Title: Locoregionally advanced oral cavity cancer: a propensity-score matched analysis on overall survival with emphasis on the impact of adjuvant radiotherapy

Running title: Adjuvant radiotherapy in locoregionally advanced oral cavity cancer

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ABSTRACT

Background: The objective of this study is to determine the impact of adjuvant radiotherapy (RT) in locoregionally advanced oral cavity cancer.

Methods: Data were extracted from the National Cancer Data Base of which overall survival (OS) is the only outcome variable available. Chi-square test and Cox regression models were employed.

Results: 6,654 patients were identified. The utilization of adjuvant RT has increased over time. A propensity matched cohort included 3,946 patients, exactly one-half of whom received adjuvant RT. Independent predictors associated with receipt of adjuvant RT included age, Charlson/Deyo comorbidity score, extracapsular extension, surgical margins, and T and N stage. On multivariable analysis, adjuvant RT remained an independent prognosticator for OS.

Conclusions: Receipt of adjuvant RT is a prognostic factor associated with improved OS, its utilization has increased over time, and it should be considered for clinically suitable patients who have undergone resection for the disease.

INTRODUCTION

In 2017, there will be an estimated 32,670 new cases of oral cavity cancer in the United States (U.S.) and an estimated 6,650 deaths.[1] Factors affecting prognosis in those with oral cavity cancer include nodal involvement, extracapsular extension, surgical margins, tumor size, perineural invasion, and tumor grade.[2] In those with locoregionally advanced oral cavity cancers, up-front resection is recommended for those who present with resectable disease.[3] These patients, however, are at significant risk for locoregional recurrence after resection and are generally recommended for adjuvant therapy.[4-9] Per National Comprehensive Cancer Network (NCCN) guidelines, post-operative adjuvant radiotherapy (RT) is the recommended treatment for those presenting with risk features including pT3 or pT4 primary, N2 or N3 nodal disease, or perineural invasion, and adjuvant systemic therapy/RT is recommended for those with extracapsular nodal extension or positive surgical margins.[3]

Limited data exists regarding the specific impact of adjuvant radiotherapy in those with locoregionally advanced disease particularly focused on primary tumors arising from the oral cavity. The objective of this hospital-based retrospective study on 6,654 patients diagnosed with squamous cell carcinoma of the oral cavity is to determine the prognostic factors for overall survival and the utilization and impact of adjuvant radiotherapy in those who have undergone resection for the disease.

MATERIALS AND METHODS

Patient population

Data were extracted from the National Cancer Data Base (NCDB) which includes hospital registry data collected from more than 1,500 Commission on Cancer (CoC)-accredited

facilities representing 70% of newly diagnosed cancer cases annually in the United States.[10] It is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The data used in our investigation are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigators. The only outcome variable available in the NCDB is overall survival (OS). This study was approved by the institutional review board of Rush University Medical Center, Chicago, Illinois, which waived the need for informed consent for use of these de-identified data.

As seen in **Figure 1**, our study population consists of 6,654 patients diagnosed with locoregionally advanced squamous cell carcinoma of the oral cavity, including the anterior two-thirds tongue, lip, gingiva, floor of mouth, hard palate, buccal mucosa, vestibule of mouth, retromolar trigone, and oral cavity not otherwise specified (NOS) (ICD-0-3 histology code 8070/3-8078/3) from 2004 to 2013. Stage groups III-IV, including those with T3-4N0M0 and T1-4N1-3M0 disease as defined by the American Joint Committee on Cancer (AJCC) 2017 staging system, were considered locoregionally advanced.[11] All study patients were 18 years or older and underwent excision of the primary tumor with curative intent. Patients receiving adjuvant radiotherapy (RT) received external beam RT. Additional exclusion criteria included patients with no record regarding T, N, or M staging, extracapsular extension or surgical margin status, or receipt of adjuvant RT or chemotherapy.

Comorbidities as described by the Charlson/Deyo comorbidity score were defined by a weighted score derived from the sum of the scores for each of the comorbid conditions listed in the Charlson Comorbidity Score Mapping Table.[12, 13] A score of 0 indicated no significant

comorbid conditions and higher scores indicated greater comorbidity burden. Because of the small proportion of cases with a Charlson Comorbidity score exceeding 2, the NCDB has truncated the data to 0, 1, and 2 (greater than 1). Insurance status was identified as the patient's primary insurance carrier at the time of initial diagnosis and/or treatment. Categories as supplied by the NCDB for insurance status include Private, Uninsured, Medicaid, Medicare, and Other governmental.

Statistical Analysis

All data analyses were performed using SPSS 23.0 (Armonk, NY: IBM Corp.). Proportional distribution of demographic and clinicopathologic factors, and treatment by receipt of adjuvant RT were compared using the two-tailed Chi-square test. The Chi-Square test of independence using Fisher's Exact Test was used to determine whether there was an association between categorical variables. A cross-tabulation was performed, and the p-value (significance level of 0.05) was used to determine if the null hypothesis (no significant difference between specified populations; any observed difference being due to sampling error) could be rejected and if a statistical association between categorical variables existed. The primary study endpoint was OS which was defined as time to death from the date of diagnosis of squamous cell carcinoma of the oral cavity. Participating CoC-accredited registries report patient follow-up to the NCDB annually. The NCDB records the number of months between the date of diagnosis and the date on which the patient was last contacted or died. The NCDB dataset does not include cause of death information, so cause-specific survival cannot be calculated. Factors significant on univariate OS analysis were included in Cox regression multivariable analysis which was used to compute hazard ratios (HR) with 95% confidence intervals (CI) to identify independent prognostic factors for OS using a forwards selection variable selection process. To further adjust

for the effect of potential confounding variables, a stepwise binary logistic regression was used to determine predictors of adjuvant RT use in our patient population. A propensity score model for the likelihood of receiving adjuvant RT was developed including the covariates age at diagnosis, gender, race, Charlson/Deyo comorbidity score, insurance status, site of disease, extracapsular extension status, surgical margin status, T stage, N stage, tumor grade, and receipt of adjuvant chemotherapy. One-to one propensity matching was then performed with the fixed-caliper width set to 0.01 which has demonstrated negligible relative bias (relative bias ranging from -2% to 3%) and greater precision for estimating treatment effects.[14] These two cohorts (i.e. adjuvant RT vs. no adjuvant RT) were compared using the log-rank test, and the HR for OS was calculated using Cox regression. A landmark analysis was also performed establishing a landmark time including only those patients who survived to this time point and followed forward in time to evaluate whether OS is associated with receipt of adjuvant RT. The 3-month landmark was chosen a priori because this time point corresponds to the usual interval at which a restaging evaluation to assess the effect of treatment would occur.[3] Kaplan-Meier methods were used to estimate survival probabilities. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Patient and Treatment Characteristics

6,654 patients diagnosed with locoregionally advanced squamous cell carcinoma of the oral cavity who underwent primary tumor resection between 2004-2013 were identified (**Table 1**). The median age was 63 years (range: 18-90). The population was predominately male, White,

had a Charlson/Deyo comorbidity score of 0, and carried private insurance or Medicare. 4,287 (64.4%) received adjuvant RT and 2,367 (35.6%) did not.

Independent predictors associated with receipt of adjuvant RT are shown in **Table 2**. These included younger age, lower Charlson/Deyo comorbidity score, extracapsular extension, positive surgical margins, and T and N stage of disease. Over the study time period 2004-2013, the utilization of adjuvant RT has significantly increased from 43.1% in 2004 to 64.1% in 2013 (p=0.019, Chi-square test) (**Figure 2**).

Overall Survival

The median time to follow-up was 22.2 months (range: 1-126). Univariate analysis demonstrated that those who received adjuvant RT (hazard ratio[HR]: 0.756, 95% confidence interval[CI]: 0.692-0.825) were associated with significantly better overall survival (OS) than those who did not (**Table 3**). Additionally, age at diagnosis, Charlson/Deyo comorbidity score, insurance status, extracapsular extension, surgical margins, T and N stage of disease, and tumor grade were statistically significant outcome factors. On Cox regression multivariable analysis, receipt of adjuvant RT (HR: 0.640, 95% CI: 0.582-0.704) remained an independent prognosticator for improved OS compared to those without receipt (**Table 3**). Additionally, older age at diagnosis ($p<0.001$), higher Charlson/Deyo comorbidity score (0 vs. 2, HR: 1.646, $p<0.001$), extracapsular extension (HR: 1.469, $p<0.001$), positive surgical margins (HR: 1.386, $p<0.001$), and higher T (1 vs. 2, HR: 1.504, $p<0.001$; 1 vs. 3, HR: 2.101, $p<0.001$; 1 vs. 4, HR: 2.160, $p<0.001$) and N stage of disease (0 vs.1, HR: 1.531, $p<0.001$; 0 vs. 2, HR: 2.318, $p<0.001$; 0 vs. 3, HR: 2.662, $p<0.001$) were significant prognostic factors associated with worse OS.

Sensitivity Analyses

The propensity model was created, and the resultant matched cohort included 3,946 patients, exactly one-half of whom received adjuvant RT. There was an expected balance of covariates between the two groups (**Table 1**). The HR from a univariate Cox regression was 0.683 ($p<0.001$), and from a multivariable Cox regression 0.642 ($p<0.001$) (**Table 4**). Landmark analysis was used to evaluate the association of adjuvant RT on OS. A 3-month landmark was chosen. For patients diagnosed from 2004 to 2013 who survived at least 3 months, the median survivals for patients treated with and without adjuvant RT were 51.3 months and 42.7 months, respectively, and the 5-year OS probabilities were 47.9% vs. 39.4% ($p<0.001$) (**Figure 3**).

Subset Analysis

In terms of patient characteristics, a statistically significant five-year OS benefit was observed in those ≥63 years (43.6% vs. 31.9%, $p<0.001$) while there was a trend towards significance in those <63 years (53.5% vs. 44.4%, $p=0.076$) (**Table 5**). Those with a Charlson/Deyo comorbidity score of 0 or 1 had an associated five-year OS benefit with receipt of adjuvant RT (0: 47.8% vs. 38.0%, $p<0.001$; 1: 54.6% vs. 33.5%, $p<0.001$) while those with a Charlson/Deyo comorbidity score of 2 did not have a demonstrated OS benefit ($p=0.635$). A five-year OS benefit was associated with adjuvant RT regardless of extracapsular extension status (no: 50.5% vs. 41.4%, $p<0.001$; yes: 32.3% vs. 15.0%, $p<0.001$) or surgical margin status (negative: 49.0% vs. 40.0%, $p<0.001$; positive: 39.9% vs. 19.8%, $p<0.001$). In those with no extracapsular extension and negative surgical margins, no derived OS benefit with adjuvant RT was observed in those with N2 disease (30.9% vs. 29.5%, $p=0.073$). Those with higher T stage

were associated with a derived five-year OS benefit with adjuvant RT (T3: 43.6% vs. 24.2%, p=0.003; T4: 47.8% vs. 38.2%, p<0.001).

DISCUSSION

We investigated the impact of adjuvant RT on OS in patients with locoregionally advanced squamous cell carcinoma of the oral cavity, and our study demonstrated important findings. First, the utilization of adjuvant radiotherapy for these patients with advanced disease has significantly increased over the past decade. Next, those younger, or with less comorbidity burden, extracapsular extension of disease, and positive surgical margins, and higher T and N stage of disease are more likely to receive adjuvant RT. Conversely, those older, with higher comorbidity burden, and with less adverse features seen on final pathology status-post resection are less likely to receive adjuvant RT. Finally, our data suggests that adjuvant RT is significantly associated with improved OS which was maintained on multivariable and landmark analyses among propensity matched patients.

For those with locoregionally advanced squamous cell carcinoma of the oral cavity, the National Comprehensive Cancer Network recommends surgery and neck dissection for resectable disease.[3] Given the extent of disease, these patients are at significant risk for local recurrence following resection. Unfavorable prognostic factors for local control in the post-operative setting include close or positive surgical margins, extracapsular extension, tumor depth, perineural invasion, and nodal metastasis, and patients with combinations of these adverse pathologic features have been associated with significantly decreased OS in addition to decreased locoregional control rates.[15, 16] A 35-year single institutional study on 226 patients

with primary oral cavity cancer treated with adjuvant RT found that these factors were significant prognosticators for locoregional control on multivariable analysis.[17]

Positive surgical margins and extracapsular extension in particular are two unfavorable high-risk factors,[18-20] and our subset analyses including propensity-matched patients suggests that a significant absolute benefit for adjuvant RT was derived in patients with either of these high-risk features. The presence of T3-4 disease without involved margins or extracapsular extension was also associated with a significant OS benefit when adjuvant RT was received. These results strongly argue for the importance of adjuvant RT for patients with adverse pathologic features. A phase III randomized trial conducted in India on 900 patients with locally advanced and resectable squamous cell carcinoma of the oral cavity found five-year locoregional control to be between 58.2% to 65.1% for those receiving adjuvant RT or chemoRT.[4] 90% had T3-T4 tumors, while 48% had N2-3 disease. Very few patients had positive margins, though 54.7% had extracapsular extension and 329 (36.5%) had multiple nodal involvement. Additionally, our data demonstrated that receipt of adjuvant RT in locoregionally advanced patients with moderately or poorly-differentiated tumors is also associated with an OS benefit, suggesting that tumor grade should be given consideration as an adverse risk feature to be employed in multivariable models in this cohort. This result is consistent with a Surveillance, Epidemiology, and End Results (SEER) study published by Thomas et al., which demonstrated a strong association between tumor grade and disease-specific survival for stage I-II patients with squamous cell carcinoma of the oral cavity and noted an adjusted risk of death 2.7 times greater if the tumor was poorly-differentiated or undifferentiated compared to well-differentiated tumors.[21]

In contrast, there may be those who may not derive an OS benefit with the addition of adjuvant RT. In a randomized trial on patients with advanced head and neck squamous cell carcinoma, 213 patients were prospectively studied with 15% having no adverse pathologic factors and receiving no adjuvant therapy, and had a 5-year local–regional control rate of 83%.[22] In the absence of extracapsular extension or positive surgical margins, our data demonstrated that adjuvant RT was not associated with an OS benefit in patients with N2 disease who underwent primary resection and lymph node dissection in our propensity matched analysis. Additionally, those with less aggressive disease, including those with T1-2 and grade 1 disease, respectively, were not associated with an OS benefit upon receipt of adjuvant RT. These findings suggest that certain patient subsets with locoregionally advanced disease undergoing primary resection with lymph node dissection and ultimately more favorable final pathologic findings have a good prognosis with surgery alone. In terms of patient characteristics, no statistically significant OS benefit associated with adjuvant RT was observed in those with a Charlson/Deyo comorbidity score of 2. Reasons for this are likely multifactorial in etiology, but previous studies related to the prognostic impact of comorbidity and cancer have found that while comorbidity does not appear to be associated with more aggressive types of cancer or other differences in tumor biology, postoperative complications and mortality are higher and the chance of completing a course of cancer treatment is lower for those with great comorbidity burden.[23]

Our data suggests that the utilization of adjuvant RT has grown over the past decade, and reasons for this can only be hypothesized given the limitations of the NCDB dataset but are also likely multifactorial in etiology. The use of intensity-modulated radiotherapy for head and neck cancer, which offers improvements in side effect profile and quality of life when compared to conventional RT techniques,[24] has significantly increased with 1.3% of patients receiving it in

2000 compared to 46.1% in 2005 ($p<0.001$) as demonstrated in a SEER-Medicare analysis on 5,487 patients, though significant geographic variation was noted.[25] We did not report IMRT use as a variable in our study given that the NCDB dataset and its radiation technique options [e.g. conventional vs. 3D conformal vs. IMRT] are not mutually exclusive. Insurance status has been associated with disparities in treatment delivery for head and neck cancers with those insured more likely to received definitive treatment than those uninsured.[26] The Affordable Care Act was introduced in 2010 and launched major regulatory changes of the U.S. healthcare system with the goal to increase patient access to health insurance coverage.[27] In 2013, 13.3% of the entire U.S. population was found to be uninsured for the entire year, and the uninsured rate had decreased to 10.4% for the calendar year 2014.[28] The observed increase in adjuvant RT utilization may also be reflective of the NCDB and the possibility of increased capture of RT data by COC institutions over time where the tumor registrar might be more likely to have access to RT records. Linking of hospital and radiation oncology electronic health records, and implementation of electronic data capture systems to prospectively population research databases and better facilitate outcomes reporting have been developed.[29, 30] Further epidemiological studies on the utilization of RT for patients with head and neck cancers are warranted.

Our study represents a large comprehensive analysis investigating prognostic factors and the impact of adjuvant RT on patients with resected locoregionally advanced squamous cell carcinoma of the oral cavity. The major strength in our investigation lies in the large patient numbers which allowed for statistical analyses powered for detection of differences in overall survival. The NCDB is a highly standardized hospital-based cancer registry, undergoing a series of quality assurance measures and checks while collecting information on 70% of newly diagnosed cancer cases annually.[10] However, intrinsic limitations to any large database

retrospective analysis must also be considered with lack of certain data variables possibly leading to confounding impact of important factors which could not be investigated in our study. Cases from the NCDB are only reported by Commission-on-Cancer-accredited facilities, thus possibly introducing hospital-selection bias. Also, the NCDB does not have record on pre- and post-operative imaging, patient adherence to treatment recommendations, disease recurrence, or any subsequent salvage therapy. There is limited information on some intermediate-risk head and neck cancer features such as perineural invasion, lymphovascular space invasion, and depth of invasion. Number of involved nodes and nodal stations involved were not specifically analyzed in our study as well. Additionally, risk factors including tobacco and alcohol use, which are among the strongest disease risk factors for squamous cell carcinoma of the oral cavity, are not specifically recorded.[31] Thus, we cannot evaluate the extent to which all of these factors may contribute to patient outcome which can present a greater risk of unmeasured confounding. Another significant limitation of this study is the short median follow-up. A shorter median follow-up may lead towards analyses biased towards patients with shorter follow-up. The interpretation of survival analyses depends on the completeness of patient follow-up, and sufficient follow-up to capture an adequate number of events is necessary to ensure sufficient statistical power for outcomes-based data analyses.[32, 33] However, the role of median follow-up in describing the stability and validity of the Kaplan-Meier curve estimates is also debatable as some argue that Kaplan-Meier curves adjust for variable lengths of follow-up and provides an unbiased estimate of the true population survival curve.[34] Regardless, median follow-up is a term that continues to be used in outcomes-based cancer research, and our short median follow-up warrants the need for future studies with more mature data and longer median follow-up. Finally,

the NCDB does not collect cancer-specific survival information which may produce different results from that of all-cause death.

Our findings from this hospital-based, retrospective, propensity-score matched analysis suggest that receipt of adjuvant radiotherapy is associated with significantly improved overall survival in those with locoregionally advanced squamous cell carcinoma of the oral cavity, and that it should strongly be considered for all clinically suitable patients who have undergone resection for the disease. As techniques for radiotherapy delivery continue to be optimized and its utilization increased, further studies are warranted to continue prospectively investigate which specific subgroups of patients truly benefit from treatment so that disease control and outcomes can be further improved, while at the same time minimizing unnecessary treatment toxicity and maintaining quality of life.

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Figure Legend

Figure 1. Flowchart describing the composition of the patient cohort

Figure 2. Utilization of adjuvant radiotherapy over the time period 2004-2013 ($p=0.019$, Chi-square test)

Figure 3. Kaplan-Meier overall survival by landmark analysis of propensity matched patients alive at 3 months ($p<0.001$)

Table 1. Patient characteristics stratified by receipt of adjuvant radiotherapy

	All patients				Propensity-matched		
	Overall	**No adjuvant radiotherapy**	**Adjuvant radiotherapy**	**Chi-square p-value**	**No adjuvant radiotherapy**	**Adjuvant radiotherapy**	**Chi-square p-value**
Total	6,654	2,367 (35.6%)	4,287 (64.4%)		1,973 (50.0%)	1,973 (50.0%)	
Age							
Median (range)	63 (18-90)			p<0.001			p=0.518
<63 years	3,154	912 (28.9%)	2,242 (71.1%)		809 (49.4%)	830 (50.6%)	
≥63 years	3,500	1,455 (41.6%)	2,045 (58.4%)		1,164 (50.5%)	1,143 (49.5%)	
Gender				p<0.001			p=0.871
Male	4,177	1,406 (33.7%)	2,771 (66.3%)		1,190 (50.1%)	1,184 (49.9%)	
Female	2,477	961 (38.8%)	1,516 (61.2%)		783 (49.8%)	789 (50.2%)	
Race				p=0.001			p=0.761
White	5,492	2,007 (36.5%)	3,485 (63.5%)		1,693 (50.0%)	1,690 (50.0%)	
Black	557	173 (31.1%)	384 (68.9%)		148 (48.8%)	155 (51.2%)	
Hispanic	267	84 (31.5%)	183 (68.5%)		78 (53.4%)	68 (46.6%)	
Asian	209	55 (26.3%)	154 (73.7%)		54 (47.4%)	60 (52.6%)	
Other	69	26 (37.7%)	43 (62.3%)		--	--	
Unknown	60	22 (36.7%)	38 (63.3%)		--	--	
Charlson/Deyo comorbidity score				p<0.001			p=0.280
0	4,927	1,654 (33.6%)	3,273 (66.4%)		1,469 (50.4%)	1,448 (49.6%)	
1	1,322	504 (38.1%)	818 (61.9%)		384 (47.8%)	419 (52.2%)	
2	405	209 (51.6%)	196 (48.4%)		120 (53.1%)	106 (46.9%)	
Insurance status				p<0.001			p=0.468
Private	2,244	668 (29.8%)	1,576 (70.2%)		627 (49.9%)	630 (50.1%)	
Uninsured	371	101 (27.2%)	270 (72.8%)		95 (44.8%)	117 (55.2%)	

(continued)

	All patients				**Propensity-matched**		
	Overall	**No adjuvant radiotherapy**	**Adjuvant radiotherapy**	**Chi-square p-value**	**No adjuvant radiotherapy**	**Adjuvant radiotherapy**	**Chi-square p-value**
Medicaid	767	234 (30.5%)	533 (69.5%)		214 (50.5%)	210 (49.5%)	
Medicare	3,026	1,277 (42.2%)	1,749 (57.8%)		1,037 (50.5%)	1,016 (49.5%)	
Other governmental	127	43 (33.9%)	84 (66.1%)		--	--	
Unknown	119	44 (37.0%)	75 (63.0%)		--	--	
Site of disease				p<0.001			p=0.386
Anterior 2/3 tongue	704	198 (28.1%)	506 (71.9%)		176 (49.0%)	183 (51.0%)	
Lip	194	77 (39.7%)	117 (60.3%)		71 (54.2%)	60 (45.8%)	
Floor of mouth	2,021	681 (33.7%)	1,340 (66.3%)		572 (50.0%)	573 (50.0%)	
Gingiva	1,683	682 (40.5%)	1,001 (59.5%)		532 (49.1%)	552 (50.9%)	
Hard palate	193	72 (37.3%)	121 (62.7%)		64 (55.7%)	51 (44.3%)	
Buccal mucosa	640	232 (36.3%)	408 (63.7%)		198 (51.4%)	187 (48.6%)	
Vestibule of mouth	46	20 (43.5%)	26 (56.5%)		18 (62.1%)	11 (37.9%)	
Retromolar trigone	717	225 (31.4%)	492 (68.6%)		196 (46.2%)	228 (53.8%)	
Oral cavity, NOS *	456	180 (39.5%)	276 (60.5%)		146 (53.3%)	128 (46.7%)	
Extracapsular extension				p<0.001			p=0.320
No	4,988	1,966 (39.4%)	3,022 (60.6%)		1,642 (49.6%)	1,666 (50.4%)	
Yes	1,666	401 (24.1%)	1,265 (75.9%)		331 (51.9%)	307 (48.1%)	
Positive surgical margins				p<0.001			p=0.964
No	5,439	2,021 (37.2%)	3,418 (62.8%)		1,681 (50.0%)	1,683 (50.0%)	
Yes	1,215	346 (28.5%)	869 (71.5%)		292 (50.2%)	290 (49.8%)	

(continued)

	All patients				Propensity-matched		
	Overall	**No adjuvant radiotherapy**	**Adjuvant radiotherapy**	**Chi-square p-value**	**No adjuvant radiotherapy**	**Adjuvant radiotherapy**	**Chi-square p-value**
T stage				p<0.001			p=0.209
1	619	216 (34.9%)	403 (65.1%)		188 (53.6%)	163 (46.4%)	
2	705	193 (27.4%)	512 (72.6%)		178 (48.5%)	189 (51.5%)	
3	447	174 (38.9%)	273 (61.1%)		146 (54.3%)	123 (45.7%)	
4	4,883	1,784 (36.5%)	3,099 (63.5%)		1,461 (49.4%)	1,498 (50.6%)	
N stage				p<0.001			p=0.171
0	2,814	1,266 (45.0%)	1,548 (55.0%)		1,002 (49.1%)	1,037 (50.9%)	
1	1,343	492 (36.6%)	851 (63.4%)		428 (50.5%)	419 (49.5%)	
2	2,450	596 (24.3%)	1,854 (75.7%)		531 (50.9%)	513 (49.1%)	
3	47	13 (27.7%)	34 (72.3%)		12 (75.0%)	4 (25.0%)	
Grade				p<0.001			p=0.341
1	1,070	440 (40.8%)	639 (59.2%)		359 (51.1%)	344 (48.9%)	
2	4,036	1,430 (35.4%)	2,606 (64.6%)		1,196 (50.4%)	1,177 (49.6%)	
3	1,273	398 (31.3%)	875 (68.7%)		338 (47.1%)	380 (52.9%)	
Unknown	266	99 (37.2%)	167 (62.8%)		80 (52.6%)	72 (47.4%)	
Adjuvant chemotherapy				p<0.001			p=1.000
No	4,405	2,264 (51.4%)	2,141 (48.6%)		1,877 (50.0%)	1,877 (50.0%)	
Yes	2,249	103 (4.6%)	2,146 (95.4%)		96 (50.0%)	96 (50.0%)	

[*] *Not otherwise specified*

Table 2. Independent predictors associated with adjuvant radiotherapy

Variable	Hazard ratio	95% Confidence interval	p-value
Age			
<63 years	Reference		
≥63 years	0.721	0.623 – 0.834	p<0.001
Gender			
Male	Reference		
Female	0.895	0.800 – 1.002	p=0.053
Race			
Black	Reference		
White	0.866	0.706 – 1.062	p=0.166
Hispanic	1.036	0.743 – 1.445	p=0.835
Asian	1.267	0.868 – 1.849	p=0.221
Charlson/Deyo comorbidity score			
0	Reference		
1	0.844	0.738 – 0.965	p=0.013
2	0.516	0.415 – 0.641	p<0.001
Insurance status			
Private	Reference		
Uninsured	1.016	0.785 – 1.314	p=0.905
Medicaid	0.832	0.689 – 1.006	p=0.057
Medicare	0.762	0.657 – 0.885	p<0.001
Site			
Anterior 2/3 tongue	Reference		
Lip	0.680	0.478 – 0.968	p=0.032
Floor of mouth	0.839	0.680 – 1.034	p=0.099
Gingiva	0.819	0.657 – 1.020	p=0.075
Hard palate	0.745	0.518 – 1.073	p=0.114
Buccal mucosa	0.797	0.622 – 1.021	p=0.073
Vestibule of mouth	0.577	0.304 – 1.097	p=0.093
Retromolar trigone	1.010	0.785 – 1.298	p=0.941
Oral cavity, NOS [§]	0.713	0.541 – 0.941	p=0.017
Extracapsular extension			
No	Reference		
Yes	1.303	1.112 – 1.527	p=0.001

(continued)

Variable	Hazard ratio	95% Confidence interval	p-value
Positive surgical margins			
No	Reference		
Yes	1.388	1.199 – 1.607	p<0.001
T stage			
1	Reference		
2	1.295	1.012 – 1.658	p=0.040
3	1.065	0.804 – 1.411	p=0.661
4	1.254	1.021 – 1.540	p=0.031
N stage			
0	Reference		
1	1.299	1.104 – 1.528	p=0.002
2	2.004	1.710 – 2.349	p<0.001
3	1.474	0.739 – 2.941	p=0.271
Grade			
1	Reference		
2	1.043	0.899 – 1.210	p=0.581
3	1.136	0.944 – 1.366	p=0.177
Unknown	0.956	0.708 – 1.290	p=0.767

Table 3. Cox regression univariate and multivariable analysis for overall survival for all patients

	Univariate			Multivariable		
Variable	**Hazard ratio**	**95% Confidence interval**	**p-value**	**Hazard ratio**	**95% Confidence interval**	**p-value**
Age at diagnosis*	1.021	1.017 – 1.025	p<0.001	1.021	1.016 – 1.026	p<0.001
Gender						
Male	Reference			N.D.μ		
Female	1.033	0.919 – 1.095	p=0.948			
Race						
Black	Reference			N.D.μ		
White	0.973	0.836 – 1.132	p=0.973			
Hispanic	0.794	0.605 – 1.043	p=0.794			
Asian	0.832	0.611 – 1.131	p=0.832			
Charlson/Deyo comorbidity score						
0	Reference			Reference		
1	1.182	1.063 – 1.314	p=0.002	1.094	0.982 – 1.219	p=0.102
2	1.870	1.602 – 2.184	p<0.001	1.646	1.404 – 1.930	p<0.001
Insurance status						
Private	Reference			Reference		
Uninsured	1.094	0.887 – 1.350	p=0.401	1.104	0.893 – 1.364	p=0.361
Medicaid	1.419	1.225 – 1.644	p<0.001	1.429	1.230 – 1.659	p<0.001
Medicare	1.650	1.492 – 1.824	p<0.001	1.263	1.118 – 1.427	p<0.001
Site						
Anterior 2/3 tongue	Reference			Reference		
Lip	0.704	0.520 – 0.951	p=0.022	0.604	0.443 – 0.824	p=0.001
Floor of mouth	1.006	0.861 – 1.175	p=0.940	0.850	0.721 – 1.002	p=0.053

(continued)

	Univariate			Multivariable		
Variable	**Hazard ratio**	**95% Confidence interval**	**p-value**	**Hazard ratio**	**95% Confidence interval**	**p-value**
Gingiva	0.861	0.731 – 1.012	p=0.070	0.716	0.599 – 0.856	p<0.001
Hard palate	1.275	0.971 – 1.674	p=0.081	0.893	0.674 – 1.185	p=0.433
Buccal mucosa	1.189	0.984 – 1.438	p=0.073	1.037	0.852 – 1.262	p=0.718
Vestibule of mouth	1.268	0.773 – 2.079	p=0.347	0.856	0.521 – 1.407	p=0.540
Retromolar trigone	0.967	0.803 – 1.165	p=0.727	0.771	0.633 – 0.939	p=0.010
Oral cavity, NOS [$]	1.011	0.817 – 1.252	p=0.917	0.813	0.649 – 1.019	p=0.073
Extracapsular extension						
No	Reference			Reference		
Yes	1.952	1.782 – 2.138	p<0.001	1.469	1.312 – 1.644	p<0.001
Positive surgical margins						
No	Reference			Reference		
Yes	1.261	1.138 – 1.396	p<0.001	1.386	1.247 – 1.541	p<0.001
T stage						
1	Reference			Reference		
2	1.556	1.259 – 1.923	p<0.001	1.504	1.213 – 1.864	p<0.001
3	1.685	1.336 – 2.125	p<0.001	2.101	1.652 – 2.673	p<0.001
4	1.580	1.329 – 1.879	p<0.001	2.160	1.797 – 2.597	p<0.001
N stage						
0	Reference			Reference		
1	1.252	1.105 – 1.417	p<0.001	1.531	1.332 – 1.760	p<0.001
2	2.121	1.926 – 2.335	p<0.001	2.318	2.046 – 2.627	p<0.001
3	2.711	1.738 – 4.229	p<0.001	2.662	1.651 – 4.295	p<0.001

(continued)

	Univariate			Multivariable		
Variable	**Hazard ratio**	**95% Confidence interval**	**p-value**	**Hazard ratio**	**95% Confidence interval**	**p-value**
Grade						
1	Reference			Reference		
2	1.094	0.968 – 1.236	p=0.152	0.997	0.878 – 1.132	p=0.964
3	1.370	1.188 – 1.578	p<0.001	1.110	0.957 – 1.287	p=0.168
Unknown	1.114	0.882 – 1.407	p=0.366	1.062	0.834 – 1.350	p=0.627
Adjuvant radiotherapy						
No	Reference			Reference		
Yes	0.756	0.692 – 0.825	p<0.001	0.640	0.582 – 0.704	p<0.001
Adjuvant chemotherapy						
No	Reference			N.D.[μ]		
Yes	1.035	0.947 – 1.132	p=0.444			

[*] *Analyzed as a continuous variable*
[§] *Not otherwise specified*
[μ] *Not determined*

Table 4. Cox regression univariate and multivariable analysis for overall survival for propensity-matched patients

	Univariate			Multivariable		
Variable	**Hazard ratio**	**95% Confidence interval**	**p-value**	**Hazard ratio**	**95% Confidence interval**	**p-value**
Age at diagnosis*	1.025	1.020 – 1.030	p<0.001	1.024	1.018 – 1.031	p<0.001
Gender						
Male	Reference			N.D.μ		
Female	1.017	0.908 – 1.138	p=0.773			
Race						
Black	Reference					
White	0.921	0.752 – 1.128	p=0.427	0.914	0.741 – 1.127	p=0.400
Hispanic	0.656	0.445 – 0.968	p=0.033	0.665	0.449 – 0.984	p=0.042
Asian	0.797	0.530 – 1.197	p=0.274	0.896	0.591 – 1.356	p=0.602
Charlson/Deyo comorbidity score						
0	Reference			Reference		
1	1.266	1.105 – 1.449	p=0.001	1.186	1.035 – 1.360	p=0.014
2	1.964	1.603 – 2.406	p<0.001	1.776	1.447 – 2.181	p<0.001
Insurance status						
Private	Reference			Reference		
Uninsured	1.170	0.875 – 1.564	p=0.290	1.192	0.889 – 1.600	p=0241
Medicaid	1.603	1.309 – 1.963	p<0.001	1.560	1.265 – 1.925	p<0.001
Medicare	1.828	1.597 – 2.093	p<0.001	1.318	1.120 – 1.550	p=0.001
Site						
Anterior 2/3 tongue	Reference			Reference		
Lip	0.644	0.435 – 0.955	p=0.029	0.570	0.383 – 0.848	p=0.006
Floor of mouth	1.054	0.846 – 1.314	p=0.636	0.992	0.788 – 1.248	p=0.946

(continued)

	Univariate			Multivariable		
Variable	**Hazard ratio**	**95% Confidence interval**	**p-value**	**Hazard ratio**	**95% Confidence interval**	**p-value**
Gingiva	0.792	0.632 – 0.993	p=0.044	0.746	0.583 – 0.953	p=0.019
Hard palate	1.322	0.924 – 1.889	p=0.126	0.921	0.637 – 1.330	p=0.660
Buccal mucosa	1.143	0.878 – 1.486	p=0.321	1.072	0.819 – 1.403	p=0.612
Vestibule of mouth	1.630	0.914 – 2.905	p=0.098	0.952	0.532 – 1.705	p=0.870
Retromolar trigone	1.014	0.787 – 1.307	p=0.912	0.884	0.678 – 1.151	p=0.359
Oral cavity, NOS [$]	0.990	0.739 – 1.325	p=0.944	0.885	0.654 – 1.197	p=0.427
Extracapsular extension						
No	Reference			Reference		
Yes	2.703	2.370 – 3.083	p<0.001	1.745	1.490 – 2.044	p<0.001
Positive surgical margins						
No	Reference			Reference		
Yes	1.654	1.438 – 1.903	p<0.001	1.425	1.236 – 1.644	p<0.001
T stage						
1	Reference			Reference		
2	1.494	1.131 – 1.972	p=0.005	1.356	1.026 – 1.792	p=0.033
3	1.590	1.183 – 2.139	p=0.002	2.018	1.480 – 2.750	p<0.001
4	1.304	1.043 – 1.630	p=0.020	1.924	1.514 – 2.444	p<0.001
N stage						
0	Reference			Reference		
1	1.409	1.210 – 1.639	p<0.001	1.578	1.329 – 1.873	p<0.001
2	2.785	2.453 – 3.162	p<0.001	2.341	1.997 – 2.745	p<0.001
3	3.947	1.764 – 8.830	p=0.001	2.481	1.091 – 5.645	p=0.030

(continued)

	Univariate			Multivariable		
Variable	**Hazard ratio**	**95% Confidence interval**	**p-value**	**Hazard ratio**	**95% Confidence interval**	**p-value**
Grade						
1	Reference			Reference		
2	1.064	0.910 – 1.243	p=0.436	0.969	0.827 – 1.136	p=0.698
3	1.395	1.162 – 1.674	p<0.001	1.086	0.899 – 1.313	p=0.392
Unknown	1.079	0.796 – 1.464	p=0.624	0.997	0.733 – 1.356	p=0.984
Adjuvant radiotherapy						
No	Reference			Reference		
Yes	0.683	0.611 – 0.764	p<0.001	0.642	0.573 – 0.719	p<0.001
Adjuvant chemotherapy						
No	Reference			N.D.[µ]		
Yes	1.208	0.942 – 1.548	p=0.136			

[*] *Analyzed as a continuous variable*
[§] *Not otherwise specified*
[µ] *Not determined*

Table 5. Kaplan-Meier five-year overall survival stratified by patient and tumor characteristics for propensity-matched patients

	No adjuvant radiotherapy	Adjuvant radiotherapy	Log-rank p-value
Overall	37.0% (±2.4)	47.7% (±2.2)	p<0.001
Age			
<63 years	44.4% (±4.3)	53.5% (±3.4)	p=0.076
≥63 years	31.9% (±2.7)	43.6% (±3.0)	p<0.001
Charlson/Deyo comorbidity score			
0	38.0% (±3.0)	47.8% (±2.7)	p<0.001
1	33.5% (±4.1)	54.6% (±3.5)	p<0.001
2	30.2% (±6.0)	26.5% (±7.7)	p=0.635
Extracapsular extension			
No	41.4% (±2.6)	50.5% (±2.5)	p<0.001
Positive margins			
No	44.1% (±2.9)	51.6% (±2.7)	p<0.001
N2	29.5% (±7.3)	30.9% (±6.7)	p=0.073
T3-4	44.2% (±3.0)	51.2% (±2.9)	p<0.001
Yes	24.6% (±5.9)	43.4% (±6.0)	p=0.001
Yes	15.0% (±3.0)	32.3% (±4.2)	p<0.001
Positive surgical margins			
No	40.0% (±2.6)	49.0% (±2.5)	p<0.001
Extracapsular extension			
No	44.1% (±2.9)	51.6% (±2.7)	p<0.001
N2	29.5% (±7.3)	30.9% (±6.7)	p=0.073
T3-4	44.2% (±3.0)	51.2% (±2.9)	p<0.001
Yes	16.6% (±3.6)	33.9% (±4.9)	p<0.001
Yes	19.8% (±4.8)	39.9% (±4.9)	p<0.001
T stage			
1	57.8% (±5.1)	50.8% (±10.3)	p=0.487
2	24.0% (±10.5)	45.1% (±6.3)	p=0.073
3	24.2% (±8.1)	43.6% (±10.0)	p=0.003
4	38.2% (±2.6)	47.8% (±2.5)	p<0.001
N stage			
0	47.0% (±3.2)	58.8% (±2.7)	p<0.001

(continued)

	No adjuvant radiotherapy	**Adjuvant radiotherapy**	**Log-rank p-value**
1	32.4% (±7.2)	43.6% (±6.9)	p=0.003
2	18.9% (±4.1)	25.3% (±4.4)	p<0.001
3	--	--	--
Grade			
1	46.8% (±5.8)	44.9% (±5.2)	p=0.161
2	38.1% (±3.0)	49.7% (±2.8)	p<0.001
3	31.3% (±3.9)	46.0% (±5.6)	p<0.001
Unknown	27.0% (±10.2)	45.8% (±9.0)	p=0.703

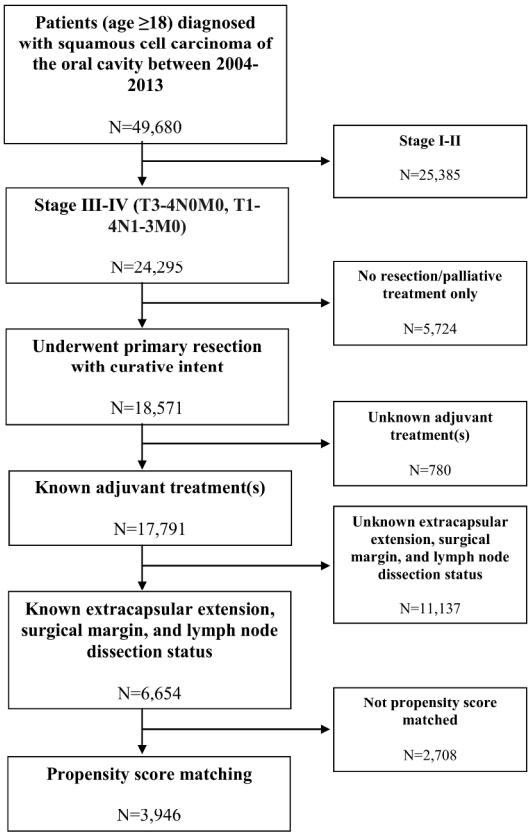

Figure 1. Flowchart describing the composition of the patient cohort

215x279mm (300 x 300 DPI)

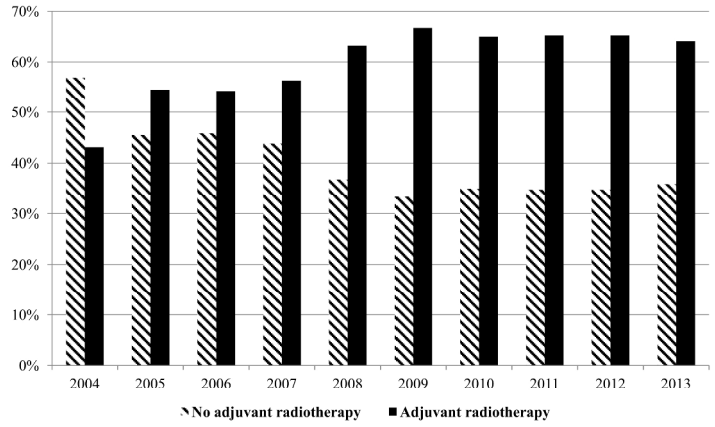

Figure 2. Utilization of adjuvant radiotherapy over the time period 2004-2013 (p=0.019, Chi-square test)

279x215mm (300 x 300 DPI)

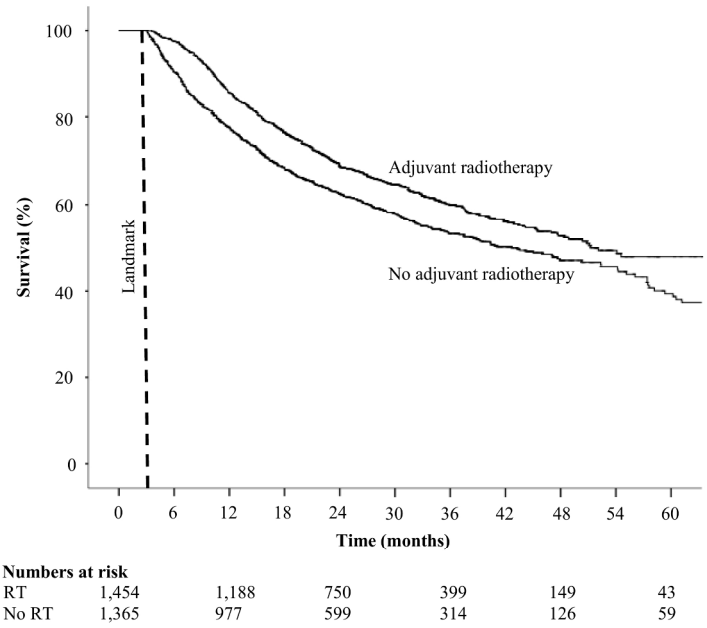

Figure 3. Kaplan-Meier overall survival by landmark analysis of propensity matched patients alive at 3 months ($p<0.001$)

215x279mm (300 x 300 DPI)