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SURVIVAL OUTCOMES AFTER TREATMENT OF CANCER OF THE ORAL CAVITY (1985-2015)

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Abstract

Objectives: To present treatment results of oral squamous cell carcinoma (OSCC) at a tertiary cancer care center from 1985 to 2015.

Materials and Methods: A total of 2082 patients were eligible for this study. Main outcomes measured were overall survival (OS) and disease specific survival (DSS). Prognostic variables were identified with bivariate analyses using Kaplan-Meier curves and log-rank testing for comparison. A p-value <0.05 was considered statistically significant and significant factors were entered into multivariate analysis. Median age was 62 years (16-100), 56% were men, 66% reported a history of tobacco use and 71% of alcohol consumption. The most common subsite was tongue (51%). Seventy-three percent of patients had cT1-2 and 71% had clinically negative necks (cN0). Surgery alone was performed in 1348 patients (65%), adjuvant postoperative radiotherapy in 608 patients (29%) and postoperative chemoradiation in 126 patients (6%). Neck dissection was performed in 920 patients with cN0, and in 585 patients with a clinically involved neck. The median follow-up was 37.6 months (range 1-382).

Results: The 5-year OS and DSS were 64.4% and 79.3%, respectively. Age, comorbidities, margin status, vascular invasion, perineural invasion, AJCC 8th edition pT, and pN were independent prognostic factors of OS (p<0.05). History of alcohol consumption, margin status, vascular invasion, perineural invasion, pT, and pN were independent prognostic factors of DSS (p<0.05).

Conclusion: pN stage is the most powerful and consistent predictor of outcome in patients with OSCC treated with primary surgery and appropriate adjuvant therapy.

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Conflict of Interest Statement

I have no financial and personal relationships with other people or organisations that could inappropriately influence or bias this work.

Keywords

mouth neoplasms; mouth cancer; oral neoplasms; oral cancer; squamous cell carcinoma; epidermoid carcinoma; head and neck neoplasms; head and neck cancer; upper aerodigestive tract neoplasms

Introduction

Oral cavity cancer is a significant cause of morbidity and mortality worldwide. The most common histologic type of cancer in the oral cavity is squamous cell carcinoma, representing over 90% of all oral cancers [1]. Tobacco and alcohol use are the main etiological factors of oral squamous cell carcinoma (OSCC) [2]. Consequent to efforts and public campaigns to educate the population on the damaging health effects of tobacco, a significant decrease in the prevalence of smoking has been observed in the United States [3]. Smoking has also been noted to be less frequent among patients with OSCC [4]. Unfortunately, a proportional decrease in incidence of OSCC has not been observed [1]. The estimated number of new cases and the anticipated deaths attributable to the disease in 2018 in the United States are 33,950 and 6,800, respectively [5].

The treatment of choice for OSCC is surgical resection. Adjuvant radiotherapy with or without chemotherapy is offered when there is a high risk of recurrence and after taking into consideration multiple factors, including patient's age and comorbidities, pathologic staging, margin status, the extent of nodal involvement and other histopathologic characteristics of the primary tumor [6–10]. Although advances have been made in imaging modalities (including computed tomography, magnetic resonance imaging, positron emission tomography and ultrasound), surgical techniques, radiation therapy sources and delivery, and combination with chemotherapy, survival rates for OSCC have improved only marginally in the United States [1].

Several studies have reported outcomes for specific subsites within the oral cavity [11–18]. In addition, large cancer registry and multi institutional series have been published [18–22]. A recent study reporting outcome of patients with OSCC included only patients who received both surgery and adjuvant therapy [23]. Two contemporary single institutional cohort studies reported survival after treatment of OSCC [24, 25]. However, these studies did not include a multivariate analysis with the factors that were found to be predictors of outcomes in their cohort.

Therefore, the aim of our study is to report an overview of surgical outcomes in OSCC of our institution's experience over a 31-year period and identify factors predicting outcomes using multivariate analysis.

Material and Methods

Following Institutional Review Board approval, an institutional database was queried based on CPT, ICD-9 procedure, ICD-9 diagnosis, and ICD-10 diagnosis codes related to surgery in the oral cavity or an oral cancer diagnosis. The query was designed for high sensitivity

and low specificity to ensure that every eligible patient was captured. Inclusion criteria were as follows: invasive squamous cell carcinoma of the oral cavity (buccal mucosa, floor of mouth, hard palate, lower gum, oral tongue, retromolar trigone, and upper gum) treated with surgery at our institution between 1985 and 2015. Exclusion criteria were as follows: prior treatment of the reference oral cancer, synchronous head and neck squamous cell carcinomas, distant metastasis at presentation, and a prior history of non-endocrine head and neck cancer. Patients with a lateral neck dissection prior to presentation and/or patients with excisional biopsies of their primary tumors were also excluded. Two thousand and eighty-two patients met the inclusion criteria and were included in this analysis.

Clinical, radiographic, pathologic, therapeutic, and outcomes data were entered into Caisis, a web-based cancer database (v6.0, BioDigital; New York, NY). All statistical analyses were conducted using SPSS (v25.0, IBM Corporation; Somers, NY). The main outcomes of interest were overall survival (OS) and disease specific survival (DSS). The follow-up interval was calculated in months from the date of initial curative surgery to the date of last known follow-up with a member of the institutional disease management team. Patients who died of other causes were censored for analysis of DSS. Details of death were extracted from the medical records and verified using the Social Security Death Index when appropriate. Prognostic variables were identified with bivariate analyses using Kaplan Meier curves and log-rank testing for comparison of outcomes. A p-value of less than 0.05 was considered statistically significant and all significant factors were entered into a multivariate Cox proportional hazard model. Parametric and non-parametric comparisons were performed using Pearson's χ^2 test.

Demographic Information

Demographic characteristics are listed in Table 1. The median age was 62 years (range 16-100), 56% were men, and 84% patients identified themselves as Caucasian. Sixty-six percent of patients reported a history of tobacco use, and 71% reported a history of alcohol consumption. The majority of the patients (73%) had a comorbidity index of 0, according to the Washington University Head and Neck comorbidity index (WUHNCI) [26]. Forty percent of all patients in this 31-year series were treated in the most recent 10-year period, indicating an increase in the number of patients seen at our institution during equivalent periods over the course of the study.

Tumor Characteristics

The most common subsite was oral tongue (51%), followed by floor of mouth (15%), and lower gum (14%). The distribution of subsites has changed over time. The proportion of floor of mouth cancers has decreased from 20.5% of all cases in the first decade of the study (1985-1995) to 14.7% in the second decade (1996-2005) and 10.3% in the last (2006-2015), while tongue cancers have increased from 45.5% to 51.1% and 55.3%, respectively ($p<0.001$).

The distribution of clinical tumor and nodal categories in the TNM staging system American Joint Committee on Cancer (AJCC) 7th Edition is shown in Table 2. We used the 7th Edition for clinical tumor and nodal categorization because depth of invasion was not routinely

recorded during the initial clinical tumor assessment for most of the patients. Seventy-three percent of patients had early primary tumors (cT1 and cT2) on a comprehensive preoperative evaluation, and 71% of patients had clinically negative necks (cN0). Preoperatively, 31% percent of patients were stage I, 27% were stage II, 14% were stage III, and 25% were stage IV. Staging had not been recorded in the chart for 2% of patients.

Treatment

Surgery alone was the definitive treatment in 1348 patients (65%), surgery combined with postoperative radiotherapy was employed in 608 patients (29%) and surgery combined with postoperative chemoradiation was administered in 126 patients (6%).

Resection of the mandible was performed in 620 (30%), maxilla in 170 (8%), and both in 54 (3%). The majority of mandibulectomies were marginal resections (58%), and the majority of maxillectomies were partial resections (91%). Primary closure of the surgical defect was employed in 1258 patients (60%), free tissue transfer in 429 patients (21%). The remaining surgical defects were managed by secondary intention healing (3%), a skin graft (11%), local flap (2%) or regional myocutaneous pedicle flap (3%). Information was not available on the nature of reconstructive procedure in 2 patients (<1%).

Neck dissection was performed in 1,506 patients (72%). Of the 1485 patients with a clinically negative neck (cN0), elective neck dissection was performed in 920 patients (62%), while 565 (38%) were closely followed in active surveillance. Five-hundred and eighty-five patients had a therapeutic neck dissection. Sixty-five percent of the neck dissections were selective neck dissections, 30% were modified radical neck dissections and 5% were radical neck dissections.

Histopathologic Characteristics

Histopathologic characteristics are described in Table 3. The median largest dimension of the primary tumor was 2 cm (range 0.04-9.0). The majority of patients (60.7%) had moderately differentiated squamous cell carcinoma. Details of vascular and perineural invasion were available in 1570 patients (75%). Vascular invasion was reported to be present in 231 patients (11%) and perineural invasion was present in 497 patients (24%). Bone involvement by the tumor was histopathologically confirmed in 44% of the patients who had bone resection as part of their treatment.

Surgical margin status was classified as positive (invasive carcinoma at the resected border), close (invasive carcinoma 5 mm from the resected border), or negative (invasive carcinoma >5 mm from the resected border). This traditional classification was used despite our recent study on oral tongue margins [27] because the current analysis includes all oral cavity subsites. Eight hundred and seven patients (39%) had negative margins, 1046 patients (50%) had close margins and 220 patients (11%) had positive margins.

The pathological TNM categories according to AJCC 8th edition are listed in Table 4. Across all subsites, 24.4% of patients were stage I, 19.4% of patients were stage II, 12.1% of patients were stage III, 31% of patients were stage IV, and 13.2% did not have sufficient information to determine tumor stage. Early staged disease (stage I and stage II) was most

common in the oral tongue (59.1%) and least common in the retromolar trigone (33.3%) and lower gum (33.8%).

Forty-four percent of all patients who underwent a neck dissection had cervical lymph node metastasis detected on histopathologic evaluation (pN+), 42% of these had extranodal extension (ENE) (Table 3). Thirty percent of patients who received elective neck dissection were pN+, 30% of which had ENE. Meanwhile, 66% of patients undergoing therapeutic neck dissection had a pathologically involved neck, 51% of which had ENE.

Treatment Outcomes

The median follow-up interval was 37.6 months (range 1-382). The 5-year OS and DSS were 64.4% and 79.3%, respectively. Table 5 lists factors predictive of OS. Age, severe comorbidities, margin status, vascular invasion, perineural invasion, pT stage, and pN stage were independent prognostic factors of OS ($p<0.05$). Table 6 lists factors predictive of DSS. History of alcohol consumption, margin status, vascular invasion, perineural invasion, pT stage, and pN status were independent prognostic factors of DSS ($p<0.05$). Of note, patients with pN3 disease were 3.1 times more likely to die of any cause (95% CI 2.481-3.914) and 3.5 times more likely to die with cancer (95% CI 2.528-4.973) compared to those with pN0 disease.

Discussion

To our knowledge this is the largest single institutional study reporting outcomes for patients with OSCC primarily treated with surgery at a tertiary care center. Two thousand and eighty-two patients were included.

The core philosophy of treatment of OSCC has not changed dramatically during the years of this study: surgery is still the preferred initial treatment. However, the paradigm for adjuvant management has evolved in more recent years based mostly on the results presented by the Radiation Therapy Oncology Group (RTOG) 9501 study [9] and the European Organization for Research and Treatment of Cancer Trial (EORTC) 22931 study [10]. The relatively small percentage (6%) of patients in our cohort treated with postoperative chemoradiation is a reflection of the long duration of the study, dating back to 1985. This proportion changes to approximately 12% for the patients in our cohort treated from 2004 until 2015.

Table 7 summarizes data from contemporary publications reporting outcomes for OSCC. Most of the more recent studies reporting outcomes for OSCC employed data from large national databases [13, 16, 18–20]. Luryi et al used the National Cancer Database (NCDB) data to study patients with exclusively early stage OSCC. Overall survival at 5 years was 69.7% in this study that analyzed 6830 cases [19]. Schwan et al also used the NCDB data to study differences in outcomes for patients treated from 1998 through 2003 and those treated from 2004 through 2006 and found an improvement in OS [20]. Other authors used the data from the Surveillance, Epidemiology, and End Results Program (SEER) data from the National Cancer Institute to study outcomes of specific subsites within the oral cavity and reported lower 5-year OS, ranging from 33 to 39% [13, 16, 18]. These studies, however, also included patients who were treated primarily with radiation therapy. The most recent SEER

cancer statistics review published by Noone et al reported a relative 5-year survival of 65.8% for patients treated for oral tongue cancer from 2008-2014 [22]. Using data from these national databases can provide a larger sample size, but the limitations of these data are well recognized [28]. Some of these limitations are: cases are recorded, not patients, so one patient with two primary tumors are counted twice; more than one provider can report the same patient and the process of checking for duplicates is not reliable; there are pitfalls related to using these large numbers, the methods of estimation, misclassification, and missing data which can change considerably the results.

Other smaller reports from single institutions have also been published. Quinlan-Davidson et al. studied 289 patients with OSCC who were treated with surgery followed by postoperative intensity modulated radiotherapy and observed a 5-year OS of 57% [23]. Another group has reported a 5-year OS of 70% for patients treated for OSCC [24]. This group, however, included in their study only a subgroup of patients that were treated by one of the surgical institutional teams and they did not perform a multivariate analysis of prognostic factors. They also included patients who had carcinoma in situ in their analysis, which could have contributed favorably to the reported outcomes. An Italian group reported 5-year OS of 71% and DSS of 73% for their cohort of 525 patients [25]. The frequency of early stage disease in their study was similar to our cohort, but they had less patients with metastatic neck nodes and a higher number of patients received adjuvant therapy. The International Consortium for Outcome Research (ICOR) in Head and Neck Cancer studied 2738 patients treated in 7 cancer centers worldwide and reported a change in 5-year OS from 59% in patients with OSCC who were treated between the years 1990 and 2000 to 70% in those treated between 2001 and 2011 [21].

The differences in OS in our experience compared to others may be attributed to variabilities in stage distribution, institutional attributes, and other variables, such as host characteristics, comorbidity, and treatment policy. Another important factor that can cause differences in OS is age (55% of our patients were older than 60 years). Presence of comorbidities is also a very important factor related to OS and is not usually reported (27% of our patients had a WUHNCI greater or equal to one). None of these previous studies used the new AJCC 8th edition to stage the patients. Depth of invasion (DOI) and ENE have been proven to be predictors of outcomes and, therefore, these factors have been incorporated into the staging system [29, 30]. We used the new staging system in our analysis, and both pT and pN performed as independent predictors of OS and DSS. DOI and ENE were significant in univariate analysis but were not included in our multivariate model since these factors were already accounted for in the new T and N categories. Restaging patients retrospectively using the new staging system can be challenging because the information needed might not be available. For this reason, although we were able to use the 8th edition for pathological staging, we could not use it to restage clinically the patients in our study cohort. In fact, evaluating DOI clinically will be challenging even prospectively. Small differences in DOI can be clinically difficult to assess and can result in up- or downstaging the tumor. Moreover, assessment of DOI can be hampered by local pain or tenderness. Imaging modalities such as ultrasonography may need to be implemented for clinical staging of patients using the new AJCC staging system.

Our analysis demonstrates the prognostic validity of traditional predictors in the context of the new AJCC staging system. Margin status was an independent predictor of OS and DSS in multivariate analysis. Presence of lymph node metastasis has also been recognized for a long time as an important predictor of adverse prognosis in OSCC [31]. In our multivariate analysis, pathologic nodal stage according to AJCC 8th edition was the most important predictor for DSS and OS. Presence of vascular invasion and perineural invasion were also independent predictors of DSS and OS on multivariate analysis.

This observational retrospective study is subject to the limitations of any retrospective study. However, auditing outcomes over a long period of time and analyzing prognostic predictors are important steps to understanding the disease, changes in epidemiology and for planning further prospective investigations. The current paradigm of reporting outcomes relies on retrospective data gathering which is subject to many flaws. Systems that provide prospective data collection can help but have traditionally required logistical support and manpower to extract information from clinical records. The advent of widespread availability of electronic data records has the potential to transform prospective data collection for audit, quality of care assessment and for clinical outcomes research. One approach is to use point-of-care synoptic recording for medical documentation as well as prospective data capture of as many details as possible [32]. However, the pressures of documentation in modern clinical practice are often a deterrent to acceptance of synoptic data capture especially in busy practices. One such example is the practice of recording T and N categories in lieu of the actual descriptors of that category (surface dimensions of tumor, depth of invasion, size of metastatic node, and laterality, etc.). The paucity of these details in existing databases not only poses significant constraints on employing data points as discrete or continuous variables for prognostic analysis, but also limits the ability to retrospectively examine the impact of any future adjustments to prognostic and staging systems. It will be incumbent on clinicians to collaborate with IT experts and develop novel platforms that surmount current roadblocks to facilitate prospective collection of good quality data at point-of-care for future studies.

Conclusion

The outcomes of OSCC reported in this large single-institution study highlight some important classic predictors of outcomes. Pathologic nodal stage according to the AJCC 8th Edition was the single most powerful and consistent predictor of outcome in patients with OSCC treated with primary surgery and appropriate adjuvant therapy.

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Abbreviations

OSCC	oral squamous cell carcinoma
OS	overall survival

DSS	disease specific survival
CPT	current procedural terminology
ICD	international classification of diseases
WUHNCI	Washington University head and neck comorbidity index
AJCC	American Joint Committee on Cancer
ENE	extranodal extension
DOI	depth of invasion
NCDB	National Cancer Database
SEER	Surveillance, Epidemiology, and End Results Program

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Research Highlights

- 2082 patients with OSCC operated at a tertiary cancer care center from 1985 to 2015 were studied.
- Age, comorbidity, margin, vascular and perineural invasion, T, N were independent predictors of OS.
- Alcohol use, margin, vascular and perineural invasion, T, and N were independent predictors of DSS.
- pN was the single most powerful and consistent predictor of outcome in patients with OSCC.

Table 1:**Patients Characteristics**

Characteristic	N	%
Gender		
Male	1174	56%
Female	908	44%
Age		
Age ≤60	931	45%
Age >60	1151	55%
Race		
Caucasian	1757	84%
Black	76	4%
Asian	207	10%
Not Reported/Other	42	2%
Comorbidities (WUHNCI ^a)		
0	1519	73%
1	563	27%
Alcohol Use		
Current	1289	62%
Discontinued	197	9%
Never	583	28%
Unknown	13	<1%
Tobacco Use		
Current	802	39%
Discontinued	576	28%
Never	695	33%
Unknown	9	<1%
Year of Treatment		
1985-1995	594	29%
1995-2005	653	31%
2005-2015	835	40%
Subsites		
Oral Tongue	1067	51%
Floor of Mouth	304	15%
Lower Gum	284	14%
Buccal Mucosa	139	7%
Upper Gum	129	6%
Retromolar Trigone	116	6%
Hard Palate	43	2%

^aWUHNCI: Washington University head and neck comorbidity index.

Table 2.Distribution of Patients by Clinical Stage (AJCC 7th Edition)

Stage		N0	N1	N2	N3	Total	(%)
I	T1	657	54	28	1	740	36.4%
II	T2	557	116	107	3	783	38.6%
III	T3	97	29	53	2	181	8.9%
IV	T4	139	67	118	3	327	16.1%
Total		1450	266	306	9	2031	100%
%		71.4%	13.1%	15.1%	0.4%	100%	

Table 3:**Histopathological Characteristics**

Characteristic	N	%
Depth of Invasion		
5 mm	720	34%
>5 mm and 10 mm	513	25%
>10 mm	618	30%
Unknown	231	11%
Bone Resection		
Bone Resected	844	
Bone Invaded	368	44%
Margin Status		
Negative	807	39%
Close	1046	50%
Positive	220	11%
Unknown	9	<1%
Vascular Invasion		
Absent	1339	64%
Present	231	11%
Unknown	512	25%
Perineural Invasion		
Absent	1073	51%
Present	497	24%
Unknown	512	25%
Pathologic Grade		
Well Differentiated	396	19%
Mod Differentiated	1264	61%
Poor Differentiated	275	13%
Unknown	147	7%
Lymph Node Status		
pN0	839	56%
pN+	667	44%
Extranodal Extension (ENE)		
Absent	306	46%
Present	282	42%
Unknown	79	12%

Table 4:Distribution by Pathologic Stage (AJCC 8th Edition)

Stage		pN0	pN1	pN2	pN3	Total	(%)
I	pT1	508	25	17	12	562	31.9%
II	pT2	403	68	57	55	583	33.1%
III	pT3	127	31	50	53	261	14.9%
IV	pT4	166	37	50	101	354	20.1%
Total		1204	161	174	221	1760	100%
%		68.4%	9.1%	9.9%	12.6%	100%	

Table 5:

Factors Predictors of Overall Survival (Univariate and Multivariate Analysis)

Factor	Variable	No. Pres.	Univariate Analysis		Multivariate Analysis		
			5-year OS	p Value	RR	CI	p Value
Age	60	931	73.3%	<0.001	Ref		<0.001
	>60	1151	57.5%		1.857	1.568-2.198	
Sex	Female	908	64.5%	0.192			NS
	Male	1174	64.4%				
Alcohol Use	Never	583	62.4%	0.683			NS
	Ever	1486	65.5%				
Tobacco Use (at presentation)	Never	695	68.4%	<0.001	Ref		0.154
	Ever	1378	62.6%		1.131	0.955-1.339	
WUHNCI	None	1519	68.5%	<0.001	Ref		<0.001
	Any	563	53.5%		1.434	1.214-1.693	
Margin Status	Negative	807	73.3%	<0.001	Ref		<0.001
	Close	1046	63.0%		1.108	0.919-1.335	
	Positive	220	37.6%		1.753	1.352-2.272	
Vascular Invasion	Absent	1339	66.3%	<0.001	Ref		0.020
	Present	231	40.5%		1.288	1.040-1.596	
Perineural Invasion	Absent	1073	70.0%	<0.001	Ref		0.012
	Present	497	46.5%		1.259	1.052-1.507	
Depth of Invasion	5 mm	720	78.2%	<0.001			NA
	>5 and 10 mm	513	64.5%				
	>10 mm	618	44.5%				
Extranodal Extension	No	306	55.4%	<0.001			NA
	Yes	282	28.8%				
Histologic grade	Well	396	74.8%	<0.001	Ref		0.756
	Moderate	1264	63.0%		1.003	0.796-1.264	
	Poorly	275	49.6%		1.084	0.811-1.448	
pT status (AJCC 8 th Edition)	pT1	569	81.0%	<0.001	Ref		<0.001
	pT2	609	64.3%		1.234	0.978-1.558	
	pT3	279	51.8%		1.396	1.062-1.834	
	pT4	367	39.1%		1.807	1.401-2.332	
pN status (AJCC 8 th Edition)	pN0/pNx	1415	74.2%	<0.001	Ref		<0.001
	pN1	175	63.0%		1.289	0.991-1.678	

Factor	Variable	No. Pres.	Univariate Analysis		Multivariate Analysis		
			5-year OS	p Value	RR	CI	p Value
	pN2	186	47.6%		1.659	1.300-2.117	
	pN3	229	23.5%		3.116	2.481-3.914	

Table 6:

Factors Predictors of Disease Specific Survival (Univariate and Multivariate Analysis)

Factor	Variable	No. Pres.	Univariate Analysis		Multivariate Analysis		
			5-year DSS	p Value	RR	CI	p Value
Age	60	931	82.2%	0.004	Ref		0.170
	>60	1151	76.7%		1.189	0.929-1.522	
Sex	Female	908	77.2%	0.119			NS
	Male	1174	80.9%				
Alcohol Use	Never	583	74.9%	0.001	Ref		0.002
	Ever	1486	81.2%		0.674	0.525-0.865	
Tobacco Use (at presentation)	Never	695	77.6%	0.254			NS
	Ever	1378	80.2%				
WUHNCI	None	1519	80.3%	0.041	Ref		0.062
	Any	563	76.1%		1.284	0.987-1.669	
Margin Status	Negative	807	86.4%	<0.001	Ref		0.002
	Close	1046	78.7%		1.207	0.876-1.662	
	Positive	220	52.2%		1.997	1.338-2.980	
Vascular Invasion	Absent	1339	81.6%	<0.001	Ref		0.022
	Present	231	57.4%		1.409	1.051-1.890	
Perineural Invasion	Absent	1073	85.1%	<0.001	Ref		0.028
	Present	497	62.4%		1.361	1.034-1.791	
Depth of Invasion	5 mm	720	92.0%	<0.001			NA
	>5 and 10 mm	513	78.2%				
	>10 mm	618	60.3%				
Extranodal Extension	No	306	66.7%	<0.001			NA
	Yes	282	46.3%				
Histologic grade	Well	396	90.9%	<0.001	Ref		0.161
	Moderate	1264	77.1%		1.598	0.978-2.611	
	Poorly	275	65.0%		1.653	0.954-2.865	
pT status (AJCC 8 th Edition)	pT1	569	92.8%	<0.001	Ref		<0.001
	pT2	609	79.6%		1.553	1.009-2.392	
	pT3	279	67.3%		1.948	1.209-3.137	
	pT4	367	54.3%		2.962	1.891-4.639	
pN status (AJCC 8 th Edition)	pN0/pNx	1415	88.6%	<0.001	Ref		<0.001
	pN1	175	70.8%		1.906	1.300-2.795	

Factor	Variable	No. Pres.	Univariate Analysis		Multivariate Analysis		
			5-year DSS	p Value	RR	CI	p Value
	pN2	186	62.8%		1.891	1.312-2.725	
	pN3	229	41.6%		3.546	2.528-4.973	

Table 7

Author	Years	Patients	Site	T			N	Stage			ND	Margins		Extranodal Extension		Adjuvant		5-y DSS	5-y OSS
				1-2	3-4	N0	N+	I-II	III-IV	Elective		Negative	Positive	No	Yes	RT	CT		
Alonso et al ^a	1973-2014	1489	100% HP	49%	50%	74%	26%	43%	57%	NR	NR	-	-	-	-	22%	NR	59%	33%
				53%	47%	56%	44%	58%	41%	60%	40%	76%	24%	76%	24%	53%	3%	69%	59%
Amit et al ^b	1990-2000 2001-2011	735 2003	NR NR	45%	55%	56%	44%	43%	57%			82%	18%	53%	47%	50%	23%	81%	70%
				NR	NR	74%	26%	58%	42%	35%	26%	10%	90%	97%	3%	42%	NR	73%	71%
Garzino-Demo et al ^c	2000-2011	525	42% T 15% BM 6% RMT 10% UG/HP 12% FOM 15% LG	100%	0	100%	0	1-65% II-35%	0	48%	0	88%	7%	-	-	18%	3%	NR	69.7%
				60%	40%	58%	42%	40%	60%	11%	42%	60%	40%	88%	12%	57%	NR	48%	44%
Ling et al ^c	1997-2017	210	100% T	60%	40%	58%	42%	40%	60%	11%	42%	60%	40%	88%	12%	57%	NR	48%	44%
Luryi et al ^d	2003-2006	6830	49% T 16% Lip 17% FOM 8% LG/UP/HP 4% RMT 5% BM	100%	0	100%	0	1-65% II-35%	0	48%	0	88%	7%	-	-	18%	3%	NR	69.7%
				47%	53%	51%	49%	31%	69%	NR	NR	76%	24%	-	-	13%	7%	60% [†]	52%
Nishi et al ^c	1992-2011	45	100% RMT	47%	53%	51%	49%	31%	69%	NR	NR	76%	24%	-	-	13%	7%	60% [†]	52%
Ong et al ^c	1973-2016	921	38% T 24% FOM 8% RMT 11% BM 12% G 3% HP 4% SP	60% CIS 4% CIS	33%	65%	35%	NR	NR	NR	NR	-	-	-	-	22%	NR	NR	70%
				52% cT 45% cT	45% cT	37% cN	62% cN	NR	NR	31%	62%	82%	18%	69%	31%	100%	51%	NR	57%
Quinlan-Davidson et al ^c	2000-2012	289	51% T 16% G 11% RMT 10% BM 9% FOM 3% HP	52% cT 45% cT	45% cT	37% cN	62% cN	NR	NR	31%	62%	82%	18%	69%	31%	100%	51%	NR	57%
				65%	35%	60%	40%	44%	56%	NR	NR	-	-	-	-	34%	NR	55%	38%
Rizvi et al ^{a,d}	1973-2012	4022	100% RMT	65%	35%	60%	40%	44%	56%	NR	NR	-	-	-	-	34%	NR	55%	38%

Author	Years	Patients	Site	T		N		Stage		ND		Margins		Extranodal Extension		Adjuvant		5-y DSS	5-y OSS
				1-2	3-4	N0	N+	I-II	III-IV	Elective	Therapeutic	Negative	Positive	No	Yes	RT	CT		
Saggi et al ^a	1973-2013	14010	100% FOM	NR	NR	NR	NR	30%	28%	NR	NR	-	-	-	-	28%	NR	59%	39%
				74%	26%	78%	22%	64%	36%	NR	NR	86%	14%	-	-	35%	5%	NR	~50% [*]
				77%	23%	80%	20%	67%	33%	NR	NR	88%	12%	-	-	34%	12%	NR	~60% [*]
Schwam et al ^d	1998-2003	7734	NR																
	2004-2006	5921	NR																
Shukla et al ^c	1995-2010	353	58% BM 42% GBS	NR	NR	65%	35%	11%	89%	20%	78%	90%	10%	-	-	63%	9%	58%	60%

^aSEER database.

^bICOR.

^cSingle institution.

^dNCDB.

Abbreviations: NR: not reported, T: tongue, G: gingiva, RMT: retromolar trigone, BM: buccal mucosa, FOM: floor of mouth, HP: hard palate, UG: upper gum, LG: lower gum, GBS: gingivobuccal sulcus, CIS: carcinoma in situ.

^{*}estimated from the curve.

[†]3-year DSS.