Survival effect of postoperative radiotherapy combined with lymph nodes examined on cavity squamous cell carcinoma patients with stage T1-2N1M0: a propensity-adjusted SEER database analysis

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Abstract

Background

To explore the association between postoperative radiotherapy (PORT) combined with lymph nodes examined (LNE) and the survival outcome for pT1-2N1M0 oral cavity squamous cell carcinoma (OCSCC) patients.

Methods

This study retrieved patients who underwent dissection of primary site and neck lymph nodes for pT1-2N1 OCSCC without adverse nodal features from the Surveillance, Epidemiology, and End Results database from 2004 to 2015. Patients were divided into groups according if PORT was conducted. Propensity score matching (PSM) analysis was conducted and the best cut-off value of the LNE was determined by X-tile. Cancer-specific survival (CSS) was the primary outcome. Univariable and multivariable analyses were performed to assess the relation between PORT and CSS, adjusting for other prognostic factors.

Results

A total of 469 patients were finally enrolled according to our exclusion criteria and then 170 pairs of patients were matched by PSM. The best cut-off value of the LNE was determined by X-tile, stratifying patients into LNE $\leq$ 16 group and LNE > 16 group. For the whole matched cohort, whether patients chose PORT had no correlation with other factors (all $p > 0.05$), and it revealed that PORT made no contribution to a better survival outcome for patients ($p = 0.253$). While stratified by the LNE, among the LNE $\leq$ 16 group, a statistically significant improved CSS was found for those who undertook PORT (hazard ratio, 0.521; 95% confidence interval, 0.294–0.925; $p = 0.022$).

Conclusions

The PORT made no contribution on CSS of OCSCC patients with pT1-2N1M0 stage on the whole cohort. While among the LNE $\leq$ 16 group, PORT conferred a superior CSS compared with surgery only, indicating the necessity for surgeons to conduct a thorough neck dissection.

Introduction

Head and neck cancers are the seventh most common malignancy in the world with annually 887,000 new cases and 453,000 deaths, and squamous cell carcinoma (SCC) accounts for approximately 90% of the whole.[1, 2] Oral cavity SCC (OCSCC) is the most common malignancy of head and neck (excluding nonmelanoma skin cancer) with a gradually increasing incidence.[3–5] Unlike the development of treatment mode, the 5-year overall survival (OS) rate of OCSCC consistently remained around 50% over the past 30 years.[3] For the early stage of OCSCC with pN0, there is a well-supported consensus on the observation after radical surgery if there are no indications for primary site radiotherapy.[6–8] While for those pN1 patients without adverse nodal features, the utilization of postoperative radiotherapy (PORT) is variable. Several previous studies supported that PORT contributed to the better survival for early stage OCSCC patients with lymph nodes positive.[9–11] While others reported that adjuvant radiotherapy made no difference for the OS or oral cancer-specific survival (CSS) of patients with early stage oral carcinoma.[12–14]

According to the updated National Comprehensive Cancer Network (NCCN) guidelines,[15] for patients with pT1-2 stage after radical dissection of primary site and neck lymph nodes, if the pathological examination proves a single lymph node positive, PORT is worth considering. Then the actually practical recommendation is finally provided based on surgeons' personally assessment, which is rather heterogeneous without a stable baseline. Actually, there is still no compelling evidence from prospective randomized study on the decision whether PORT should be applied for the pT1-2N1 OCSCC. Based on the growing pool of evidence which was mainly derived from retrospective study, the American Society of Clinical Oncology (ASCO) stated more precise suggestions that the PORT is ought to be administrated to OCSCC patients with pN1 stage and simultaneously without an adequate neck dissection conducted.[16] Unlike the colorectal cancer, for which the minimum of 12 lymph nodes has been included in the NCCN guidelines,[17] there is still no established consensus regarding the threshold on the number of lymph nodes that should be removed along with the excision of primary carcinoma for OCSCC.

Therefore, to make a contribution to the evidence for a better assessment system, our study was designed to explore whether PORT conferred a survival benefit for OCSCC patients with pT1-2N1M0 stage and if the results would be different when the patients were stratified on the number of lymph nodes examined (LNE).

Methods

Data Source

The Surveillance, Epidemiology, and End Results (SEER) database was used to extract data on patients diagnosed with OCSCC between 2004 and 2015 for the present study. Sponsored by the National Cancer Institute, the SEER program collects demographic, clinicopathologic and survival data from eighteen population-based cancer registries (SEER-18) in the United States. Since the SEER-18 covers 27.8% of the population in the US with a typical distribution, it is thought to be representative of the US population as a whole. Information of each patient was retrieved, including age at diagnosis, sex, race, marital status, site of primary tumor, survival months, vital status, grade, TNM staging (reevaluated according to the American Joint committee on Cancer (AJCC) TNM staging system, 8th edition, 2017), histology, the number of LNE, the number of positive lymph nodes, the receipt of surgery and adjuvant therapy (including radiotherapy and chemotherapy), the sequence of radiotherapy and causes of death.

Subjects

The process for patient selection is clearly shown in Fig. 1. Patients were identified for study according to the International Classification of Diseases for Oncology, Third Edition, topography codes for oral cavity (tongue C02.0-02.9, gum C03.0-03.9, floor of mouth C04.0-04.9, palate C05.0-05.9, other parts of mouth C-06.0-06.9), and morphologically coding 8052, 8070–8076, 8083–8084, 8094, and 8560 for squamous cell carcinoma. For the purpose of our study, specific patients were included who stated with T1 or T2 stage and N1 stage and without distant metastasis. Then a total of 1987 cases were retrieved from SEER database. Ineligible cases were excluded for further analysis according the following requirements: (1) surgery not performed for various reasons; (2) chemotherapy conducted; (3) not one primary only; (4) follow-up < 60 months; (5) regional nodes examined was 0 or 1 and regional positive nodes was more than 1 or unknown; (6) radiation applied before surgery or sequence unknown; (7) age < 18 years old; (8) essential information incomplete. Finally, a cohort of 469 patients were diagnosed with OCSCC and underwent resection of primary carcinoma and neck lymph nodes with or without PORT between 2004 and 2015 in US. The main outcome of the analysis was CSS, which was defined as the number of months from diagnosis to the date of death due to OCSCC. Those who were still alive or dead of other cancers at the end of the follow-up period were defined as censored.

Propensity Score Matching (PSM)

The number of LNE was analyzed by using the X-tile plot[18, 19] to determine the appropriate cut-off value, and according to the cut-off value, patients were stratified into LNE ≤ 16 group and LNE > 16 group. To improve the evidence level of the study group, we performed a 1:1 patient pairing (nearest-neighbor matching) by using PSM.[20, 21] We used LNE and several other variables (sex, pT stage, age at diagnosis, race, marital status, grade) as covariates in this PSM model. Finally, 170 pairs of OCSCC patients were matched after 129 cases were discarded. The differences in propensity score in each pair were no more than 0.01. Baseline demographic and tumor characteristics stratified by the number of LNE among the original groups are shown in Table 1.

Table 1
Associations between lymph nodes examined or postoperative radiotherapy and clinicopathological characteristics of OCSCC patients.

Variables	Total	LNE		*P*	PORT		*P*
		≤ 16 (%)	> 16 (%)		Yes (%)	No (%)	
Total	469	123 (26.2)	346 (73.8)		267 (56.9)	202 (43.1)	
Sex				0.345*			0.196*
Male	269	75 (61.0)	194 (56.1)		160 (59.9)	109 (54.0)	
Female	200	48 (39.0)	152 (43.9)		107 (40.1)	93 (46.0)	
Age (year)				0.050*			0.412*
≤ 60	239	55 (44.7)	184 (53.2)		141 (52.8)	98 (48.5)	
60–80	200	55 (44.7)	145 (41.9)		112 (42.0)	88 (43.6)	
> 80	30	13 (10.6)	17 (4.9)		14 (5.2)	16 (7.9)	
Grade				0.280*			0.125*
Well	42	11 (9.0)	31 (9.0)		18 (6.7)	24 (11.9)	
Moderate	329	80 (65.0)	249 (72.0)		189 (70.8)	140 (69.3)	
Poor	98	32 (26.0)	66 (19.0)		60 (22.5)	38 (18.8)	
Subsite				0.101**			0.225**
Tongue	286	84 (68.3)	202 (58.4)		160 (59.9)	126 (62.3)	
Gum	31	11 (8.9)	20 (5.8)		13 (4.9)	18 (8.9)	
Floor of mouth	75	13 (10.6)	62 (17.9)		45 (16.9)	30 (14.9)	
Palate	17	3 (2.4)	14 (4.0)		9 (3.3)	8 (4.0)	
Others	60	12 (9.8)	48 (13.9)		40 (15.0)	20 (9.9)	
T stage				0.919*			0.138*
T1	223	58 (47.2)	165 (47.7)		119 (44.6)	104 (51.5)	
T2	246	65 (52.8)	181 (52.3)		148 (55.4)	98 (48.5)	
Race				0.571*			0.893*
White	413	107 (87.0)	306 (88.4)		236 (88.4)	177 (87.6)	

LNE, Lymph nodes examined; PORT, postoperative radiotherapy; *Chi-squared test; **Fisher exact test.

Variables	Total	LNE		P	PORT		P
		≤ 16 (%)	> 16 (%)		Yes (%)	No (%)	
Black	23	5 (4.1)	18 (5.2)		12 (4.5)	11 (5.5)	
Other	33	11 (8.9)	22 (6.4)		19 (7.1)	14 (6.9)	
Marital status				0.224**			0.022**
Married	266	76 (61.8)	190 (54.9)		166 (62.2)	100 (49.5)	
Unmarried	186	45 (36.6)	141 (40.8)		92 (34.4)	94 (46.5)	
Unknown	17	2 (1.6)	15 (4.3)		9 (3.4)	8 (4.0)	

LNE, Lymph nodes examined; PORT, postoperative radiotherapy; *Chi-squared test; **Fisher exact test.

Statistical analysis

We used frequencies and proportions for categorical variables to describe the patient characteristics and compared the differences between the two groups using the Chi-squared test and Fisher exact test. The Kaplan–Meier method and the log-rank test were performed to evaluate the role of LNE in the survival of OCSCC patients. We also performed a multivariate Cox regression analysis to identify the independent risk factors of OCSCC patients. Hazard ratios (HR) with 95% confidence intervals (95% CIs) were calculated by univariable and multivariable Cox proportional hazard regression analyses. All statistical tests were two-sided, with statistical significance evaluated at the 0.05 a-level. All calculations were performed using SPSS Statistics 25.0 software (IBM SPSS, Inc., Chicago, IL, USA) and X-tile software version 3.6.1 (http://tissuearray.org).

Results

Patients Demographics

The Clinical Research Ethic Committee of Sun Yat-sen University Cancer Center considered this study exempt because we used existing data without patient identifiers. From January 2004 to December 2015, there were totally 1987 patients with pT1-2N1M0 OCSCC, and only 469 patients were enrolled into our study according to the criteria before PSM with the median age of 60 years old (range, 20 to 91). The median survival time was 40 months (range, 2 to 155). Of the whole cohort, tongue was the most common primary site and the majority was moderately differentiated squamous cell carcinoma. Male took up 57.4% of the total and the male were slightly more likely to accept adjuvant radiotherapy compared with that in female group but without statistical significance (59.5% vs. 53.5%, $p = 0.196$). The detailed characteristics of patients before PSM were listed in Table 1.

After PSM, a total of 170 pairs of patients were matched (according to the treatment of surgery only or surgery with PORT), and the clinicopathological characteristics were listed in Table 2. In the matched cohort, the median age of 60 years old (range, 20 to 91), and the median survival time was 42 months (range, 2 to 155). The majority were male (57.6%), married (56.2%) and white (87.9%). Of the whole, 215 patients (63.2%) died and 157 (46.2%) of them were specific to OCSCC. According to the Chi-squared test and Fisher exact test based on the analysis of sex, LNE, age, grade, subsite, pT stage, race, marital status, whether OCSCC patients chose to take adjuvant radiotherapy after radical surgery had no statistically relationship with these factors mentioned above (all $p > 0.05$, Table 2).

Table 2
Associations between adjuvant radiation and clinicopathological characteristics of OCSCC matched patients.

Variables	Total	PORT		P
		Yes (%)	No (%)	
Total	340	170 (50)	170 (50)	
Sex				1.000*
Male	196 (57.6)	98 (57.6)	98 (57.6)	
Female	144 (42.4)	72 (42.4)	72 (42.4)	
LNE				0.548*
≤ 16	97 (28.5)	51 (30)	46 (27.1)	
> 16	243 (71.5)	119 (70)	124 (72.9)	
Age (year)				0.159*
≤ 60	179 (52.6)	81 (47.6)	98 (57.6)	
60–80	97 (28.5)	52 (30.6)	45 (26.5)	
> 80	64 (18.9)	37 (21.8)	27 (15.9)	
Grade				0.441*
Well	33	14 (8.2)	19 (11.2)	
Moderate	231	114 (67.1)	117 (68.8)	
Poor	76	42 (24.7)	34 (20.0)	
Subsite				0.302*
Tongue	207 (60.9)	97 (57.1)	110 (64.7)	
Gum	21 (6.2)	10 (5.9)	11 (6.5)	
Floor of mouth	56 (16.5)	30 (17.6)	26 (15.3)	
Palate	14 (4.1)	6 (3.5)	8 (4.7)	
Others	42 (12.4)	27 (15.9)	15 (8.8)	
pT stage				0.745*
T1	179 (52.6)	88 (51.8)	91 (53.5)	

PORT: postoperative radiotherapy; LNE: lymph nodes examined; *Chi-squared test; **Fisher exact test.

Variables	Total	PORT		P
		Yes (%)	No (%)	
T2	161 (47.4)	82 (48.2)	79 (46.5)	
Race				0.548*
White	299 (87.9)	149 (87.6)	150 (88.2)	
Black	19 (5.6)	8 (4.7)	11 (6.5)	
Other	22 (6.5)	13 (7.7)	9 (5.3)	
Marital status				0.839**
Married	191 (56.2)	97 (57.0)	94 (55.3)	
Unmarried	139 (40.9)	69 (40.6)	70 (41.2)	
Unknown	12 (2.9)	4 (2.4)	6 (3.5)	

PORT: postoperative radiotherapy; LNE: lymph nodes examined; *Chi-squared test; **Fisher exact test.

Relationship between PORT and CSS of LNE stratified patients

We used X-tile plot to determine the best cut-off value on the number of LNE and it turned out to be 16. Then the whole group was divided into LNE ≤ 16 and LNE > 16. According to the results of Kaplan−Meier analysis, the LNE > 16 group presented with a superior CSS than the LNE ≤ 16 in general ($p = 0.004$, Table 3), and the CSS revealed no difference between the surgery only group and PORT group both before ($p = 0.264$, Fig. 2) and after ($p = 0.253$, Fig. 3) PSM. When stratified by LNE, for the LNE ≤ 16 group, patients who underwent PORT had a superior survival compared with that took surgery only both before ($p = 0.009$, Fig. 2) and after ($p = 0.022$, Fig. 3) PSM. While the results revealed no significance in LNE > 16 group both before ($p = 0.878$, Fig. 2) and after ($p = 0.983$, Fig. 3) PSM.

Table 3
Univariable and multivariable analysis on CSS by Cox regression model

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Before PSM				
Sex				
Male	1 (ref)			
Female	1.231 (0.945, 1.602)	0.124		
Age (year)				
≤ 60	1 (ref)			
60–80	1.079 (0.821, 1.418)	0.587		
> 80	1.578 (0.921, 2.705)	0.097		
Grade				
Well	1 (ref)			
Moderate	1.468 (0.850, 2.535)	0.168		
Poor	1.730 (0.955, 3.134)	0.071		
Lymph nodes examined				
≤ 16	1 (ref)		1 (ref)	
> 16	0.686 (0.515, 0.914)	**0.010**	0.653 (0.488, 0.872)	**0.004**
Treatment				
Surgery only	1 (ref)			
Radiation after surgery	1.160 (0.892, 1.510)	0.269		
Subsite				
Tongue	1 (ref)			
Gum	1.313 (0.781, 2.208)	0.304		
Floor of mouth	1.251 (0.872, 1.797)	0.224		
Palate	1.553 (0.815, 2.957)	0.181		
Other	1.098 (0.734, 1.642)	0.650		

PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; CSS, cancer-specific survival; PORT, postoperative radiotherapy.

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
pT stage				
T1	1 (ref)			
T2	1.243 (0.955, 1.618)	0.106		
Race				
White	1 (ref)			
Black	1.435 (0.834, 2.469)	0.192		
Other	1.290 (0.805, 2.067)	0.290		
Marital status				
Married	1 (ref)		1 (ref)	
Unmarried	1.394 (1.068, 1.820)	**0.015**	1.474 (1.125, 1.931)	**0.005**
Unknown	0.488 (0.180, 1.322)	0.158	0.520 (0.192, 1.408)	0.198
After PSM				
Sex				
Male	1 (ref)			
Female	1.206 (0.880, 1.651)	0.243		
Age (year)				
≤ 60	1 (ref)		1 (ref)	
60–80	0.846 (0.574, 1.245)	0.396	0.792 (0.536, 1.168)	0.239
> 80	1.619 (1.095, 2.395)	**0.016**	1.760 (1.182, 2.619)	**0.005**
Grade				
Well	1 (ref)			
Moderate	1.494 (0.804, 2.778)	0.204		
Poor	1.787 (0.911, 3.504)	0.091		
Lymph nodes examined				
≤ 16	1 (ref)			

PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; CSS, cancer-specific survival; PORT, postoperative radiotherapy.

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
> 16	0.763 (0.543, 1.072)	0.119		
Treatment				
Surgery only	1 (ref)			
PORT	0.834 (0.609, 1.142)	0.257		
Subsite				
Tongue	1 (ref)			
Gum	1.038(0.524, 2.059)	0.914		
Floor of mouth	1.231 (0.802, 1.889)	0.343		
Palate	1.599 (0.776, 3.294)	0.203		
Other	1.065 (0.657, 1.727)	0.799		
pT stage				
T1	1 (ref)			
T2	1.296 (0.948, 1.773)	0.104		
Race				
White	1 (ref)			
Black	1.377 (0.744, 2.547)	0.308		
Other	1.307 (0.740, 2.311)	0.356		
Marital status				
Married	1 (ref)		1 (ref)	
Unmarried	1.483 (1.080, 2.038)	**0.015**	1.659 (1.197, 2.298)	**0.002**
Unknown	0.763 (0.241, 2.414)	0.645	0.834 (0.263, 2.651)	0.759

PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; CSS, cancer-specific survival; PORT, postoperative radiotherapy.

In the matched group, we performed a univariate analysis based on sex, age, grade, LNE, treatment, subsite, T stage, race and marital status, and found that for the whole group, age (p = 0.016) and marital status (p = 0.015, Table 3) were statistically significant. While for the LNE ≤ 16 group, sex (p = 0.003), treatment (p = 0.026) and marital status (p = 0.007) were statistically significant, and then these factors were included into multivariate COX regression analysis, indicating that sex, treatment and marital status were independent risk factors for OCSCC (all $p < 0.05$, Table 4). Female compared with male, had a HR of 1.963 (95% CI 1.008, 3.542; $p = 0.025$). Compared with patients who underwent surgery only, patients with PORT had a HR of 0.519 (95% CI 0.289, 0.930; $p = 0.028$), and the unmarried group had a HR of 2.104 (95% CI 1.154, 3.897; $p = 0.015$) compared with the married group.

Table 4
Univariable and multivariable analysis on CSS by Cox regression model (after PSM and lymph nodes examined ≤ 16).

Variables	**Univariable analysis**		**Multivariable analysis**	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Sex				
Male	1 (ref)		1 (ref)	
Female	2.425 (1.365, 4.305)	**0.003**	1.963 (1.008, 3.542)	**0.025**
Age (year)				
≤ 60	1 (ref)			
60–80	0.745 (0.344, 1.610)	0.396		
> 80	1.612 (0.851, 3.055)	0.143		
Grade				
Well	1 (ref)			
Moderate	2.209 (0.677, 7.204)	0.189		
Poor	1.914 (0.540, 6.784)	0.315		
Treatment				
Surgery only	1 (ref)		1 (ref)	
PORT	0.520 (0.293, 0.924)	**0.026**	0.519 (0.289, 0.930)	**0.028**
Subsite				
Tongue	1 (ref)			
Gum	0.608 (0.186, 1.980)	0.408		
Floor of mouth	1.050 (0.372, 2.968)	0.926		
Palate	0.972 (0.133, 7.121)	0.978		
Other	1.384 (0.580, 3.301)	0.463		
pT stage				
T1	1 (ref)			
T2	1.036 (0.587, 1.827)	0.904		
Race				

PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; CSS, cancer-specific survival; PORT, postoperative radiotherapy.

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
White	1 (ref)			
Black	0.445 (0.061, 3.243)	0.424		
Other	1.584 (0.671, 3.743)	0.294		
Marital status				
Married	1 (ref)		1 (ref)	
Unmarried	2.207 (1.242, 3.923)	**0.007**	2.104 (1.154, 3.897)	**0.015**
Unknown	0.980 (0.000, NA)	0.980	NA (NA, NA)	0.973

PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; CSS, cancer-specific survival; PORT, postoperative radiotherapy.

Discussion

Despite the increasing incidence of OCSCC in the US,[4, 5, 22] limited evidence was provided by the pool of prospective study on the inconsistent consensus regarding to whether PORT ought to be applied to OCSCC patients with pT1-2N1M0 stage for the improved survival benefit. According to the NCCN guidelines, there remained considerable flexibility with surgeon's assessment when they made decisions on the adjuvant radiotherapy for those who had only one pathologically positive lymph node without adverse risk features.[15] And studies regarding the impact of adjuvant radiotherapy on the survival for patients with OCSCC were variable. Shrime *et al.* retrospectively reported an improved OS and CSS among OCSCC patients with T2N1 stage based on the analysis of SEER database from 1983 to 2004, while no difference was found among the T1N1 group in this study.[10] Furthermore, Chen *et al*. found that PORT conferred obviously elevated OS for OCSCC patients with T1-2N1 stage, especially for those younger than 70 years old and those with T2 disease, by reviewing the National Cancer Database from 2004 to 2013.[23] Only one small randomized study showed improved CSS in patients with oral cavity (buccal) cancer, but it was restricted in the stage III-IV group.[24] While there were some converse results from other retrospective studies that they suggested a rather low risk of isolated regional recurrence for patients with pN1 OCSCC, and an uncertain survival benefit was demonstrated, supporting a surveillance after radical surgery rather than the PORT.[12–14] Though the suggestions from ASCO demonstrated more clearly that pT1-2N1 patients without adverse risk factors had no need to undergo PORT if adequate neck dissection was conducted, but no direct research focused on the association between PORT and the survival benefit for OCSCC patients with pT1-2N1M0 stage when they were stratified by the number of LNE.

Thus, our study retrieved the demographic and clinical information of OCSCC patients from SEER database (2004–2015), and performed a 1:1 patient pairing by PSM to elevate the level of evidence. The analysis of these highly matched 170 pairs of patients revealed that the pN1 OCSCC patients without adverse nodal features had no statistically different CSS regardless of whether they took PORT or not. We found that whether patients took adjuvant radiotherapy or not had no statistically significance with other factors. And after the stratification of LNE, we found that the LNE ≤ 16 group had inferior CSS than the LNE > 16 group. Among the LNE ≤ 16 group, PORT was the independent factor associated with statistically significant superior CSS, while the difference was absent in the LNE > 16 group. This was quite different from some previous studies that indicated a significantly improved survival among the PORT group than that only undertook the radical surgery.[10, 23, 24]

It is noticeable that the study of Vanessa Torrecillas *et al*. analyzed on nearly the same period (year ranging from 2004 to 2013) of patients from SEER as our study, but the results were totally different. They indicated that treatment with adjuvant radiation therapy was significantly associated with improved 5-year CSS and OS for both patients with T1-2N1 tumors.[9] The reason responsible for the difference might mainly lie in that we excluded patients whose lymph nodes examined were 0 or 1 to avoid enrolling patients did not undergone neck dissection as possible for the SEER database doesn't exactly record whether neck dissection is conducted. This might effectively smooth the interference from the lymph nodes. Though the benefit of neck dissection in patients with early stage oral cavity cancer has been controversial over the decades,[25] a recently published prospective, randomized clinical trial has shed light on this controversy.[26] D'Cruz *et al*. compared patients of cT1-2N0M0 oral cancers who underwent elective neck dissection along with glossectomy with those who underwent therapeutic neck dissection only when regional metastasis happened. And the results indicated that those who received upfront elective neck dissection had significantly improved OS and CSS compared with those who took therapeutic dissection afterwards. The enrollment of those who just take the biopsy of neck lymph nodes might turn the results to a different direction for the absence of neck dissection may mix upper N stage with pN1, and the former group was demonstrated to benefit certainly from PORT.[27, 28] Furthermore, our group had set rather tough exclusions on the database as mentioned ahead, like the exclusion of those with chemotherapy conducted and follow-up < 60 months, trying to reduce the disturbance from other confounding factors by PSM.

We found that whether patients took adjuvant radiotherapy or not had no statistically significance with other factors (all $p < 0.05$). And after the stratification of LNE, we found that among the LNE ≤ 16 group, PORT was the independent factor associated with statistically significant superior CSS. While the difference was absent in the LNE > 16 group. Unlike the well-established metrics of LNE for colorectal cancer,[29] there was not an exact threshold of LNE act as a predictor of survival for patients with OCSCC. Several prior studies had demonstrated that patients with over 16–18 LNE tend to present with a superior OS.[30–32] And Phoebe Kuo *et al*. demonstrated that survival of the whole group improved as higher lymph node yields.[30] In this present study, the best cut-off value of LNE was identified as 16 by the use of X-tile. Several reasons may be the potential explanations for the superior survival for those who underwent

PORT compared with those who underwent surgery only among the LNE $\leq$ 16 group. Unsatisfactory neck dissection might reduce the diagnostic benefit by removing insufficient lymph nodes, detecting a low incidence of extracapsular spread and facilitating an inaccurate N staging, which subsequently might interfere the decisions on adjuvant treatment.[26, 33] Several studies had stated that extensive neck dissection could certainly reduce the regional recurrence, which might be compensated by PORT among patients who underwent unsatisfactory neck dissection or with advanced N stage.[34–36] The unmarried status was found correlated with decreased CSS, including windowed, single, separated and divorced. It has been well-discussed that marriage acts as a significantly protective factor for various carcinomas in an extensive extent of literature, for married patients are more likely to undertake aggressive treatment and enjoy more comprehensive care both physically and psychologically, inducing less likelihood to die from carcinomas.[37, 38]

Limitations are inherent to this retrospective study based on the SEER database. The most obvious limitation of the database is that no specific record regarding whether patients took unilateral or bilateral neck dissections. Therefore, we were not able to exclude the patients whose positive lymph node came from contralateral neck, and they were supposed to be stated as pN2c. Another limitation is that the information about margin status, or vascular or perineural invasion was not available in SEER, which was demonstrated to benefit from PORT. Therefore, given the natural defects in the retrospective study, more prospective and randomized research is needed to further validate our findings.

Conclusions

In conclusion, in this study, we found PORT made no contribution on the oral CSS of patients with pT1-2N1M0 stage on the whole cohort. While among the LNE $\leq$ 16 group, PORT conferred a superior CSS, indicating the necessity for surgeons to conduct a thorough neck dissection.

Abbreviations

PORT: postoperative radiotherapy; LNE: lymph nodes examined; PSM: propensity score matching; CSS: cancer-specific survival; SCC: squamous cell carcinoma; OCSCC: oral cavity squamous cell carcinoma; OS: overall survival; CSS: cancer-specific survival; NCCN: National Comprehensive Cancer Network; ASCO: American Society of Clinical Oncology; SEER: Surveillance, Epidemiology, and End Results; AJCC: American Joint committee on Cancer; HR: hazard ratios; CI: confidence interval.

Declarations

Ethics approval and consent to participate: The study protocol was approved by the Ethics Committee of Sun Yat-sen University Cancer Center; the requirement of informed consent was waived

Consent for publication: All authors agree with publication in this journal.

Availability of data and materials: Any researches interested in this study could contact us for requiring the data.

Competing interests: The authors declare that they have no competing interests.

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Author contributions statement: Conception and design: ZQ and JWM. Administrative support: YAK and ZQ. Provision of study materials or patients: ZQ, CYF and YAK. Collection and assembly of data: JWM, LYD, WHY and FZY. Data analysis and interpretation: JWM and FZY. Manuscript writing: JWM. Final approval of manuscript: JWM, FZY, LYD, WHY, YAK, CYF and ZQ.

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Figures

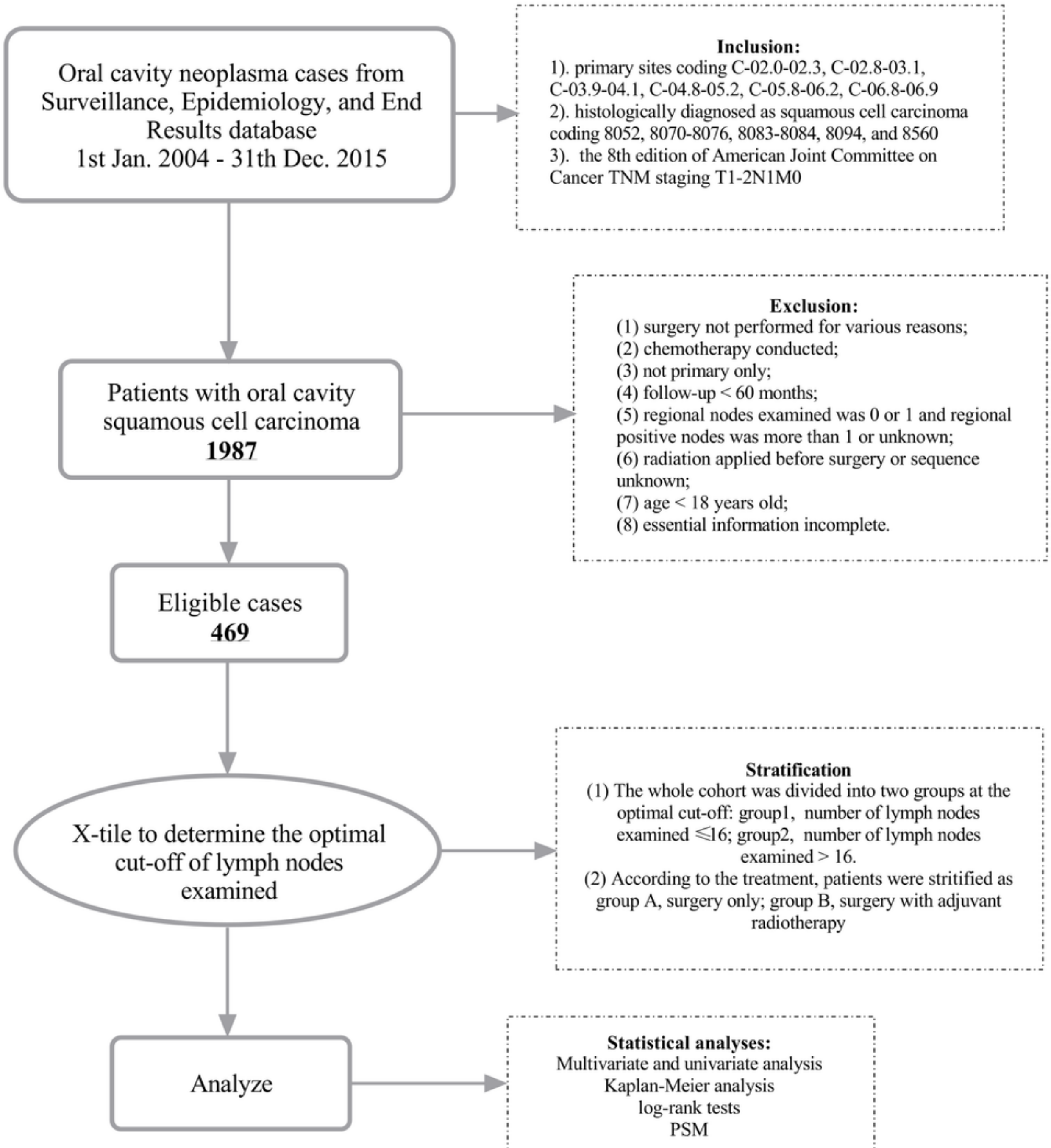

Figure 1

The diagram of the patient screening process in the Surveillance Epidemiology and End Results database.

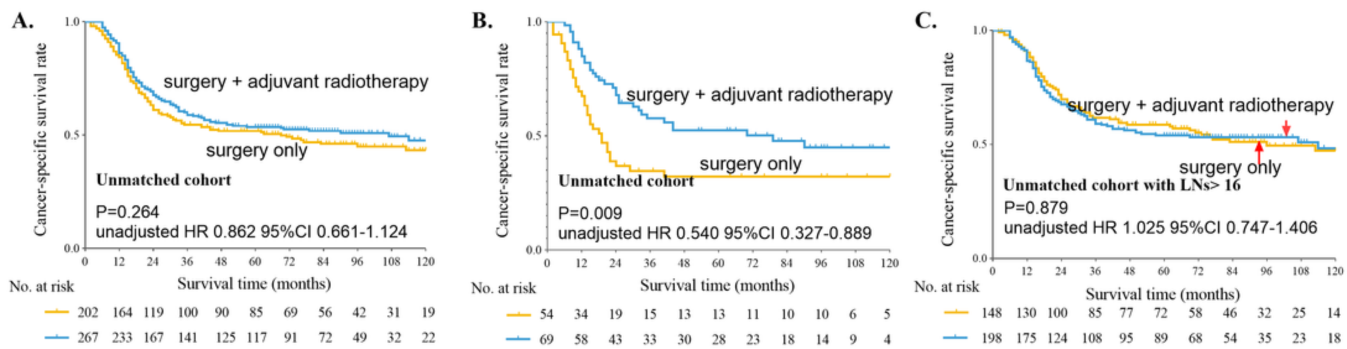

Figure 2

Cancer-specific survival curve for oral cavity squamous cancer patients with stage T1-2N1M0 according to the treatment approaches in the unmatched cohort of Surveillance Epidemiology and End Results database (A. whole cohort, B. patients with lymph nodes examined ≤16, C. patients with lymph nodes examined >16).

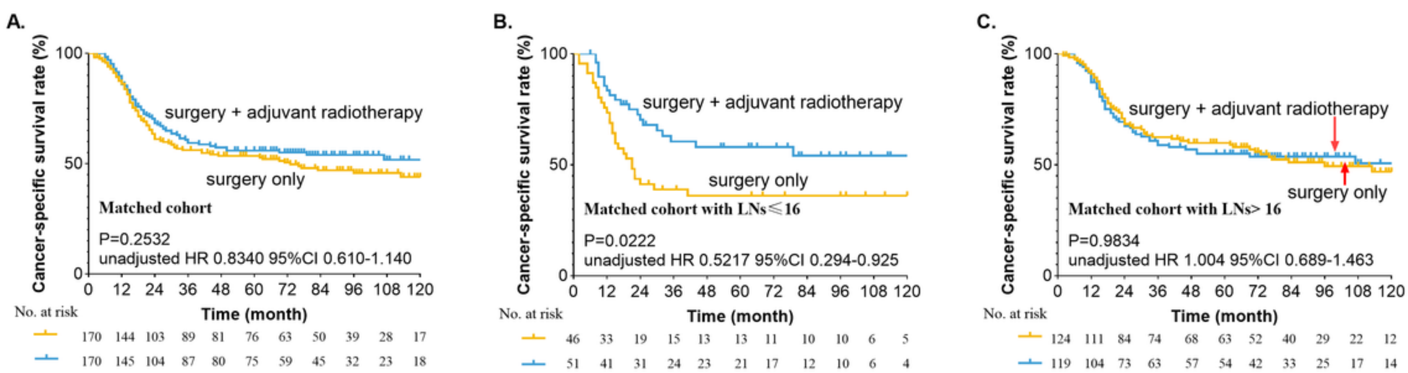

Figure 3

Cancer-specific survival curve for oral cavity squamous cancer patients with stage T1-2N1M0 according to the treatment approaches in the matched cohort of Surveillance Epidemiology and End Results database (A. whole cohort, B. patients with lymph nodes examined ≤16, C. patients with lymph nodes examined >16).