioids might have a significant impact on the biology of oral SCC as it occurs in laryngeal and esophageal SCC. We hypothesized that the intraoperative use of opioids is associated with the recurrence-free survival (RFS) and overall survival (OS) of patients with oral cancer undergoing primary surgical resection. If indeed intraoperative opioids are associated with shorter RFS or OS after oral cancer surgery, new analgesic strategies

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should be considered in this population of patients.

Methods

We captured data from 268 patients who underwent primary oral cancer surgery at the University of Texas MD Anderson Cancer Center from July 2003 through January 2016. The data was collected after Institutional Review Board (#PA16-1033). Patients were included in the study if they were over 18 years old, and had surgery for a primary oral cancer. Patients with second primaries were also included. We excluded patients who underwent emergency surgeries. The demographic and tumor-related information was extracted from electronic medical records and included: age, gender, body mass index (BMI), American Society of Anesthesiologist (ASA) physical status, duration of anesthesia, type of opioid used and total dose during surgery, neoadjuvant and adjuvant cancer treatment modality (chemotherapy, radiotherapy, surgery or a combination of them), recurrence status and survival data. Tumor pathology and related data were also collected, including tumor location, histologic findings (type and differentiation), extranodal extension, perineural invasion, lymph nodal involvement, surgical margins and red blood cell transfusion intraoperatively and during surgical hospitalization. All patients had general anesthesia with intraoperative opioid analgesia. The total amount of opioids was calculated as fentanyl equivalents as follows: 1 μg of fentanyl equal to 0.1 μg of sufentanil, 1 μg of remifentanil, 10 μg of hydromorphone, and 100 μg of morphine sulfate [10].

Statistical analysis

Primary clinical outcomes were RFS and OS. RFS was defined as the time from the day of surgery to the date of recurrence or death, whichever happened first. Patients were censored at the last known date if neither death nor recurrence was registered. OS was defined as the time from the date of surgery to the date of death or last known follow-up. Patients were censored at the last known date if death was not registered.

Summary statistics were reported as a median, and interquartile range for continuous variables such as age and BMI, anesthesia duration and frequency counts and percentages for categorical variables such as ASA, and cancer staging. The Chi-square test was used to evaluate the association between two categorical variables. Wilcoxon rank sum test or Kruskal-Wallis test was used to assess the difference in the continuous variable between/among patient groups. Kaplan-Meier method was used for time-to-event analysis including RFS and OS. Median time to event in months with 95% confidence interval was calculated. We used the Log-rank test to evaluate the difference in time-to-event endpoints between patient groups. Multivariable Cox proportional hazards models were used for multivariate analysis to include relevant and significant covariates. A $p < 0.05$ was considered statistically significant. Statistical software SAS 9.3 (SAS, Cary, NC) and S-Plus 8.2 (TIBCO Software Inc., Palo Alto, CA) was used for all the analyses.

Results

The median (IQR) age of the patients included in the study was 60.5 years (53–71). The vast majority of the patients were male (70.52%) and had an American Society of Anesthesiology (ASA) physical status of 3 or 4 (86.84%) (Table 1). The most common tumor location and histology types were the tongue (48.8%) and infiltrative squamous cell carcinoma (82.42%), respectively. Tumors presented moderate-poor to poor differentiation in 20.8% of the patients. Perineural invasion and extranodal extension were observed in 31.47% and 27.61% of all patients, respectively. Margins were positive in 6.64% of the specimens (Table 2).

The median (IQR) amount of fentanyl equivalents administered to patients during surgery was 1081.63 μg (591.1–1753.67). The total dosage of fentanyl equivalents administered during surgery was affected by the duration of anesthesia, which in turn, was associated with the pT, node staging, and perineural invasion. Briefly, patients with early stage disease (pT stage 1 and 2) required significantly less opioid (median [IQR] 800 μg, [431.1–1376.73]) than those with advanced tumors (pT stage 3 and 4) (1504.2 μg, [946.21–1951.93], $p < 0.0001$). The median (IQR) amount

Table 1
Patients' demographic and tumor related data.

Variable	n = 268
Age (years) median (IQR)	60.5 (53.00–71.00)
BMI (kg/m^2), median (IQR)	27.22 (23.89–31.98)
Gender, female/male n (%)	79 (29.48%) / 189 (70.52%)
ASA physical status	
1–2	35 (13.16%)
3–4	226 (86.84%)
Duration of anesthesia (min), median (IQR)	601.5 (319–710)
Fentanyl equivalents (μg), median (IQR)	1081.63 (591.1–1753.67)
Overall treatment for disease	
Surgery	96 (35.82%)
Surgery and radiotherapy	106 (39.55%)
Surgery, chemotherapy and radiotherapy	66 (24.63%)
Previous treatment for oral cancer	
Previous surgery for oral cancer	19 (7.12%)
Previous radiotherapy for oral cancer	15 (5.64%)
Previous chemotherapy for oral cancer	5 (1.89%)
pT Staging	
1	58 (21.64%)
2	91 (33.96%)
3	19 (7.09%)
4	100 (37.31%)
Perioperative blood transfusions	77 (28.73%)
Alive in last follow up	196 (73.13%)

BMI: Body mass index. ASA: American Society of Anesthesiologist. Min: minutes. IQR: interquartile. μg: micrograms.

Table 2
Tumor-related data.

Variable	n = 268
Histologic type	
Infiltrative	221 (82.42%)
Pushing	18 (6.71%)
Verrucous	7 (2.61%)
Basaloid	2 (0.74%)
Spindle	1 (0.37%)
Unknown	19 (0.7%)
Location	
Tongue	131 (48.88%)
Floor of mouth	32 (11.94%)
Alveolar ridge	37 (13.81%)
Retromolar trigone	26 (9.7%)
Buccal mucosa	20 (7.46%)
Gingiva	12 (4.48%)
Differentiation	
Well	50 (20%)
Moderate-well	11 (4.4%)
Moderate	137 (54.8%)
Moderate-poorly	15 (6%)
Poorly	37 (14.8%)
Perinerural invasion	
No	172 (68.53%)
Yes	79 (31.47%)
Extranodal extension	
No	194 (72.39%)
Yes	74 (27.61%)
Margins	
Positive	17 (6.64%)
Negative	239(93.36%)