Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation®

Original Research

Current-Smoking-Related COPD or COPD With Acute Exacerbation is Associated With Poorer Survival Following Oral Cavity Squamous Cell Carcinoma Surgery

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Abstract

Background: The survival effect of smoking-related chronic obstructive pulmonary disease (COPD) and COPD with acute exacerbation (COPDAE) before surgery on patients with oral cavity squamous cell carcinoma (OCSCC) is unclear.

Methods: Using the Taiwan Cancer Registry Database, we enrolled patients with OCSCC (pathologic stages I–IVB) receiving surgery. The Cox proportional hazards model was used to analyze all-cause mortality. We categorized the patients into 2 groups by using propensity score matching based on the pre-existing COPD status (≤1 year before surgery) to compare overall survival outcomes: Group 1 (never smokers without COPD) and Group 2 (current smokers with COPD).

Results: In multivariate Cox regression analyses, the adjusted hazard ratio (aHR; 95% confidence interval [CI]) of all-cause mortality in Group 2 compared with Group 1 was 1.07 (1.02–1.16, *P*=0.041). The aHR (95% CIs) of all-cause mortality for ≥1 hospitalizations for COPDAE within 1 year before surgery for patients with OCSCC was 1.31 (1.02–1.64; *P*=0.011) compared with no COPDAE in patients with OCSCC receiving surgery. Among patients with OCSCC undergoing curative surgery, current smokers with smoking-related COPD demonstrated poorer survival outcomes than did nonsmokers without COPD, for both OCSCC death and all-cause mortality. Hospitalization for COPDAE within 1 year before surgery was found to be an independent risk factor for overall survival in these patients with OCSCC.

Conclusion: Prevention of COPD progression to COPDAE may lead to an increase in overall survival in patients with OCSCC receiving curative surgery.

Abbreviations: chronic obstructive pulmonary disease, **COPD**; COPD with acute exacerbation, **COPDAE**; oral cavity squamous cell carcinoma, **OCSCC**; adjusted hazard, **aHR**; confidence interval, **CI**; head and neck squamous cell carcinoma, **HNSCC**; concurrent chemoradiotherapy, **CCRT**; Global initiative for chronic Obstructive Lung Disease, **GOLD**; parallel propensity scores-matching, **PSM**; National Comprehensive Cancer Network, **NCCN**; pathological tumor, **pT**; pathological-nodal, **pN**; American Joint Committee on Cancer, **AJCC**; survival outcome, **SO**; chronic kidney disease, **CKD**; International Classification of Diseases, 10th Revision, Clinical Modification, **ICD-10-CM**; Kaplan-Meier, **KM**

Funding Support: Lo-Hsu Medical Foundation, LotungPoh-Ai Hospital, supports Szu-Yuan Wu's work (Funding Numbers: 10908, 10909, 11001, 11002, 11003, 11006, and 11013).

Date of Acceptance: February 24, 2022 | **Published Online Date:** March 4, 2022

Citation: Zhang J, Lin W-C, Chiu K-C, Wu S-Y. Current smoking-related COPD or COPD with acute exacerbation is associated with poorer survival following oral cavity squamous cell carcinoma surgery. *Chronic Obstr Pulm Dis.* 2022;9(2):181-194. doi: https://doi.org/10.15326/jcopdf.2022.0286

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Keywords:

oral cavity squamous cell carcinomas; COPD; acute exacerbations; cigarette smoking; survival

Introduction

Oral cavity squamous cell carcinoma (OCSCC) is a type of head and neck squamous cell carcinoma (HNSCC) and includes tumors that originate in the lip, lower alveolar ridge, upper alveolar ridge, retromolar trigone, hard palate, oral tongue, floor of the mouth, and buccal mucosa.[1] HNSCC is endemic in Asia, particularly in Taiwan and India.[2-4] In Taiwan, more than 80% of HNSCC originates in the oral cavity rather than in the oropharynx.[2-10] The distribution of HNSCC in Taiwan is distinct from that in other countries where most HNSCCs are oropharyngeal squamous cell carcinomas.[11-13] For young or older patients with early or advanced OCSCC, surgery, rather than definitive radiotherapy or concurrent chemoradiotherapy (CCRT), is considered the first option.[10,14-24] Because surgery is the primary treatment for OCSCC,[10,14-19] understanding the prognostic factors of overall survival before surgery is imperative and valuable for establishing health policy and improving overall survival.

Smoking is the principal risk factor of OCSCC[25] and chronic obstructive pulmonary disease (COPD).[26-28] Current smoking status is also the primary risk factor for COPD with acute exacerbation (COPDAE).[29,30] Thus, pre-existing COPD and current smoking status are highly prevalent in patients with OCSCC.[25,31] Smoking[32-39] and overwhelming comorbidity such as COPD[20-24] are independently associated with poorer survival in patients with cancer as well as greater resistance to cancer treatments such as radiotherapy or CCRT. Surgical complications or perioperative risk of morbidity and mortality also increase in patients with cancer because of current smoking status or COPD.[20-24,40] Hospitalization of patients with COPDAE occurs in the severe stages of COPD (similar to the Global initiative for chronic Obstructive Lung Disease [GOLD][30] classification groups 3–4),[41] which might represent the severity of current-smoking-related COPD and could be straightforwardly used as an obvious predictor of overall survival before surgery in patients with OCSCC. However, although surgery is generally recommended as the initial therapy for early or locally advanced OCSCC,[10,14-19] unclear risk factors of mortality, including current smoking status and smoking-related COPD, before surgery still remain in patients with OCSCC.

Sufficient prognostic factors of overall survival before surgery are lacking. Consequently, establishing the prognostic factors before surgery in patients with OCSCC is crucial and might support preventive medicine in the future. Preclinical and clinical studies have indicated that current-smoking-related COPD or COPDAE might be significant prognostic factors.[33,40,42-47] Nevertheless, no clinical data for parallel comparative study exists for never-smoking non-COPD, current-smoking COPD, and hospitalization of patients with COPDAE before surgery for patients with OCSCC. Therefore, we conducted a parallel propensity scores matching (PSM) study to estimate the influence of COPD on overall survival for patients with current-smoking-related COPD and patients with never-smoking non-COPD with OCSCC who underwent surgery.

Patients and Methods

Study Population

We enrolled patients from the Taiwan Cancer Registry Database with a diagnosis of OCSCC between January 1, 2009, and December 31, 2017. The index date was the date of surgery, and the follow-up duration was from the index date to December 31, 2019. The Taiwan Cancer Registry Database contains detailed cancer-related data of patients, including the clinical stage, cigarette smoking habit, treatment modalities, pathologic data, and grade of differentiation.[10,48-51] Our protocols were reviewed and approved by the institutional review board of Tzu-Chi Medical Foundation (IRB109-015-B).

Inclusion and Exclusion Criteria

The diagnoses of the enrolled patients were confirmed after reviewing their pathological data, and the patients with newly diagnosed OCSCC were confirmed to have no other cancers or distant metastases. All patents with OCSCC received curative-intent surgery including tumor resection, neck lymph node dissection, or both. Adjuvant treatments such as adjuvant CCRT or adjuvant radiotherapy were guided and performed with adherence to the National Comprehensive Cancer Network (NCCN) guidelines[19] depending on risk features such as margin positive finding, pathological tumor (pT) stages, pathological nodal (pN) stages, extranodal extension, lymphovascular invasion, or perineural invasion.[19,52] The chemotherapy regimens administered concurrently with radiotherapy in our study were cisplatin-based regimens.[52] The patients were included if they received an OCSCC diagnosis and curative-intent surgery, were ≥20 years old, and had a diagnosis of pathologic stage I–IVB OCSCC without metastasis according to the American Joint Committee on Cancer criteria (AJCC).[53] Patients were excluded if they had a history of other cancers before the index date, an unknown pathologic stage, missing sex data, missing smoking record, unclear differentiation of tumor grade, or non-squamous-cell carcinoma pathologic type. Patients who had received an adjuvant radiotherapy dose <60 Gy were excluded because this dose is considered insufficient for OCSCC according to the NCCN guidelines.[19] All of the radiotherapy techniques were intensity-modulated radiation therapy in the enrolled patients receiving adjuvant radiotherapy. We categorized the enrolled patients into 2 groups on the basis of their current smoking and COPD status to compare all-cause mortality: Group 1 (OCSCC, never smokers without COPD) and Group 2 (OCSCC, current smokers with smoking-related COPD). We also estimated the survival outcome (SO) associated with the severity of smoking-related COPD (frequency of hospitalization for patients with COPDAE with 0 and ≥1 hospitalizations within 1 year before curative-intent surgery) and patients with pathologic stage I–IVB OCSCC. The incidence of comorbidities was scored using the Charlson Comorbidity Index.[9,54] Some specific comorbidities associated with COPD death (cardiovascular diseases, hyperlipidemia, hypertension, diabetes, and chronic kidney disease [CKD]) were excluded from the Charlson Comorbidity Index scores to prevent repetitive adjustment in multivariate analysis. Only comorbidities or COPD diagnosis within 12 months before the index date were included; they were coded and classified according to the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes at the first admission or after >2 appearances of a diagnosis code at outpatient visits.

Propensity Score Matching and Covariates

To reduce the effects of potential confounders when all-cause mortality between Groups 1 and 2 were compared, we performed 3:1 PSM with a caliper of 0.2 for the following variables: age, sex, diabetes, hyperlipidemia, CKD, hypertension, cardiovascular diseases, Charlson Comorbidity Index score, grade of differentiation, pT, pN, extranodal extension, lymphovascular invasion, perineural invasion, margin status, adjuvant CCRT, and adjuvant radiotherapy alone. A Cox proportional hazards model was used to regress all-cause mortality on various COPD statuses with a robust sandwich estimator used to account for clustering within matched sets.[55] Multivariate Cox regression analyses were performed to calculate HRs to determine whether the factors of distinct COPD status or frequency of hospitalization for patients with COPDAE within 1 year before the index date were potential independent predictors of all-cause mortality. Age, sex, diabetes, hyperlipidemia, CKD, hypertension, cardiovascular diseases, Charlson comorbidity index score, grade of differentiation, pT, pN, extranodal extension, lymphovascular invasion, perineural invasion, margin status, adjuvant CCRT, and adjuvant radiotherapy alone are potential prognostic factors of all-cause death for patients with OCSCC

receiving curative surgery; these categories also might be independent prognostic factors of all-cause death with residual imbalance.[56,57] Potential confounding factors of OCSCC death or COPD death were controlled for in the PSM (Table 1), and all-cause mortality was the primary endpoint in both groups. COPD death and OCSCC death were also estimated according to the Cause of Death database (Table 1). After well-matched PSM, the actual real-world data would indicate the survival impact of COPD and COPDAE within 1 year before OCSCC surgery for all-cause death, COPD death, and OCSCC death for patients with OCSCC.

Statistics

After adjustment for confounders, all of the analyses were performed using SAS version 9.3 software (SAS Institute, Cary, North Carolina,). In a 2-tailed Wald test, $P<0.05$ was considered significant. The overall survival was estimated using the Kaplan–Meier method, and differences among the patient categories—non-COPD, COPD, and hospitalization for COPDAE—were determined using the stratified log-rank test to compare survival curves (stratified according to matched sets).[58]

Results

Propensity Score Matching and Study Cohort

The PSM yielded a final cohort of 1208 patients with pathologic stage I–IVB OCSCC undergoing curative-intent surgery (906 and 302 in Groups 1 and 2, respectively) eligible for further analysis; their characteristics are presented in Table 1. Age, sex, diabetes, hyperlipidemia, CKD, hypertension, cardiovascular diseases, Charlson comorbidity index score, grade of differentiation, pT, pN, extranodal extension, lymphovascular invasion, perineural invasion, margin status, adjuvant CCRT, and adjuvant radiotherapy alone were similar between the 2 groups because of the PSM design (Table 1).

All-Cause Mortality, COPD Death, and Oral Cavity Squamous Cell Carcinoma Death

After well-matched PSM, the COPD death rate was higher in the current-smoking with COPD group than it was in the never-smoking without COPD group ($P<0.001$); the all-cause death and OCSCC death were also significantly higher in the current-smoking with COPD group than in the never-smoking without COPD group ($P<0.001$; Table 1). Multivariate Cox regression analysis indicated that COPD with ≥1 hospitalizations for COPDAE within 1 year before surgery in patients with OCSCC was associated with poor overall survival (Table 2). No significant differences were observed regarding age, sex, diabetes, hyperlipidemia, CKD, hypertension, cardiovascular diseases, Charlson comorbidity index score, grade of differentiation, pT, pN, extranodal extension, lymphovascular invasion, perineural invasion, margin status, adjuvant CCRT, or adjuvant radiotherapy alone (Table 2) because a well-matched parallel PSM design was employed without residual imbalance.[56,57] The adjusted HR (aHR; 95% CI) of all-cause mortality for Group 2 compared with Group 1 was 1.07 (1.02–1.16, $P=0.041$). The aHR (95% CIs) of all-cause mortality for ≥1 hospitalizations for patients with COPDAE within 1 year before surgery for OCSCC was 1.31 (1.02–1.64; $P=0.011$) compared with no COPDAE in patients with OCSCC undergoing curative-intent surgery.

Kaplan–Meier Overall Survival Among Non-COPD, COPD, and Hospitalization for Patients With COPD With Acute Exacerbation

The Kaplan–Meier overall survival curves for the 2 groups are illustrated in Figure 1. The overall survival of the current-smoking-related COPD group was significantly inferior to that of the never-smoking without COPD group ($P=0.039$). The overall survival of patients with ≥1 hospitalization for COPDAE within 1 year before surgery for OCSCC was significantly inferior to that of patients with 0 hospitalization for COPDAE ($P<0.001$; Figure 2).

Discussion

Smoking-Related COPD and Oral Cavity Squamous Cell Carcinoma

Smoking is increasingly being established as a causal factor in the development of squamous cell tumors, at several sites in the head and neck, including OCSCC.[25] Evidence is accruing that smoking may also be causally related with a range of adverse outcomes in patients with cancer, including higher all-cause and cancer-specific death and increased risk of second primary cancers.[32] For HNSCC specifically, several strands of evidence implicate smoking in poorer outcomes[32] but

Table 1. Characteristics of Patients With Oral Cavity Squamous Cell Carcinoma With or Without Current-Smoking-Related COPD Before Surgery After Propensity Score Matching

	Non-Smoking-Non-COPD Patients N=906 (100%)		Current-Smoking With COPD Patients N=302 (100%)		*P* value
Age (mean ± SD)	(62.09 ± 12.36)		(62.93 ± 13.30)		0.355
Age					0.765
Age ≤ 65 y	528	58.28%	175	57.95%	
65 y < Age ≤ 75 y	235	25.94%	75	24.83%	
75 y < Age ≤ 85 y	128	14.13%	45	14.90%	
Age > 85 y	15	1.66%	7	2.32%	
Sex					0.824
Female	149	16.45%	52	17.22%	
Male	75	83.55%	250	82.78%	
Diabetes					0.741
No	643	70.97%	218	72.19%	
Yes	263	29.03%	84	27.81%	
Hyperlipidemia					0.483
No	645	71.19%	222	73.51%	
Yes	261	28.81%	80	26.49%	
Chronic Kidney Disease					1.000
No	891	98.34%	297	98.34%	
Yes	15	1.66%	5	1.66%	
Hypertension					0.607
No	562	62.03%	193	63.91%	
Yes	344	37.97%	109	36.09%	
Cardiovascular Disease					0.677
No	788	86.98%	261	86.42%	
Yes	118	13.02%	41	13.58%	
Charlson Comorbidity Index Score					0.757
= 0	688	75.94%	226	74.83%	
≥ 1	218	24.06%	76	25.17%	
Grade					0.992
Well	270	29.81%	88	29.14%	
Intermediate	543	59.93%	182	60.26%	
Poor	93	10.26%	32	10.60%	
pT[a]					0.8890
pT1–2	525	57.95%	173	57.28%	
pT3–4	381	42.05%	129	42.72%	
pN[a]					0.971
pN0	543	59.93%	179	59.27%	
pN1	135	14.90%	46	15.23%	
pN2	135	14.90%	45	14.90%	
pN3	93	10.26%	32	10.60%	

continued on next page

Extranodal Extension					0.992
No	741	81.79%	249	82.45%	
Yes	165	18.21%	53	17.55%	
Lymphovascular Invasion					1.000
No	618	68.21%	206	68.21%	
Yes	288	31.79%	96	31.79%	
Perineural Invasion					1.000
No	744	82.12%	248	82.12%	
Yes	162	17.88%	54	17.88%	
Margin Positive					0.989
No	852	94.04%	281	93.05%	
Yes	54	5.96%	21	6.95%	
Adjuvant CCRT					0.705
No	574	63.36%	187	61.92%	
Yes	332	36.64%	115	38.08%	
Adjuvant Radiotherapy Alone					0.789
No	780	86.10%	259	86.76%	
Yes	126	13.90%	43	14.24%	
Frequency of Hospitalizations for COPDAE Before Surgery for OCSCC					<0.001
= 0	906	100.00%	226	74.83%	
≥ 1	0	0.00%	76	25.17%	
Follow-up Time, years, mean (mean ± SD)	(5.35 ± 4.24)		(4.52 ± 3.34)		<0.001
All-cause Death					<0.001
No	320	35.32%	88	29.14%	
Yes	586	64.68%	214	70.86%	
COPD Death	0	0.00%	8	2.65%	<0.001
OCSCC Death	244	26.93%	106	35.10%	<0.001

[a]Amin MB et al[53]

COPD=chronic obstructive pulmonary disease; SD=standard deviation; pT=pathologic tumor stage; pN= pathologic nodal stage; CCRT=concurrent chemoradiotherapy; COPDAE=COPD with acute exacerbation; OCSCC=oral cavity squamous cell carcinoma

not specifically in OCSCC or for specific treatment such as surgery. In total, >20 studies have reported associations between smoking and perioperative complications after extirpative or reconstructive surgery.[40] Studies have indicated that smoking during treatment is associated with more resistance to radiotherapy[33] and that a history of smoking is associated with nonresponse to platinum-based chemotherapy.[34] Several studies of various head and neck sites have reported associations of smoking pre-diagnosis or a history of smoking with poorer survival.[35-39] However, these findings are not universal; several studies have reported no association between smoking and patient outcomes.[40,59-61] These inconsistent data might be attributed to the analyses of different cancer sites in the head and neck, smoking-related comorbidities, and surgery or non-surgery in these studies.[35-40,59-61] Moreover, COPD has been associated with poor survival in lung and extrapulmonary cancer treatments.[20-23] Patients with cancer and COPD have poorer survival than those without COPD[20-24] because COPD increases C-reactive protein levels, a biomarker of systemic inflammation that is associated with an increased risk of cancer mortality, including that for extrapulmonary cancers.[24] Similarly, in the largest meta-analysis of its type, Danesh et al indicated that plasma fibrinogen, another nonspecific marker of systemic inflammation, is associated with both pulmonary and extrapulmonary cancers in smokers and never smokers.[47] Therefore, a reasonable assumption is that current-smoking-related COPD and COPD severity, such as hospitalization for patients with COPDAE, before surgery might be associated with poorer survival in patients undergoing curative surgery for OCSCC compared with those who never smoked and do not have COPD. To elucidate the

Table 2. Cox Proportional Hazards Analysis of All-Cause Mortality for Patients With Oral Cavity Squamous Cell Carcinoma With or Without Current-Smoking-Related COPD Before Surgery

	Crude HR (95% CI)	Adjusted HR (95% CI)[a]	*P* value
COPD Status (ref.: non-COPD)			
COPD	1.20 (1.09, 1.46)	1.07 (1.02, 1.16)	0.041
Frequency of Hospitalizations for COPDAE Before Surgery for OCSCC (ref.: = 0)			
≥ 1	1.73 (1.27, 2.35)	1.31 (1.02, 1.64)	0.011
Gender (ref.: Female)			
Male	1.06 (0.83, 1.37)	1.03 (0.88, 1.47)	0.428
Age (ref.: Age ≤ 65 y)			
65y < Age ≤ 75 y	1.06 (0.86, 1.11)	1.03 (0.73, 1.13)	0.385
75y < Age ≤ 85 y	1.19 (0.81, 1.24)	1.23 (0.96, 1.57)	0.2733
Age > 85 y	1.28 (0.79, 2.07)	1.35 (0.97, 2.66)	0.2160
Charlson Comorbidity Index Score (ref.: = 0)			
≥ 1	1.09 (0.91, 1.32)	1.03 (0.78, 1.24)	0.344
Diabetes (ref.: No)			
Yes	1.56 (0.93, 1.87)	1.04 (0.95, 1.71)	0.181
Hyperlipidemia (ref.: No)			
Yes	1.15 (0.95, 1.41)	1.09 (0.72, 1.11)	0.296
Hypertension (ref.: No)			
Yes	1.28 (1.07, 1.53)	1.11 (0.89, 1.39)	0.358
Cardiovascular Diseases (ref.: No)			
Yes	1.15 (0.88, 1.50)	1.03 (0.66, 1.29)	0.650
Chronic Kidney Disease (ref.: No)			
Yes	2.14 (1.17, 3.89)	1.53 (0.80, 2.90)	0.196
Grade (ref.: well)			
Intermediate	1.31 (0.94, 1.76)	1.05 (0.86, 1.45)	0.684
Poor	1.56 (0.97, 2.49)	1.29 (0.80, 2.11)	0.792
pT (ref.: pT1–2)			
pT3–4	1.04 (0.87, 1.25)	1.03 (0.88, 1.15)	0.683
pN (ref.: pN0)			
pN1	1.13 (0.82, 1.89)	1.05 (0.81, 1.33)	0.431
pN2	1.19 (0.79, 1.78)	1.07 (0.77, 1.56)	0.394
pN3	1.26 (0.91, 2.49)	1.3 (0.79, 2.37)	0.894
Extranodal Extension (ref.: No)			
Yes	1.06 (0.86, 1.30)	1.04 (0.84, 1.36)	0.714
Lymphovascular Invasion (ref.: No)			
Yes	1.03 (0.91, 1.17)	1.01 (0.94, 1.12)	0.891
Perineural Invasion (ref.: No)			
Yes	1.02 (0.89, 1.22)	1.05 (0.77, 1.16)	0.803
Margin Positive (ref.: No)			
Yes	1.04 (0.94, 1.56)	1.27 (0.91, 1.82)	0.670
Adjuvant CCRT (ref.: No)			
Yes	0.83 (0.63, 1.39)	0.82 (0.67, 1.35)	0.512
Adjuvant Radiotherapy (ref.: No)			
Yes	0.89 (0.75, 1.06)	0.87 (0.72, 1.05)	0.135

[a]All of the covariates listed in Table 2 were adjusted.

COPD=chronic obstructive pulmonary disease; HR=hazard ratio; CI=confidence interval; COPDAE=COPD with acute exacerbation; OCSCC=oral cavity squamous cell carcinoma; pT=pathologic tumor stage; pN=pathologic nodal stage; CCRT=concurrent chemoradiotherapy

survival impact of smoking-related COPD (COPD is a highly common smoking-related comorbidity[62]) on patients with OCSCC receiving surgery, we conducted the parallel PSM analysis.

Smoking-Related COPD and Surgery for Oral Cavity Squamous Cell Carcinoma

OCSCC differs from other HNSCC sites because surgery is the first choice for OCSCC as part of primary therapy according to NCCN guidelines,[10,14-19] unlike oropharyngeal, larynx, or hypopharyngeal squamous cell carcinoma, which can be treated by radiotherapy or definitive CCRT as the first-line therapy. Thus, surgery is a crucial curative treatment for OCSCC.[10,14-19] However, Linda et al revealed that the relationship between smoking and overall survival was stronger among those who underwent cancer-directed surgery than those who did not, and in the treatment combination analysis, the hazards for current versus never smokers were most substantial in the groups who had surgery, either alone or with radiotherapy or chemotherapy.[63] Numerous epidemiologic studies have indicated that smoking is overwhelmingly the foremost risk factor for COPD and COPDAE.[26-28] Additionally, a high prevalence of COPDAE requiring hospital admission was noted in patients who continue to smoke.[29] Diagnosis of COPD and COPDAE before cancer is an independent prognostic factor of overall survival for breast cancer and lung cancer.[22,64] COPD is a common comorbidity in patients with lung and head and neck cancer.[31] Although patients with lung cancer who also have COPD have a poorer prognosis than do patients with lung cancer and no COPD,[22] no report exists of the influence of smoking-related COPD or COPDAE on the overall survival of patients with OCSCC receiving surgery. No solid evidence is available to clarify the importance of prevention of COPD progression to COPDAE for patients with OCSCC receiving curative-intent surgery. Our study is the first to use current-smoking-related COPD or COPDAE within 1 year before surgery for patients with OCSCC as a straightforward prognostic factor of overall survival. Our findings may serve as a reference for shared decision-making by physicians and patients with OCSCC in the future and health policy establishment for preventing COPD progression to COPDAE before surgery in patients with OCSCC.

COPD Death, Oral Cavity Squamous Cell Carcinoma Death, and All-Cause Death

After the application of PSM, we observed not only significant difference for COPD death between the 2 groups but also significantly higher OCSCC death and all-cause death in the current-smoking-related COPD group compared with the never-smoking COPD group with OCSCC receiving surgery (Table 1). These findings suggest that smoking-related COPD is a predominant factor of overall survival for patients with OCSCC and not only contributes to COPD death but also to OCSCC death and all-cause death. The higher OCSCC death and all-cause death observed in the current study is consistent with the findings of preclinical and clinical studies reporting that cigarette smoking causes resistance to cisplatin,[42-46] surgical complications,[40] or lower response to radiotherapy.[33] Thus, COPD and COPDAE within 1 year before surgery for patients with OCSCC is likely an independent prognostic factor of overall survival for patients with OCSCC.

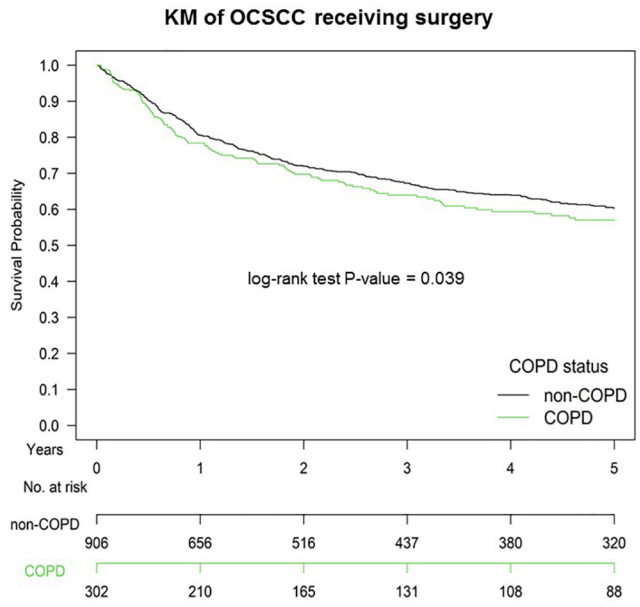
Potential Cofounding Factors in Propensity Score Matching

According to NCCN guidelines and relevant evidence,[19,52] the prognostic factors of overall survival in patients with OCSCC are age, sex, Charlson Comorbidity Index score, pathologic T stage, pathologic N stage, differentiation tumor grade, lymphovascular invasion, perineural invasion, extranodal extension, margin positive, adjuvant radiotherapy, or adjuvant CCR. All of the confounding factors were matched and are listed in Table 1. We also matched the possible confounding factors of COPD death[65] such as diabetes, hyperlipidemia, hypertension, cardiovascular diseases, and CKD in our PSM design. The possible confounding factors were considered in our PSM analysis. No selection bias was noted for therapeutic choice between the 2 groups because pathologic stages, pathologic risk features, and adjuvant treatments were matched in the study. Therefore, COPD or hospitalization of patients with COPDAE are the independent prognostic factors of overall survival in patients with OCSCC receiving curative surgery (Table 2, Figures 1 and 2).

Clinical Practice and Value

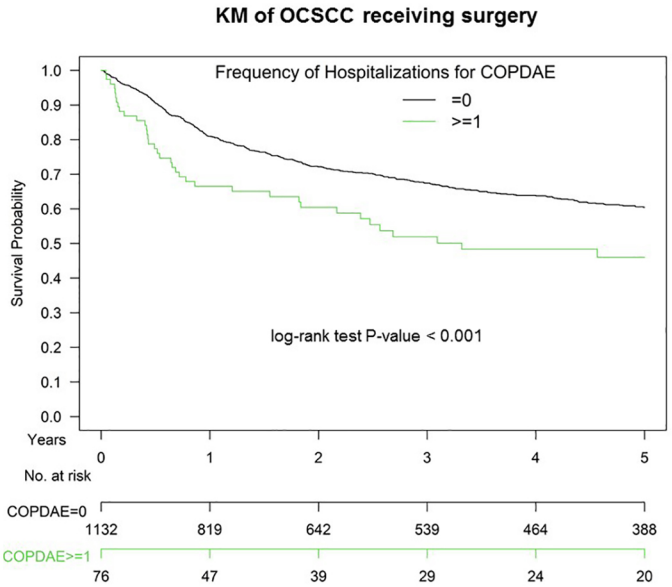
All potential confounding factors were matched and had no residual imbalance without statistical significance in the covariates (Table 2).[56,57] The independent

Figure 1. Kaplan–Meier Survival Curves of Patients With Oral Cavity Squamous Cell Carcinoma With or Without Current-Smoking-Related COPD Before Surgery



KM=Kaplan–Meier; OCSCC=oral cavity squamous cell carcinoma; COPD=chronic obstructive pulmonary disease

Figure 2. Kaplan–Meier Survival Curves of Patients With Oral Cavity Squamous Cell Carcinoma With Frequency of Hospitalization for COPD With Acute Exacerbation Within 1 Year Before Surgery



KM=Kaplan–Meier; OCSCC=oral cavity squamous cell carcinoma; COPDAE=chronic obstructive pulmonary disease with acute exacerbation

prognostic factors of overall survival were pre-existing COPD and COPDAE within 1 year before surgery for patients with OCSCC (Table 2, Figures 1 and 2). This insightful finding may serve as a reference for shared decision-making between physicians and patients regarding the selection of surgery or other treatments for OCSCC, especially in patients with OCSCC with COPDAE within 1 year before surgery. Moreover, pre-existing COPD and COPDAE before surgery for patients with OCSCC could be considered in future clinical trials to correct the confounding factors. Finally, prevention of pre-existing COPD progression to COPDAE is paramount for patients with OCSCC receiving surgery as curative-intent treatment.

Strength

The strength of our study is the fact that it is the first and largest cohort study to estimate the SO of current smokers with smoking-related COPD compared with nonsmokers without COPD in patients with OCSCC receiving curative-intent surgery based on NCCN guidelines.[19] The use of PSM resulted in consistent covariates between the 2 groups, and no selection bias for therapeutic choice existed between the 2 groups. No other study has estimated the influence of pre-existing COPD and hospitalization for COPDAE within 1 year before surgery in patients with OCSCC undergoing surgery; moreover, we controlled for most confounding factors. Our findings may serve as a reference for shared decision-making by physicians and patients who select surgery for treating OCSCC with COPD or COPDAE in the future. Preventing COPD from progressing to COPDAE is crucial to improving overall survival in patients with OCSCC receiving curative surgery (Table 2 and Figure 2).

Limitations

This study has some limitations. First, all of the patients with OCSCC were enrolled from an Asian population; thus, our results should be cautiously extrapolated to non-Asian populations. However, no evidence has indicated distinctions between Asian and non-Asian populations in oncologic outcomes for patients with OCSCC undergoing curative surgery. Second, the diagnoses of all comorbid

conditions were based on ICD-10-CM codes. The Taiwan Cancer Registry administration randomly reviews charts and interviews patients to confirm the accuracy of the diagnoses, and hospitals with outlier charges or practices are audited and severely penalized if malpractice or discrepancies are identified. Nevertheless, to obtain crucial information on population specificity and disease occurrence, a large-scale randomized trial comparing carefully selected patients undergoing suitable treatments is essential. Third, selection bias and residual or unmeasured confounding factors are likely, as they are in all retrospective studies. Despite these limitations, a major strength of this study is the use of a nationwide, population-based registry with detailed baseline and treatment information. Lifelong follow-up was possible because of linkage with the National Cause of Death database. Considering the magnitude and statistical significance of the observed effects in the current study, these limitations are unlikely to affect the conclusions.

Conclusions

Among patients with OCSCC undergoing curative surgery, current smokers with smoking-related COPD had poorer SO than nonsmokers without COPD, regardless of whether the outcome was OCSCC death or all-cause mortality. Hospitalization for patients with COPDAE within 1 year before surgery was found to be an independent risk factor for overall survival in these patients with OCSCC. Prevention of COPD progression to COPDAE is likely to be associated with an increased overall survival in patients with OCSCC receiving curative surgery.

Acknowledgements

Author contributions: Conception and Design: Jiaqiang Zhang, MD, PhD; Kuo-Chin Chiu, MD; Wei-Chun Lin, MD; Szu-Yuan Wu, MD, MPH, PhD. Collection and Assembly of Data: Jiaqiang Zhang, MD, PhD; Kuo-Chin Chiu, MD; Wei-Chun Lin, MD. Data Analysis and Interpretation: Jiaqiang Zhang, MD, PhD; Kuo-Chin Chiu, MD; Wei-Chun Lin, MD; Szu-Yuan Wu, MD, MPH, PhD. Administrative Support: Szu-Yuan Wu. Manuscript Writing: Jiaqiang Zhang, MD, PhD; Kuo-Chin Chiu, MD; Wei-Chun Lin, MD; Szu-Yuan Wu, MD, MPH, PhD. Final Approval of Manuscript: All authors

Data availability: The data sets supporting the study conclusions are included in this manuscript and its supplementary files.

Declaration of Interest

The authors have no conflicts of interest to declare.

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