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Positive Margins And Other Factors Associated With Survival In Early Stage Oral Cavity Squamous Cell Cancer: Prognostic Impact And Quality Measure

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Positive Margins and Other Factors Associated with Survival in Early Stage Oral Cavity Squamous Cell Cancer: Prognostic Impact and Quality Measure

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Objective: The aim of this work was to determine the prognostic impact of positive margins in early oral cavity squamous cell cancer and evaluate the utility of positive margin incidence as a surgical quality measure.

Study design and setting: Retrospective analysis of the National Cancer Data Base

Subjects and methods: Patients with oral cavity squamous cell cancer diagnosed between 1998 and 2011 who were treated with surgical resection were sampled. Univariate and multivariate analyses of overall survival and incidence of positive margins were performed.

Results: A total of 6,830 patients were included in the survival analysis. Overall survival at 5-years was 69.7%. On multivariate analysis, neck dissection (HR 0.79, 95% CI 0.76-0.94) and treatment at academic/research institutions (HR 0.88, 95% CI 1.01-0.99) were associated with improved survival, while positive margins (HR 1.27, 95% CI 1.08-1.49), insurance through Medicare (HR 1.45, 95% CI 1.25-1.69) or Medicaid (HR 1.96, 95% CI 1.60-2.39), and adjuvant radiotherapy (HR 1.31, 95% CI 1.16-1.49), or adjuvant chemotherapy (HR 1.34, 95% CI 1.03-1.75) were associated with compromised survival. A total of 20,602 early oral cancer patients were identified for analysis of factors associated with positive margins. Margin status was reported in 94.8% of cases, and positive margins occurred in 7.5% of those cases. Incidence of positive margins by institution varied from 0% to 43.8%, with median incidence of 7.1%. Positive margins were associated with clinical factors including stage II disease (OR 1.75; 95% CI 1.55-1.98), intermediate grade (OR 1.20; 95% CI 1.04-1.37), high grade (OR 1.68; 95% CI 1.39-2.03), and floor of mouth (OR 1.78; 95% CI 1.52-2.08), buccal mucosa (OR 2.06 95% CI 1.59-2.68), and retromolar locations (OR 2.40, 95% CI 1.85-3.11). Positive

margins were also associated with treatment at non-academic cancer centers (OR 1.23; 95% CI 1.04-1.44) and institutions with low oral cancer case volume (OR 1.45; 95% CI 1.23-1.69).

Conclusion: Positive margins portend a poor prognosis in early oral squamous cell cancer. The incidence of positive margins is associated with clinicopathologic factors as well as treatment and institution factors and can serve as an effective surgical quality measure for early oral cavity squamous cell cancer.

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Epidemiology:

Head and neck cancer is a significant cause of mortality in the United States, with approximately 53,000 cases and 11,500 deaths predicted in 2014. Combining the sub-sites of the oral cavity, pharynx and larynx, head and neck cancer is the 10th most common cancer in the United States accounting for approximately 3% of all adult malignancies[1]. The oral cavity is the most common site of head and neck cancer and oral cavity squamous cell cancer (OCSCC) accounts for the vast majority of oral cancer cases in the United States with approximately 27,000 cases and 5,500 deaths predicted in 2014[2]. OCSCC is 4 times more common in males than females, and occurs more frequently in African Americans[1,3]. It is primarily a disease of the adult population, with 95% of cases occurring in patients over 40 years and 45% in patients over 65 years[4].

The majority of OCSCC cases are related to alcohol or tobacco use and are preventable[5]. The incidence of oral cancer in the United States has been decreasing over the last 3 decades, a trend thought to be related to decreasing smoking rates[6]. However, this trend is non-uniform among various demographic and social groups, suggesting continued need for education and early detection and prevention programs, particularly in groups of low socioeconomic status[7]. Multiple studies have found that public knowledge of oral cancer signs and symptoms is low[8-12]. Furthermore, despite decreasing overall incidence, the stage at presentation of oral cancer has remained constant over the last several decades[13] and the largest contributor to delay in diagnosis has been the period between patients first noticing a lesion and subsequently presenting to a care provider[14].

These trends suggest that improved awareness of oral cancer could lead to decreased incidence as well as earlier diagnosis, and that increased educational and awareness efforts could be practical and cost-effective strategies to decrease the burden of this preventable disease.

Clinical Presentation

OCSCC is frequently asymptomatic and therefore often does not prompt patient self-referral in its early stages[15]. The most common sites for tumor formation within the oral cavity are the tongue (40%) and the floor of mouth (30%), although OCSCC is known to present in other sites, including the lip, gum, buccal mucosa, and retromolar trigone[16]. Approximately 60% of patients with OCSCC present with only localized disease and approximately 30% present with regional lymph node involvement or distant metastases[4].

OCSCC frequently arises from one of several premalignant lesions. Leukoplakia is a white patch or plaque which cannot be removed and cannot be attributed to a pre-existing disease process[17]. Approximately 20% of leukoplakias represent an invasive squamous cell carcinoma or a carcinoma in situ at the time of presentation[18], and non-malignant leukoplakias have a rate of transformation to squamous cell carcinoma of approximately 1% per year[19]. Likewise, erythroplakia is defined as a red patch or plaque which cannot be removed and is not attributable to a pre-existing disease process. Erythroplakia carries a worse prognosis than leukoplakia, with 90% of lesions representing invasive OCSCC or carcinoma in situ and many of the remaining 10% exhibiting mild to moderate dysplasia[15]. Therefore, any unidentified red or white oral

lesion demands prompt evaluation, and many non-malignant lesions require surgical removal.

Diagnosis and Staging

Patients with oral lesions suspicious for OCSCC should be evaluated with a thorough history and physical examination including visual and tactile examination of the nasal cavity, oral cavity, oropharynx, and neck, as well as indirect mirror or direct fiberoptic examination of the larynx and hypopharynx. Histologic diagnosis is made with fine needle aspiration. Imaging studies (PET or CT) may be indicated to identify metastases to the neck lymph node basin or to sites of the lower aerodigestive tract[20].

Primary tumor	
T0	No evidence of primary tumor
T1	Tumor is ≤ 2 cm in size
T2	Tumor is > 2 cm and ≤ 4 cm in size
T3	Tumor is > 4 cm
T4a	Tumor is growing into nearby structures, including the bones of the jaw of face, deep muscles of tongue, facial skin, maxillary sinus, or for lip cancers, the floor of mouth or inferior alveolar nerve
T4b	Tumor is growing into deeper tissues, including the pterygoid plates, skull base, masticator space, or surrounds the carotid artery.
Lymph nodes	
N0	No lymph node involvement
N1	One ipsilateral lymph node involved, ≤ 3 cm in size
N2a	One ipsilateral lymph node involved, > 3 cm and ≤ 6 cm in size
N2b	Two or more ipsilateral lymph nodes involved, all ≤ 6 cm in size
N2c	At least one contralateral lymph node involved, ≤ 6 cm in size
N3	At least one lymph node involved and > 6 cm in size
Distant metastasis	
M0	No distant spread
M1	Distant metastasis present

Table 1: Staging schema for OCSCC. Adapted from the American Cancer Society[21].

Staging of OCSCC is done by TNM classification (Table 1). Overall stage 1 disease refers to T1N0M0 tumors, stage 2 to T2N0M0, stage 3 to T3N0M0 or T1-3N1M0, and stage 4 to any T4, N2, N3, or M1 lesions[21]. "Early stage" in this work refers to stage 1 and 2 disease, and includes only tumors of diameter < 4 cm without invasion into adjacent structures, lymph node involvement, or distant metastasis.

Treatment

When possible, the treatment for OCSCC is surgical resection, with adjuvant post-operative radiotherapy (RT) or chemoradiotherapy (CRT) indicated for certain high risk clinical or pathologic features[22]. Adjuvant RT is usually recommended in the treatment of patients whose tumors are pathologically staged T3, T4, N2, or N3 or exhibit perineural invasion or vascular embolism, while CRT is usually recommended for cases of extracapsular nodal spread or positive margins which cannot be re-resected. The majority of patients with OCSCC present with early stage (stage I or II) disease and are treated with surgical resection alone, with adjuvant therapy only indicated for positive resection margins and several other high risk features[23,24]. Therefore, the success of treatment of OCSCC, particularly in its early stages, depends on the adequacy of surgical management.

Prognosis

Prognosis in OCSCC depends on many factors including patient age, stage at diagnosis, and primary site of disease. Average 5-year relative survival for patients with OCSCC is approximately 65%[25,26]. Patients with early stage OCSCC have a 5-year

survival ranging from approximately 75% for tongue and floor of mouth cancers to 93% for lip cancers[26].

The effects of several pathologic and clinical factors on survival in early OCSCC are unknown or debated. Histologic grade was previously thought not to affect prognosis in early OCSCC but recent reports have suggested a more important role[27]. Some reports suggest that patients treated for head and neck cancer in academic or research institutions have favorable outcomes compared to those treated in community cancer centers, mirroring trends in cancers of other tissues[28]. Ipsilateral neck dissection and adjuvant RT or CRT are indicated for OCSCC with high risk features; however, these recommendations have not been validated by comprehensive prospective trial in early OCSCC, and the survival benefit of these interventions is unknown[29]. Finally, the goal of surgery in OCSCC is complete eradication of tumor; however, positive margins have been reported following up to 21% of oral cancer resections and are more common in oral cancer than in other cancers of the head and neck[30]. The effect of positive margins on prognosis in early OCSCC is a subject of confusion and debate[31-33].

Positive Margins in Early OCSCC

A positive surgical margin refers to remaining tumor at or close to the line of surgical resection. For decades, there has been consensus among practicing head and neck surgeons that the largest cause of death in patients with squamous cell carcinomas of the head and neck was the failure to completely eradicate the primary tumor site[31,34]. However, there is significant evidence both to support and to refute this claim, particularly in the setting of OCSCC. Several issues have complicated the analysis of

positive margins and their effect on prognosis in early OCSCC. Firstly, the definitions of "positive," "negative," and "close" margins vary among both head and neck surgeons and pathologists. A survey of 476 members of the American Head and Neck Society conducted in 2005 demonstrated the variability in these definitions. In defining what classified a margin as "clear," the most common response among head and neck surgeons was a histologically clear margin of 5 mm, selected by 46% of responders. However, other metrics, including an absence of ink on the tumor (14%), a 1 cm gross margin (11%), one microscopic high powered field (8%), and other measurements or combinations therein, were used by significant proportions of the surveyed group[35]. The definition of a "close" margin varied similarly. Furthermore, the pathological definition of tumor presence was also inconsistently defined. Carcinoma in situ at the margin was considered positive by 83% of respondents, whereas dysplasia at the margin was considered positive by 17%. Finally, tremendous variation exists among surgeons and pathologists regarding what constitutes a positive margin, both in terms of width and pathologic or histologic characteristics[35]. Margin harvesting techniques differ as well, with some surgeons sending tumor specimen alone for margin evaluation and others harvesting additional tissue of varying size. This variability complicates any attempt at multi-institutional analysis or meta-analysis of previous work to determine the effect of positive margins in early OCSCC.

Nevertheless, there have been many studies over the last several decades analyzing the effects of surgical margins on patient outcomes in head and neck cancers. Several single-institution reports have demonstrated that positive margins portend significantly greater mortality and poorer prognosis. Chen et al. reported 270 patients

with head and neck carcinoma of varying stages using a definition of margin adequacy of ≥5mm. In patients with positive margins, 5 year disease free survival rates were 7% with a local recurrence rate of 55%, compared to 39% and 17% for patients with negative margins[36]. Liao et al. reported a large cohort of 827 patients who had undergone surgery for OCSCC and reported that a standard margin of 7 mm had the highest hazard ratio between negative and positive resection margins, with 5-year survival rates of 68.5% and 62.5%, respectively ($p = 0.04$)[23]. In this study, 41% of patients had early stage disease. Garzino-Demo et al. reported a similar cohort of 245 patients with resected OCSCC, in which the 5-year survival in patients with positive margins was 47.7%, compared to 65.0% in those with negative margins; rates of recurrence and the effects of margins for individual tumor stages were not reported[37]. Nason and colleagues reported a cohort of 277 patients with approximately equal groups with involved, ≤ 2 mm, 3-4 mm, and > 4 mm margins, and showed that each 1 mm increase in clear margin was independently associated with a decrease in 5-year risk of mortality of 8%[38]. These studies suggest that positive margins lead to poorer prognosis in OCSCC. However, these analyses did not examine early OCSCC specifically and could have been confounded by the fact that larger or more advanced tumors or tumors which were closely related to vital structures would be more difficult to excise with negative margins and would incidentally have greater associated mortality.

Other studies demonstrate more equivocal results regarding the association between positive margins survival in head and neck and oral cancers. Loree and Strong reported 398 patients with oral cancer, 129 of which (32%) had positive margins defined by a 5 mm standard. Combined, patients with positive margins had double the rate of

local recurrence over 5 years compared to those with negative margins (36% vs. 18%) and likewise had slightly decreased 5-year survival rates (52% vs 60%, $p = 0.025$)[39]. However, these relationships were not conserved specifically among early stage oral cancers (defined as T1-2, N0 tumors); while there was an increase in local recurrence among the positive margin group (25% vs. 17%), there was no statistically significant difference in 5 year survival. Jones and colleagues reported 352 patients with squamous cell carcinoma of the head and neck, 49 of which had positive resection margins. Patients with positive margins had greater risk of disease recurrence (66% vs. 47%, $p = 0.03$) and lower survival ($p = 0.02$), but these associations did not persist on multivariate analysis[30]. Amaral et al. reported a cohort of 193 patients with stage I and II cancer of the oral cavity and found no significant difference in 5 year disease free or overall survival between patients with positive margins and those with negative margins ($p = 0.381$)[40]. In this study, positive margins were designated as the presence of carcinoma in situ at the margin itself. Chen et al. reported a cohort of 407 patients with early stage OCSCC and demonstrated a significant difference in disease free and overall survival at 5 years between pathologically positive, close, and safe margins, with 50.8%, 61.4%, and 78.2% disease free survival ($p = 0.002$) and 70.1%, 85.1%, and 91.2% overall survival ($p = 0.003$), respectively. However, neither metric demonstrated statistical significance when accounting for the presence of other adverse clinical or pathologic features, such as perineural or lymphovascular invasion[33].

Prior reports investigating the effects of margin status on survival have been been single-institution studies with small sample sizes. These data are inconsistent and contradictory, and few studies have examined positive margins specifically in early stage

OCSCC. As a result, the impact of positive margins in early OCSCC remains a subject of debate. A standardized, population-level analysis of the association between margin status and survival would therefore be very informative in the treatment of this disease.

Quality measures

Care quality standards are essential for clinical and economic success of oncologic practice in the evolving global healthcare environment[41]. As healthcare in the United States moves towards a value-based care system, the importance of quality indicators and their role in determining care and reimbursement schemata will continue to grow. The Patient Protection and Affordable Care Act already includes provisions for reduction of hospital payments based on failures in certain quality metrics for certain conditions, such as 30-day readmission rates for heart failure, pneumonia, and acute myocardial infarction admissions[42]. However, at this point, no quality measures have been adopted for surgical procedures beyond a single-institution level. Several quality measures have been suggested in the past for the treatment of oral cancer[43]. Among these metrics were compliance with standards of pre-operative documentation (smoking and alcohol history, tumor description, imaging), intraoperative documentation (frozen sections, pathologic reporting of tumor size, grade, lymphovascular and perineural invasion), and integrity of follow-up care[44]. No measures have been suggested that reflect the quality of the surgical resection itself.

In order to be useful as a quality indicator, a metric must meet several criteria. The metric 1) must be feasible to measure, 2) must be under the influence of care providers, 3) must have strong evidence suggesting that it affects important outcomes,

and 4) must have variable levels, such that substandard performance exists based on it[44,45]. The status of surgical margins is largely under the control of the attending surgeon and surgical team[46], and is one of few measures that directly reflects events occurring within the operating room. Positive margins have been associated with increased risk of disease recurrence, and successful initial surgical treatment is vital for cure in head and neck cancers, with risk of disease-related death increasing up to 16-fold after recurrence of disease[47]. Therefore, the incidence of positive margins is a promising candidate for surgical quality measurement in early OCSCC, particularly if positive margins are well-reported, are shown to exert an independent detrimental effect on survival, and their incidence is shown to vary across institutions. Margin status is particularly relevant for early stage OCSCC, as negative margins should be achievable in nearly all cases.

Statement of purpose and hypotheses

The aims of this work were to report the association between positive margins as well as other clinical or pathologic features and survival in early stage OCSCC, to report incidence and trends of positive margins in early OCSCC, and to evaluate the suitability of the incidence of positive margins as a quality measure for OCSCC surgery. Data from the Commission on Cancer's National Cancer Data Base (NCDB) was examined to evaluate surgical margins on a population level. Owing to the large sample size afforded by the NCDB, this work analyzes positive margins with much greater statistical power than prior work, and without the potential for institutional bias. We hypothesized that positive margins would be independently associated with decreased survival, and that margin status would be well-reported and would vary with both clinical and non-clinical

factors. Therefore, we believe margin status meets criteria be a valuable quality measure for surgery in early OCSCC.

Methods:

Data source:

The NCDB is a nationwide, hospital-based cancer registry jointly sponsored by the American College of Surgeon's Commission on Cancer (CoC) and the American Cancer Society. It is the world's largest oncology outcomes database, capturing approximately 70% of all cancer cases in the United States[48]. Data reported to the National Cancer Data Base are retrospective and compliant with the requirements of the Health Insurance Portability and Accountability Act[49]. The Yale University Institutional Review Board (IRB) determined this study exempt from IRB review.

Study population and outcomes:

Survival analysis

Patients diagnosed with stage 1 or 2 OCSCC between 2003 and 2006 were identified using *International Classification of Diseases for Oncology, Third Edition* (ICD-O-3) topography codes 8052, 8070-8078, 8083, and 8084. Patients who did not undergo surgery, those with multiple malignant primary tumors, and those with undocumented pathologic stage were excluded from analysis. Overall and 5-year survival were investigated as outcomes.

Quality measure analysis

Patients diagnosed with stage I or II OCSCC between 1998 and 2011 were identified using the ICD-O-3 topography codes 8052, 8070-8078, 8083, and 8084. Patients with multiple primary malignant tumors, undocumented pathologic stage, and those treated without surgery or with local tumor destruction alone were excluded from analysis. Status of surgical margins was investigated as an outcome variable.

Predictor variables

Factors investigated for association with overall survival included treatment factors (radiation, chemotherapy, neck dissection, surgical margins, facility type, facility case volume and insurance) and non-treatment factors (patient age, race, gender, and comorbidity index, and tumor primary site, pathologic stage, and grade). Radiation, chemotherapy, and neck dissection were reported as "received" or "not received," and "regional lymph node surgery" as reported by the NCDB was considered to constitute neck dissection. Margin status was divided into positive margins (reported as "microscopic residual tumor," "macroscopic residual tumor," or "residual tumor, NOS,") and negative margins ("No residual tumor"). Residual tumor was considered present by the NCDB if it was within 5 mm of the margin, and final margin status was reported in cases of re-resection. Facility type was based on CoC accreditation criteria and was divided into academic / research programs and non-academic programs, which included community cancer programs, comprehensive community cancer programs, and other programs[50]. Case volume was calculated as average number of oral cancer cases reported by an institution to the NCDB per year from 1998-2011, and was divided into categories

of ≤10 and >10 cases / year. Insurance was reported as private, Medicare, Medicaid, other government (including active military personnel, TRICARE, and Veterans Affairs), and no insurance. Race was reported as white, African American or black, and other. Comorbid conditions were analyzed using the Deyo modified Charlson comorbidity index[51], and divided into indices of 0 and ≥1. Tumor primary site was divided into tongue (ICD-O-3 topography codes C020-9), lip (C000-9), floor of mouth (C040-9), gum and hard palate (C030-9 and C050), retromolar trigone (C062), buccal mucosa (C060) and other mouth, including unspecified or overlapping sites and tumors of the vestibule of mouth. Tumors of the base of tongue, lingual tonsil, uvula, and soft palate, traditionally considered sites of the oropharynx, were excluded. Tumors were staged according to AJCC 7th edition guidelines for pathologic staging. Grade was reported as low grade (well differentiated), intermediate grade (moderately differentiated), and high grade (poorly differentiated or anaplastic).

Factors examined for association with margin status were patient age, race, gender, comorbidity index, insurance status, and travel distance to treatment facility; tumor primary site, stage, and grade; and facility type, location, and oral cancer case volume. Travel distance was determined as "great circle" distance from the center of the patient's home zip code to the center of the reporting facility's zip code, and was divided into categories of ≤ 50 miles and > 50 miles. Facility location was reported as one of nine United States Census Bureau divisions. Oral cancer case volume was calculated as the average number of oral cancer cases reported to the NCDB per year by institution, and was divided into categories of ≤ 20 cases and > 20 cases per year. All other covariates were analyzed as for the survival analysis.

Statistical analysis

All statistical analysis was performed using SPSS statistical software for Windows, version 20 (IBM, Armonk, New York). Pearson's chi-squared tests were used to determine association between categorical variables and overall survival or margin status. Overall and 5 year survival were calculated by the Kaplan-Meier method. Cases were entered by the reported date of their last contact or death in months from diagnosis. Significance in survival differences was determined by the log-rank test. Multivariate analysis was conducted by Cox logistic regression with survival effects of covariates reported as hazard ratios (HRs). Binary logistic regression was used to identify independent predictors of increased positive margin incidence, with an inclusion threshold of $p < 0.1$. Patient comorbidity index was found not to contribute to the regression model for associations with positive margins ($p = 0.328$) and was removed from analysis to allow inclusion of cases with missing values. Effects of categorical variables were reported as odds ratios (ORs), while the effect of patient age was measured as OR per additional year. Cases with covariate data missing or unknown were excluded from multivariate analyses. Margins were also evaluated on an institutional level, sampling institutions reporting ≥10 total cases meeting our criteria to the NCDB. These data were displayed in box-and-whisker plots depicting the median (line within the box), 25^{th} to 75^{th} percentiles (bottom and top borders of the box), and 1.5 interquartile ranges above and below the 75^{th} and 25^{th} percentiles, respectively (whiskers), with outliers individually marked. The incidence of positive margins was compared between institutions divided by facility type and case volume, with statistical significance

calculated by non-parametric tests. Institutions were not weighted based on number of reported cases. Significance in all cases was set at $p < 0.05$.

Results:

Association between Margin Status and Survival

Patient, disease and treatment characteristics of 6,830 cases of surgically treated early OCSCC are shown in Table 2. Age was normally distributed with a mean of 61.7 years; 61.5% of subjects were male, and 90.4% identified as white. Overall survival at 5 years was 69.7%. Univariate analysis of survival revealed that positive margins were associated with compromised survival (5-year overall survival 53.8% vs. 71.5%, $p < 0.001$, Figure 1). Other treatment factors associated with decreased survival included radiation ($p < 0.001$), chemotherapy ($p < 0.001$), treatment at non-academic cancer centers ($p < 0.001$), treatment at low-volume facilities ($p < 0.001$), and surgery without neck dissection ($p = 0.001$, Table 3). The difference in 5-year overall survival between patients who received and did not receive neck dissections was greater in stage 2 disease (63.9% vs. 49.1%, respectively, $p < 0.001$) than in stage 1 disease (78.3% vs. 74.2%, $p = 0.001$). The difference in 5-year overall survival between patients who received and did not receive radiation was greater in stage 1 disease (63.5% vs. 77.6%, respectively, $p < 0.001$) than in stage 2 disease (53.5% vs. 61.2%, $p = 0.002$).

Treatment factors		**% (*n*=6,830)**
Neck Dissection	No	50.5
	Yes	48.3
	Unknown	1.2
Radiation	No	80.1
	Yes	18.0
	Unknown	1.9
Chemotherapy	No	95.0
	Yes	2.7
	Unknown	2.2
Facility type[a]	ARP	46.6
	NAP	53.4
Case volume	≤10 per year	29.1
	>10 per year	70.9
Insurance	Private insurance	45.0
	No insurance	4.4
	Medicaid	5.2
	Medicare	40.1
	Other government insurance	0.8
	Unknown	4.4
Margins	Negative	88.1
	Positive	6.8
	Unknown	5.2

Non-treatment factors		**% (*n*=6,830)**
Age	≤ 45 years	13.7
	46-55 years	21.6
	56-65 years	23.5
	66-75 years	21.5
	> 75 years	19.6
Gender	Male	61.5
	Female	38.5
Race	White	90.4
	AA[b]	3.6
	Other race	3.9
	Unknown	2.0
Comorbidity score	0	81.6
	≥ 1	18.4
Pathologic Stage	Stage 1	64.9
	Stage 2	35.1
Primary Site	Tongue	48.8
	Lip	15.8
	Floor of mouth	16.7
	Gum / hard palate	7.7
	Retromolar trigone	4.0
	Buccal mucosa	4.8
	Other mouth	2.2
Grade	Low grade	29.1
	Intermediate grade	47.3
	High grade	11.1
	Unknown	12.6

Table 2: Patient, disease, and treatment characteristics of sample pool.
[a]ARP, academic or research program; NAP, non-academic program
[b]African American or Black

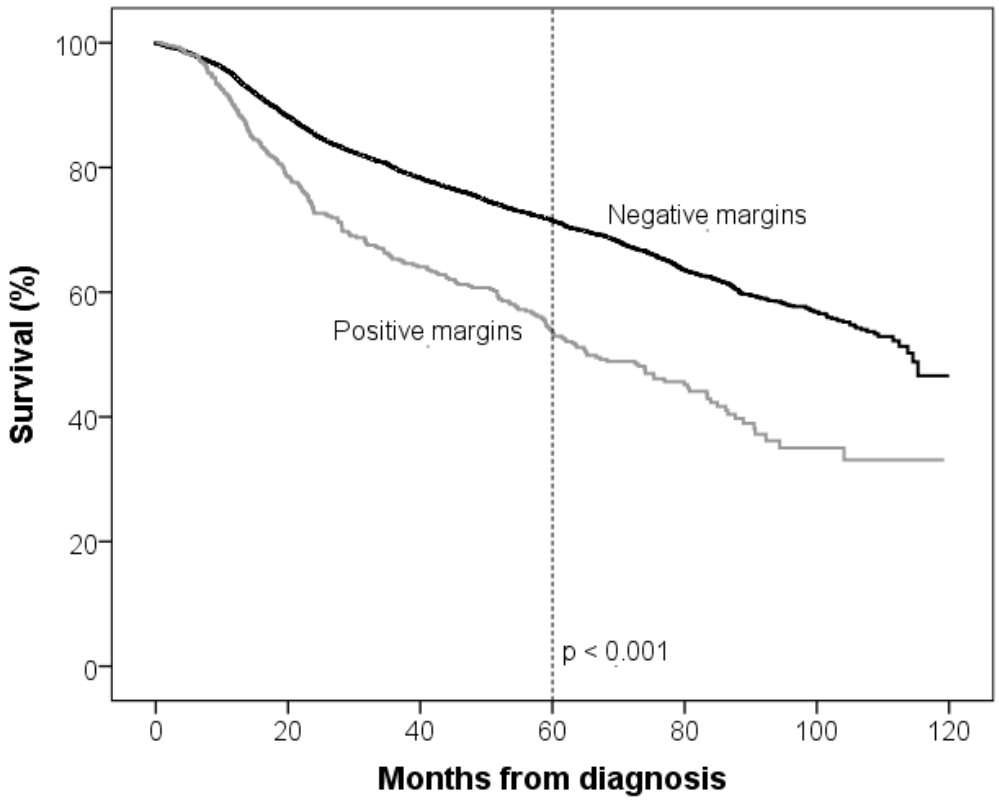

Figure 1: Kaplan-Meier curve of overall survival, positive margins vs. negative margins.

Treatment factors		**OS % (SE)[a]**	***p* value**
Neck Dissection	No	68.0 (0.8)	0.001
	Yes	71.7 (0.8)	
Radiation	No	72.7 (0.6)	< 0.001
	Yes	57.5 (1.5)	
Chemotherapy	No	69.9 (0.6)	< 0.001
	Yes	53.5 (3.9)	
Facility type[b]	ARP	73.5 (0.8)	< 0.001
	NAP	66.4 (0.8)	
Case volume	≤10 per year	64.4 (1.2)	< 0.001
	>10 per year	71.8 (0.7)	
Insurance	Private insurance	80.0 (0.8)	< 0.001
	No insurance	78.9 (2.6)	
	Medicaid	62.2 (2.7)	
	Medicare	58.0 (1.0)	
	Other government insurance	70.9 (6.7)	
Margins	Negative	71.5 (0.6)	< 0.001
	Positive	53.8 (2.5)	

Non-treatment factors		**OS % (SE)**	***p* value**
Age	≤ 45 years	84.9 (1.3)	< 0.001
	46-55 years	79.3 (1.1)	
	56-65 years	73.8 (1.2)	
	66-75 years	66.3 (1.3)	
	> 75 years	48.6 (1.4)	
Gender	Male	70.7 (0.8)	0.05
	Female	68.2 (1.0)	
Race	White	69.5 (0.6)	0.004
	AA[c]	64.8 (3.2)	
	Other race	76.1 (2.8)	
Comorbidity score	0	72.7 (0.6)	< 0.001
	≥ 1	56.8 (1.5)	
Pathologic Stage	Stage 1	75.8 (0.7)	< 0.001
	Stage 2	58.5 (1.1)	
Primary Site	Tongue	71.8 (0.8)	< 0.001
	Lip	74.8 (1.5)	
	Floor of mouth	64.3 (1.5)	
	Gum / hard palate	67.4 (2.1)	
	Retromolar trigone	67.7 (3.0)	
	Buccal mucosa	60.4 (2.8)	
	Other mouth	62.5 (4.2)	
Grade	Low grade	75.0 (1.0)	< 0.001
	Intermediate grade	66.9 (0.9)	
	High grade	60.1 (1.9)	

Table 3: Univariate survival by treatment and non-treatment characteristics.
[a]OS, overall 5-year survival; SE, standard error
[b]ARP, academic or research program; NAP, non-academic program
[c]African American or Black

Multivariate analysis revealed that positive margins (HR 1.27, 95% CI 1.08-1.49), radiation (HR 1.31, 95% CI 1.16-1.49), and chemotherapy (HR 1.34, 95% CI 1.03-1.75) were associated with reduced survival, while neck dissection (HR 0.85, 95% CI 0.76-0.94) was associated with improved survival (Table 4). Treatment at non-academic cancer centers (HR 1.13, 95% CI 1.01-1.26) and insurance through Medicaid (HR 1.96, 95% CI 1.60-2.39) and Medicare (HR 1.45, 95% CI 1.25-1.69) were also associated with compromised survival. Patient and disease features that were associated with compromised survival included age > 75 (HR 3.65, 95% CI 2.85-4.66), comorbidity score ≥ 1 (HR 1.45, 95% CI 1.30-1.61), stage 2 disease (HR 1.56, 95% CI 1.41-1.73), disease of the floor of mouth (HR 1.58, 95% CI 1.39-1.80) and buccal mucosa (HR 1.39, 95% CI 1.13-1.71), intermediate grade (HR 1.27, 95% CI 1.14-1.43), and high grade (HR 1.56, 95% CI 1.33-1.82).

Differences between academic and non-academic cancer centers were further examined by evaluating differences in treatment trends between these two facility types. Patients treated at academic / research cancer centers were more likely to receive a neck dissection ($p < 0.001$) and less likely to receive radiation ($p < 0.001$) or to have positive margins ($p < 0.001$) than those treated at non-academic centers (Table 5). Pathologic characteristics, including stage ($p = 0.9$) and grade ($p = 0.2$), did not vary between patients at academic and non-academic cancer centers.

			HR (95% CI)[a]	*p* value
Treatment factors				
Neck Dissection		No	Ref.	0.003
		Yes	0.85 (0.76-0.94)	
Radiation		No	Ref.	< 0.001
		Yes	1.31 (1.16-1.49)	
Chemotherapy		No	Ref.	0.03
		Yes	1.34 (1.03-1.75)	
Facility type[b]		ARP	Ref.	0.03
		NAP	1.13 (1.01-1.26)	
Insurance	Private insurance		Ref.	< 0.001
	No insurance		1.18 (0.88-1.58)	
	Medicaid		1.96 (1.60-2.39)	
	Medicare		1.45 (1.25-1.69)	
	Other government insurance		1.42 (0.83-2.42)	
Margins		Negative	Ref.	0.005
		Positive	1.27 (1.08-1.49)	
Non-treatment factors				
Age	≤ 45 years		Ref.	< 0.001
	46-55 years		1.29 (1.03-1.62)	
	56-65 years		1.69 (1.35-2.10)	
	66-75 years		2.03 (1.59-2.59)	
	> 75 years		3.65 (2.85-4.66)	
Comorbidity score		0	Ref.	< 0.001
		≥ 1	1.45 (1.30-1.61)	
Pathologic Stage		Stage 1	Ref.	< 0.001
		Stage 2	1.56 (1.41-1.73)	
Primary Site		Lip	Ref.	< 0.001
		Tongue	1.31 (0.97-1.76)	
		Floor of mouth	1.58 (1.39-1.80)	
		Gum / hard palate	1.11 (0.93-1.33)	
		Retromolar trigone	1.17 (0.91-1.50)	
		Buccal mucosa	1.39 (1.13-1.71)	
		Other mouth	1.62 (1.18-2.22)	
Grade		Low grade	Ref.	< 0.001
		Intermediate grade	1.27 (1.14-1.43)	
		High grade	1.56 (1.33-1.82)	

Table 4: Multivariate analysis of treatment and non-treatment factors' associations with overall survival. Variables which were not significant contributors to the multivariate model ($p > 0.05$) are not shown.
[a]HR, adjusted hazard ratio
[b]ARP, academic or research program; NAP, non-academic program
[c]African American or Black

Treatment characteristic		ARPs (%)	NAPs (%)	*p* value
Neck Dissection		59.2	40.1	< 0.001
Radiation		15.7	20.7	< 0.001
Chemotherapy		2.9	2.7	0.7
Positive margins		5.5	8.6	< 0.001
Case volume	>10 per year	94.8	50.1	< 0.001
Insurance	Private insurance	48.6	45.9	< 0.001
	No insurance	5.7	3.8	
	Medicaid	6.5	4.5	
	Medicare	38.3	45.1	
	Other government insurance	0.9	0.8	

Table 5: Comparison of treatment factors between academic / research programs (ARPs) and non-academic programs (NAPs).

Incidence of Positive Margins and Quality of Care

Patient, disease, and facility characteristics of 20,602 cases of early OCSCC receiving surgical treatment are shown in Table 6. Age was normally distributed with a mean age of 61.7 years; 61.5% of patients were male, while 91.2% self-identified as white. Margin status was reported in 94.8% of cases, and 7.5% of those reported positive margins. On univariate analysis, factors associated with increased incidence of positive margins included treatment at non-academic cancer programs and at institutions with oral cancer case volume ≤ 20 cases per year ($p < 0.001$, Table 7).

Characteristic		**% (*n* = 20602)**
Average age		61.7 years
Gender	Male	61.5
	Female	38.5
Race	White	91.2
	AA[b]	3.7
	Other race	3.1
Comorbidity index	0	48.3
	≥1	11.8
	Unknown	39.9
Stage	Stage 1	66.1
	Stage 2	33.9
Site	Tongue	46.5
	Lip	18.4
	Floor of mouth	17.1
	Gum / hard palate	7.6
	Retromolar trigone	3.7
	Buccal mucosa	4.1
	Other mouth	2.4
Grade	Low grade	30.8
	Intermediate grade	46.1
	High grade	10.3
Insurance	Private insurance	45.4
	No insurance	4.4
	Medicaid	4.9
	Medicare	39.8
	Other government insurance	0.8
Facility type[c]	ARP	44.5
	NAP	55.5
Volume	≤20 cases / year	52.3
	>20 cases / year	47.7
Travel distance	≤50 miles	79.0
	>50 miles	16.9
Location	South Atlantic	22.1
	Middle Atlantic	12.1
	New England	4.6
	East North Central	16.3
	East South Central	8.6
	West North Central	9.0
	West South Central	9.7
	Mountain	4.5
	Pacific	13.0
Margins	Negative	87.7
	Positive	7.1
	Unknown / unreported	5.2

Table 6: Demographic, disease, and treatment characteristics of NCDB sample pool. Percentages may not sum to 100% due to missing or unreported data.
[b]African American or Black
[c]ARP, academic / research cancer program; NAP, non-academic cancer program

Characteristic		*n*[a]	% Positive margins	*p*-value
Gender	Male	12135	7.6	NS
	Female	7495	7.3	
Race	White	17814	7.4	0.002
	AA[b]	711	10.5	
	Other race	605	7.1	
Comorbidity index	0	9571	7.0	0.008
	≥1	2396	8.6	
Stage	Stage 1	13012	5.8	< 0.0005
	Stage 2	6518	10.9	
Site	Tongue	9118	6.0	< 0.0005
	Lip	3625	5.7	
	Floor of mouth	3340	10.3	
	Gum / hard palate	1458	8.2	
	Retromolar trigone	711	13.2	
	Buccal mucosa	803	11.3	
	Other mouth	475	10.9	
Grade	Low grade	6052	6.3	< 0.0005
	Intermediate grade	9004	8.0	
	High grade	1984	10.7	
Insurance	Private insurance	9054	6.7	< 0.0005
	No insurance	865	8.7	
	Medicaid	964	8.4	
	Medicare	7920	8.0	
	Other government insurance	159	15.1	
Facility type[c]	ARP	8494	6.0	< 0.0005
	NAP	11036	8.6	
Volume	≤20 cases / year	10377	8.8	< 0.0005
	>20 cases / year	9153	5.9	
Travel distance	≤50 miles	15562	7.8	< 0.0005
	>50 miles	3154	5.7	
Location	South Atlantic	4468	7.5	< 0.0005
	Middle Atlantic	2453	6.7	
	New England	926	10.9	
	East North Central	3165	7.7	
	East South Central	1744	6.4	
	West North Central	1779	5.3	
	West South Central	1650	8.1	
	Mountain	864	6.1	
	Pacific	2481	8.9	
Total		19630	7.5	

Table 7: Univariate analysis of factors associated with positive margins.
[a]Totals may be unequal due to missing data; cases with missing margin status are excluded
[b]African American or Black
[c]ARP, academic / research cancer program; NAP, non-academic cancer program

Institutional incidence of positive margins among 541 facilities reporting at least 10 total cases to the NCDB ranged from 0% to 43.8%, with a median incidence of 7.1% (Figure 2). The median incidence of positive margins among institutions with oral cancer case volume >20 per year was 5.9% compared to 7.7% for institutions reporting ≤ 20 cases/year ($p < 0.0005$). The median incidence of positive margins among academic / research cancer centers was 6.4% compared to 7.7% for non-academic cancer centers ($p = 0.028$). Over 50% of facilities documented margin status in 100% of reported cases, and 93% of facilities documented margin status in at least 90% of reported cases.

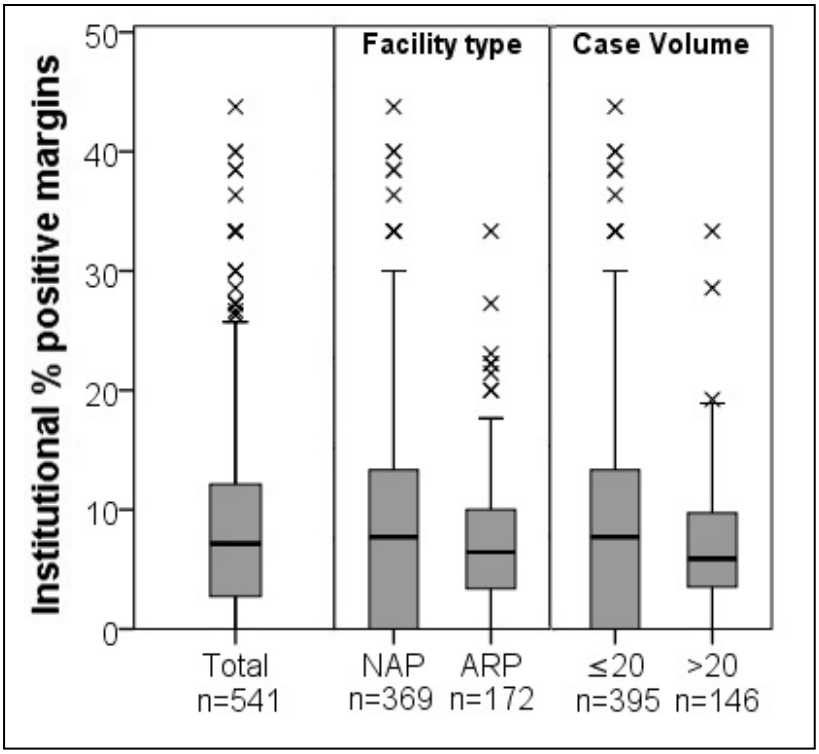

Figure 2: Institutional incidence of positive margins among facilities reporting ≥20 cases to the NCDB. Case volume in OCSCC cases annually (average); line within box, median; bottom and top borders of box, 25th and 75th percentiles; whiskers, 1.5 interquartile ranges above and below the 75th and 25th percentiles; outliers individually marked. NAP, non-academic cancer program; ARP, academic / research cancer program.

Multivariate analysis (Table 8) revealed that clinical factors most strongly associated with positive margins were stage II disease (OR 1.75, 95% CI 1.55-1.98), high

grade disease (OR 1.68 relative to low grade disease, 95% CI 1.39-2.03), and floor of mouth (OR 1.78, 95% CI 1.52-2.08), retromolar trigone (OR 2.40, 95% CI 1.85-3.11), and buccal mucosa (OR 2.06, 95% CI 1.59-2.68) tumor sites. Treatment at non-academic cancer centers (OR 1.23, 95% CI 1.08-1.44) and treatment in New England (OR 1.42 relative to South Atlantic reference, 95% CI 1.08-1.86) were also independently associated with increased incidence of positive margins, while treatment at institutions reporting >20 oral cancer cases annually (OR 0.70; 95% CI 0.59-0.82) and travel distance > 50 miles (OR 0.81; 95% CI 0.67-0.98) were associated with decreased positive margin incidence.

Characteristic		**OR (95% CI)**	***p* value**
Stage	Stage 1	Ref.	< 0.0005
	Stage 2	1.75 (1.55-1.98)	
Grade	Low grade	Ref.	< 0.0005
	Intermediate grade	1.20 (1.04-1.37)	
	High grade	1.68 (1.39-2.03)	
Site	Tongue	Ref.	< 0.0005
	Lip	1.07 (0.88-1.31)	
	Floor of mouth	1.78 (1.52-2.08)	
	Gum / hard palate	1.46 (1.15-1.84)	
	Retromolar trigone	2.40 (1.85-3.11)	
	Buccal mucosa	2.06 (1.59-2.68)	
	Other mouth	1.73 (1.23-2.44)	
Facility type[b]	ARP	Ref.	0.013
	NAP	1.23 (1.04-1.44)	
Volume	≤20 cases / year	Ref.	< 0.0005
	>20 cases / year	0.70 (0.59-0.82)	
Travel distance	≤50 miles	Ref.	0.028
	>50 miles	0.81 (0.67-0.98)	
Location	South Atlantic	Ref.	0.001
	Middle Atlantic	0.91 (0.73-1.14)	
	New England	1.42 (1.08-1.86)	
	East North Central	1.00 (0.82-1.22)	
	East South Central	0.98 (0.76-1.25)	
	West North Central	0.71 (0.54-0.92)	
	West South Central	1.10 (0.87-1.40)	
	Mountain	0.96 (0.70-1.33)	
	Pacific	1.26 (1.03-1.55)	

Table 8: Multivariate analysis of factors associated with positive margins[a].
[a]Variables without significant association to margin status ($p < 0.05$) are not shown.
[b]ARP, academic / research cancer program; NAP, non-academic cancer program

Discussion:

The association of positive margins with reduced survival is widely reported, but whether this is a direct result of residual disease or a consequence of other correlated clinicopathologic or surgical features has been unclear[31,33]. There is also tremendous variation in the reported strength of association between positive margins and outcomes, with associated decreases in 5-year survival ranging from 0% to over 80%[23,32,36]. As a result, there has been ongoing debate regarding the optimal level of aggressiveness of surgery for oral cancer, with some reports recommending surgical de-escalation[52]. Our population level analysis provides compelling evidence about the importance of margin status in oral cancer and confirms the association between positive margins and poor outcomes. These findings suggest that aggressive resection to achieve negative margins is justified in OCSCC. In addition, these findings support the role of margin status in determining adjuvant therapy use in early OCSCC, although the difference in margin positivity between treatment institutions also suggests that more complete resection is possible in some patients.

Analyzing differences in survival associated with other treatment factors may reveal opportunities to improve outcomes through systems-based approaches. Overall 5-year survival in the NCDB data was consistent with reports over the last several decades at approximately 70%[25,53,54] and was associated with multiple treatment and non-treatment factors. Our data revealed associations between survival and healthcare delivery factors such as insurance and treating facility type, suggesting potential differences in quality of care that may be viable targets for quality improvement efforts. For example, care at academic / research cancer centers was associated with improved

survival compared to care at non-academic centers, consistent with prior reports on head and neck and other cancer outcomes[28,55]. This may be due to increased provider expertise, as suggested by the lower incidence of positive margins and greater oral cancer case volume among these academic centers, or increased surgical aggressiveness, as evidenced by the greater proportion of patients receiving neck dissection. However, high case volume was not associated with increased survival in the NCDB data despite traditionally being viewed as a surrogate marker for high-quality surgical care[56]. Patients insured through Medicare or Medicaid experienced compromised outcomes compared to similar patients with private insurance. Previous reports have similarly shown that lack of insurance and federal insurance are independently associated with compromised outcomes in head and neck cancers[57]. This troubling trend may reflect inconsistent treatment and follow-up due to tenuous access to healthcare or worse baseline health, which has been reported in these patients[58]. Identifying the underlying causes of the survival differences associated with these healthcare delivery factors could enable improvement of outcomes through the spread of optimal care practices.

The National Comprehensive Cancer Network (NCCN) currently recommends selective neck dissection of at minimum levels I-III for tumors of depth ≥ 4 mm and at the discretion of the surgeon for tumors of depth ≥ 2 mm[24]. However, these guidelines are based on consensus with no supporting high-level evidence[59] and the optimal treatment of a clinically N0 neck in early OCSCC with no adverse features remains a subject of controversy[60]. Neck dissection was associated with increased survival in our data, suggesting that END could confer a survival benefit to patients for whom it is not currently indicated, especially since patients who underwent neck dissection may have

had a greater initial burden of disease. The difference in survival was greater for patients with stage 2 disease compared to those with stage 1 disease, suggesting a greater prevalence of resected occult neck disease. However, the association between END and improved survival in our data should be interpreted with caution, since patients with clinically N0 disease who underwent END and were found to have occult nodal metastasis would have been pathologically restaged and thus removed from this sample pool, leading to a sampling bias. Although prospective data is lacking, a recent meta-analysis of limited existing data also reported improved survival among patients with stage 1 or 2 oral cancer and no additional high-risk features treated with END compared with observation of the neck[61]. Further study with prospective trials is necessary to elucidate the role of END in early OCSCC.

Conversely, radiation and chemotherapy were associated with decreased survival. Although positive margins are the most common indication for adjuvant CRT in early OCSCC, other high risk pathologic features, such as lymphovascular or perineural invasion, also result in the recommendation for adjuvant therapies[24]. We were unable to adjust for perineural and lymphovascular invasion in this analysis because these characteristics were not reported in the NCDB. Although these factors are inconsistently reported and their prognostic impact is debatable, they could confound the impact of radiation and chemotherapy on survival[62-64]. In addition, use of radiotherapy or chemotherapy could be a surrogate marker for less aggressive resection in patients with very localized disease. This could explain our finding that radiotherapy was associated with a greater decrease in survival in stage 1 than in stage 2 disease. Further study is necessary to determine the role of these adjuvant therapies in early stage OCSCC.

Among other covariates evaluated, patient age, pathologic stage, comorbid conditions and primary tumor site were the most influential independent predictors of survival. The deleterious effects of advanced age and tumor stage (which depends entirely on tumor size in early stage OCSCC) are well documented in oral cancer[25,64]. Tumors of the lip were associated with the best prognosis while tumors of the floor of the mouth were associated with poorest prognosis (HR 1.58 compared to tumors of the lip, $p < 0.001$), likely reflecting ease of resection and propensity toward invasion.

Histologic grade was found to carry an independent predictive role in survival, with high and intermediate grade disease independently associated with compromised survival compared with low grade disease. The prognostic relevance of grade in oral cancer has been a subject of debate for decades. Broder's classification system of squamous cell carcinomas of the head and neck was the first widely used grading system for OCSCC and was based on the proportion of differentiated to undifferentiated cells. Until recently, Broder's schema and other purely cytologic analyses were thought to have little prognostic value, and more complex grading systems incorporating other histologic signs (mitotic activity, lymphovascular invasion, mode of invasion, etc.) were favored as more accurate predictors of prognosis[27]. More recently, several single-institution reports have suggested that histologic grade alone is an independent prognostic indicator[65]. The present data from the NCDB supports these reports and suggests that poor differentiation is related to increased tumor aggression and invasion. It is therefore possible that treatment guidelines could be improved if modified to consider tumor degree of differentiation.

The NCDB data analyzed in this study allow a representative assessment of surgical margins in early OCSCC in the United States. Positive margins were present in 7.5% of cases, which is within the wide range demonstrated in prior reports on OCSCC[33,38,66]. Patients with stage II disease, intermediate or high grade tumors, and tumors located in the mouth floor, buccal mucosa, or retromolar trigone were at high risk for positive margins, reflecting larger, more aggressive, and poorly accessible tumors, leading to greater technical difficulty of resection[27,65,67,68].

Margin status also varied significantly with non-clinical factors, including the type, location, oral cancer case volume, and travel distance of treating facilities. Treatment at institutions reporting >20 cases per year was associated with a 33% decrease in the incidence of positive margins and an independent decrease in the risk of positive margins compared to institutions with ≤ 20 cases per year. The incidence of positive margins was also lower among patients treated at academic cancer centers. These findings are consistent with prior data reporting compromised outcomes in head and neck and other cancers that are managed at small, non-academic facilities, and may be attributable to increased expertise, experience and resources in high volume academic settings[28,69]. Patients treated in New England were at greater risk of positive margins, possibly because a greater proportion of patients in New England were treated at low-volume facilities than in any other region (data not shown), or because of regional differences in physician practices or disease severity at presentation. Patients at greater distance from their treating facilities also had a lower incidence of positive margins, possibly due to travel to high-volume institutions. These associations between positive margins and non-clinical factors suggest potential variation in quality of care.

Easily quantifiable quality measures are vital for the success of OCSCC treatment but are lacking in many surgical fields[70]. A 2005 committee of the American Head and Neck Society developed several quality measures for treatment of oral cancer based on contemporary pretreatment evaluation, treatment, and post-treatment surveillance guidelines[43]. However, the quality measures suggested measured adherence to guidelines, standards of care and documentation rather than strictly surgical outcomes. We sought to evaluate the utility of the incidence of positive margins as a quality measure for early stage oral cancer. The status of surgical margins in early oral cancer is under the direct control of the attending surgeon and treating care team[44]. Our data show that margin status is well-reported and easily measured, with 95% of our sample having a documented margin status and a median rate of margin documentation among reporting institutions of 100%. This is consistent with one prior retrospective study of tongue cancer from Texas M.D. Anderson Cancer Center, which found the institutional rate of margin status documentation to be similarly high at 97.4%[44]. Furthermore, significant variability in positive margin incidence was present among reporting facilities, with some reporting no positive margins and others reporting positive margins in up to 44% of cases, which could be considered sub-standard care. The incidence of positive margins also varied significantly by facility type, case volume, and location, further suggesting differences in quality of care. Finally, we showed that positive margins are associated with compromised survival on a population level in our survival analysis. In the absence of a prospective trial, which is impractical in the context of margin status, this is the strongest available evidence that positive margins lead to poor outcomes. Based on these

results, the incidence of positive margins meets criteria to be a useful quality measure for treatment of early OCSCC.

This study is the largest contemporary report of surgical margins in early stage OCSCC. However, several limitations of this study should be considered in interpreting its results. This study is subject to shortcomings common to all large retrospective database studies, including the potential for errors in reporting and inconsistencies in institutional reporting habits. Due to the retrospective nature of the study, the physician and patient decisions prior to and during surgery are unknown, so more detailed exploration of technical factors leading to positive margins is not possible. In addition, a significant proportion of cases were excluded from multivariate analysis because covariate data was unknown or missing. The reasons for these missing data and whether they alter the sample pool are unknown. Finally, there was no centralized review of pathology to determine margin status in the NCDB, and no possibility of controlling for variation among surgeons in margin harvesting techniques or for variation among pathologists what constitutes a positive margin. Positive margins are explicitly defined as <5 mm in the NCDB reporting guidelines. However, variations in surgical and pathologic technique could have contributed to the variation in positive margin incidence and were not accounted for in this analysis.

Conclusion:

Although tumor eradication is the goal of oral cancer surgery, 7.5% of early OCSCC resections have positive final tumor margins and this leads to decreased survival. Care at non-academic cancer centers and insurance through Medicare and Medicaid are also associated with reduced survival, which may reflect issues of access to health care. The incidence of positive margins ranged from 0% to 44% by institution and is related to many demographic and clinical factors including stage of disease, type of treating facility and geographic region. Because margins are well-reported, affect outcomes, are under the surgeon's control, and vary widely among institutions, the incidence of positive margins is a promising surgical quality indicator for early OCSCC.

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