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

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Impact of COPD on Oral Cavity Squamous Cell Carcinoma

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 OCSCC25 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 Smoking32-39 and overwhelming comorbidity such as COPD20-24 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.

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

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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. 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 patients 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 depending on risk features such as margin positive finding, pathological tumor (pT) stages, pathological nodal (pN) stages, extranodal extension, lymphovascular invasion, or perineural invasion. The chemotherapy regimens administered concurrently with radiotherapy in our study were cisplatin-based regimens. 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). Patients were excluded if they had a history of other cancers before the index date, an unknown pathologic stage 1–IVB OCSCC without metastasis according to the American Joint Committee on Cancer criteria (AJCC), or had a diagnosis of pathologic stage I–IVB OCSCC without metastasis according to the American Joint Committee on Cancer criteria (AJCC).

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. Multivariate Cox regression analyses were performed to calculate HRs to determine whether the factors of distinct COPD status or frequency of hospitalization 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 1–IVB OCSCC. The incidence of comorbidities was scored using the Charlson Comorbidity Index. 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.
receiving curative surgery; these categories also might be independent prognostic factors of all-cause death with residual imbalance.\textsuperscript{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).\textsuperscript{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 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{32} For HNSCC specifically, several strands of evidence implicate smoking in poorer outcomes 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 55.28%                                | 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<sup>a</sup>          |                                           |                                                 | 0.8890  |
| pT1–2                   | 525 57.95%                                | 173 57.28%                                     |         |
| pT3–4                   | 381 42.05%                                | 129 42.72%                                     |         |
| pN<sup>a</sup>          |                                           |                                                 | 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*
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. Studies have indicated that smoking during treatment is associated with more resistance to radiotherapy and that a history of smoking is associated with nonresponse to platinum-based chemotherapy. Several studies of various head and neck sites have reported associations of smoking pre-diagnosis or a history of smoking with poorer survival. However, these findings are not universal; several studies have reported no association between smoking and patient outcomes. 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. Moreover, COPD has been associated with poor survival in lung and extrapulmonary cancer treatments. Patients with cancer and COPD have poorer survival than those without COPD 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. 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. 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

| Extranodal Extension | 0.992 |
|----------------------|-------|
| No                   | 741   | 81.79% |
| Yes                  | 165   | 18.21% |
| Lymphovascular Invasion | 1.000 |
| No                   | 618   | 68.21% |
| Yes                  | 288   | 31.79% |
| Perineural Invasion | 1.000 |
| No                   | 744   | 82.12% |
| Yes                  | 162   | 17.88% |
| Margin Positive | 0.989 |
| No                   | 852   | 94.04% |
| Yes                  | 54    | 5.96%  |
| Adjuvant CCRT      | 0.705 |
| No                   | 574   | 63.36% |
| Yes                  | 332   | 36.64% |
| Adjuvant Radiotherapy Alone | 0.789 |
| No                   | 780   | 86.10% |
| Yes                  | 126   | 13.90% |
| Frequency of Hospitalizations for COPDAE Before Surgery for OCSCC | <0.001 |
| = 0                 | 906   | 100.00% |
| ≥ 1                 | 0     | 0.00%  |
| Follow-up Time, years, mean (mean ± SD) | <0.001 |
| (5.35 ± 4.24)       | (4.52 ± 3.34) |
| All-cause Death | <0.001 |
| No                   | 320   | 35.32% |
| Yes                  | 566   | 64.68% |
| COPD Death           | <0.001 |
| 0                    | 8     | 2.65%  |
| OCSCC Death          | <0.001 |
| 244                  | 26.93% |

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

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| Variable                                      | Crude HR (95% CI) | Adjusted HR (95% CI) | 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, 1.67) | 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   |

*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) 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, 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. 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. Numerous epidemiologic studies have indicated that smoking is overwhelmingly the foremost risk factor for COPD and COPDAE. Additionally, a high prevalence of COPDAE requiring hospital admission was noted in patients who continue to smoke. Diagnosis of COPD and COPDAE before cancer is an independent prognostic factor of overall survival for breast cancer and lung cancer. COPD is a common comorbidity in patients with lung and head and neck cancer. Although patients with lung cancer who also have COPD have a poorer prognosis than do patients with lung cancer and no COPD, 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, surgical complications, or lower response to radiotherapy. 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, 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 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). The independent
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
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.

**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.

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**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.
References

1. Law CP, Chandra RV, Hoang JK, Phal PM. Imaging the oral cavity: key concepts for the radiologist. Br J Radiol. 2011;84(1006):944-957. doi: https://doi.org/10.1259/bjr/70520972

2. Liao CT, Kang CJ, Chang JT, et al. Survival of second and multiple primary tumors in patients with oral cavity squamous cell carcinoma in the betel quid chewing area. Oral Oncol. 2007;43(8):811-819. doi: https://doi.org/10.1016/j.oraloncology.2006.10.003

3. Liao CT, Wallace CG, Lee LY, et al. Clinical evidence of field cancerization in patients with oral cavity cancer in a betel quid chewing area. Oral Oncol. 2014;50(8):721-731. doi: https://doi.org/10.1016/j.oraloncology.2014.04.010

4. Chang JH, Wu CC, Yuan KS, et al. Locoregionally recurrent head and neck squamous cell carcinoma: incidence, survival, prognostic factors, and treatment outcomes. Oncotarget. 2017;8(33):55600-55612. doi: https://doi.org/10.18632/oncotarget.16340

5. Chen JH, Yen YC, Chen TM, et al. Survival prognostic factors for metachronous second primary head and neck squamous cell carcinoma. Cancer Med. 2017;6(1):142-153. doi: https://doi.org/10.1002/cam4.976

6. Chang CL, Yuan KS, Wu SY. High-dose or low-dose cisplatin concurrent with radiotherapy in locally advanced head and neck squamous cell cancer. Head Neck. 2017;39(7):1364-1370. doi: https://doi.org/10.1002/hed.24763

7. Chen JH, Yen YC, Liu SH, et al. Dementia risk in irradiated patients with head and neck cancer. Medicine (Baltimore). 2015;94(45):e1983. doi: https://doi.org/10.1097/MD.0000000000001983

8. Chen JH, Yen YC, Liu SH, et al. Outcomes of induction chemotherapy for head and neck cancer patients: a combined study of two national cohorts in Taiwan. Medicine (Baltimore). 2016;95(7):e2845. doi: https://doi.org/10.1097/MD.0000000000002845

9. Chen JH, Yen YC, Yang HC, et al. Curative-intent aggressive treatment improves survival in elderly patients with locally advanced head and neck squamous cell carcinoma and high comorbidity index. Medicine (Baltimore). 2016;95(14):e5268. doi: https://doi.org/10.1097/MD.0000000000005268

10. Liu WC, Liu HE, Kao YW, et al. Definitive radiotherapy or surgery for early oral squamous cell carcinoma in old and very old patients: a propensity-score-matched, nationwide, population-based cohort study. Radiother Oncol. 2020;151:214-221. doi: https://doi.org/10.1016/j.radonc.2020.08.016

11. Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med. 2007;357(17):1695-1704. doi: https://doi.org/10.1056/NEJMoa071028

12. Lorch JH, Goloubeva O, Haddad RI, et al. Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX 324 randomised phase 3 trial. Lancet Oncol. 2011;12(2):153-159. doi: https://doi.org/10.1016/S1470-224X(10)70279-5

13. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009;92(1):4-14. doi: https://doi.org/10.1016/j.radonc.2009.09.014

14. Liu WC, Liu HE, Kao YW, et al. Definitive intensity-modulated radiotherapy or surgery for early oral cavity squamous cell carcinoma: propensity-score-matched, nationwide, population-based cohort study. Head Neck. 2021;43(4):1142-1152. doi: https://doi.org/10.1002/hed.26575

15. Ellis MA, Graboyes EM, Wahlquist AE, et al. Primary surgery vs radiotherapy for early stage oral cavity cancer. Otolaryngol Head Neck Surg. 2018;158(4):649-659. doi: https://doi.org/10.1177/0194599817746909

16. de Visscher JG, Grond AJ, Botke G, van der Waal I. Results of radiotherapy for squamous cell carcinoma of the vermilion border of the lower lip. A retrospective analysis of 108 patients. Radiother Oncol. 1996;39(1):9-14. doi: https://doi.org/10.1016/0167-8140(96)01716-1

17. Sykes AJ, Allan E, Irwin C. Squamous cell carcinoma of the lip: the role of electron treatment. Clin Oncol (R Coll Radiol). 1996;8(6):384-386. doi: https://doi.org/10.1016/S0936-6555(96)80086-0

18. Iyer NG, Tan DS, Tan VK, et al. Randomized trial comparing surgery and adjuvant radiotherapy versus concurrent chemoradiotherapy in patients with advanced, nonmetastatic squamous cell carcinoma of the head and neck: 10-year update and subset analysis. Cancer. 2015;121(10):1599-1607. doi: https://doi.org/10.1002/cncr.29251

19. National Comprehensive Cancer Network (NCCN). NCCN guidelines: prostate cancer. NCCN website. Published February 2021. Updated March 2022. Accessed January 2022. https://www.nccn.org/guidelines/guidelines-detail?category=1&iid=1459

20. Gao YH, Guan WJ, Liu Q, et al. Impact of COPD and emphysema on survival of patients with lung cancer: a meta-analysis of observational studies. Respir Med. 2016;21(2):269-279. doi: https://doi.org/10.1111/resp.12661
21. Saji H, Miyazawa T, Sakai H, et al. Survival significance of coexisting chronic obstructive pulmonary disease in patients with early lung cancer after curative surgery. Thorac Cancer. 2018;9(1):19-24. doi: https://doi.org/10.1111/1759-7714.12507

22. Chiu KC, Lin WC, Chang CL, Wu SY. Impact of chronic obstructive pulmonary disease on survival in patients with advanced stage lung squamous cell carcinoma undergoing concurrent chemoradiotherapy. Cancers (Basel). 2021;13(13):3231. doi: https://doi.org/10.3390/cancers1313231

23. van Gestel YR, Heeks SE, Sin DD, et al. COPD and cancer mortality: the influence of statins. Thorax. 2009;64(11):963-967. doi: https://doi.org/10.1136/thx.2009.116731

24. Man SFP, Connett JE, Anthonisen NR, Wise RA, Tashkin DP, Sin DD. C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. Thorax. 2006;61:849-853. doi: https://doi.org/10.1136/thx.2006.059808

25. International Agency for Research on Cancer (IARC) Working Group on the Evaluation of Carcinogenic Risks to Humans. Personal Habits and Indoor Combustions. Volume 100 E. A Review of Human Carcinogens; IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. World Health Organization; 2012. https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Personal-Habits-And-Indoor-Combustions-2012.

26. Burney P, Patel J, Minelli C, et al. Prevalence and population attributable risk for chronic airflow obstruction in a large multinational study. Am J Respir Crit Care Med. 2020;203(11):33171069. doi: https://doi.org/10.1164/rcrm.202005-1990OC

27. Wang C, Xu J, Yang L, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. Lancet. 2018;391(10131):1706-1717. doi: https://doi.org/10.1016/S0140-6736(18)30841-9

28. Mokdad AH, Ballesteros K, Echko M, et al. The state of US health, 1990-2016: burden of diseases, injuries, and risk factors among US states. JAMA. 2018;319(14):1444-1472. doi: https://dx.doi.org/10.1001%2Fjama.2018.0158

29. Badaran E, Ortega E, Bujalance C, Del Puerto L, Torres M, Riesco JA. Smoking and COPD exacerbations. Eur Respir J. 2014;40(Suppl 56):1055. https://erj.ersjournals.com/content/40/Suppl_56/P1055

30. Au DH, Bryson CL, Chien JW, et al. The effects of smoking cessation on the risk of chronic obstructive pulmonary disease exacerbations. J Gen Intern Med. 2009;24(2):457-463. doi: https://doi.org/10.1007/s11606-009-0907-y

31. Gottlieb M, Mellemgaard A, Marsaa K, Godtfredsen N. Optimizing COPD treatment in patients with lung- and head and neck cancer does not improve quality of life - a randomized, pilot, clinical trial. Eur Clin Respir J. 2020;7(1):1731277. doi: https://doi.org/10.1080/20018525.2020.1731277

32. U.S. Department of Health and Human Services (HHS). The health consequences of smoking: 50 years of progress. A report of the Surgeon General. HHS website. Published January 2014. Accessed January 2022. https://www.ncbi.nlm.nih.gov/books/NBK179276/pdf/Bookshelf_NBK179276.pdf

33. Brownman GP, Wong G, Hudson I, et al. Influence of cigarette smoking on the efficacy of radiation therapy in head and neck cancer. N Engl J Med. 1993;328(3):159-163. doi: https://doi.org/10.1056/NEJM199301123280302

34. Fountzilas G, Kosmidis P, Avramidis V, et al. Long-term survival data and prognostic factors of a complete response to chemotherapy in patients with head and neck cancer treated with platinum-based induction chemotherapy: a Hellenic co-operative oncology group study. Med Pediatr Oncol. 1997;26(4):401-410. doi: https://doi.org/10.1002/(SICI)1096-911X(19970612)6<401::AID-MPO2>3.0.CO;2-K

35. Boffetta P, Merletti F, Faggiano F, et al. Prognostic factors and survival of laryngeal cancer patients from Turin, Italy. A population-based study. Am J Epidemiol. 1997;145(12):1100-1105. doi: https://doi.org/10.1093/oxfordjournals.aje.a009072

36. Agarwal JP, Mallick I, Bhutani R, et al. Prognostic factors in oropharyngeal cancer-analysis of 627 cases receiving definitive radiotherapy. Acta Oncol. 2009;48(7):1026-1033. doi: https://doi.org/10.1080/02841860902845839

37. Duffy SA, Ronis DL, McLean S, et al. Pretreatment health behaviors predict survival among patients with head and neck squamous cell carcinoma. J Clin Oncol. 2009;27(12):1969-1975. doi: https://doi.org/10.1200/JCO.2008.18.2188

38. Hilgert E, Bergmann C, Fichtner A, Gires O, Issing W. Tobacco abuse relates to significantly reduced survival of patients with oropharyngeal carcinomas. Eur J Cancer Prev. 2009;18(2):120-126. doi: https://doi.org/10.1097/CEJ.0b013e32831012a4

39. Mayne ST, Cartmel B, Kirsh V, Goodwin WJ. Alcohol and tobacco use prediagnosis and postdiagnosis, and survival in a cohort of patients with early-stage cancers of the oral cavity, pharynx, and larynx. Cancer Epidemiol Biomarkers Prev. 2009;18(12):3368-3374. doi: https://doi.org/10.1158/1055-9965.EPI-09-0944

40. Lassig AA, Yueh B, Joseph AM. The effect of smoking on perioperative complications in head and neck oncologic surgery. Laryngoscope. 2012;122(8):1800-1808. doi: https://doi.org/10.1002/lary.23308
41. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2018 Report. GOLD website. Published 2018. Accessed January 2022. https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf

42. Cacciari GE, Ghodousipour S, Mari A, et al. Association between smoking exposure, neoadjuvant chemotherapy response and survival outcomes following radical cystectomy: systematic review and meta-analysis. J Urol. 2020;204(4):649-660. doi: https://doi.org/10.1097/JU.0000000000000813

43. Boeri I, Soligo M, Frank I, et al. Cigarette smoking is associated with adverse pathological response and increased disease recurrence amongst patients with muscle-invasive bladder cancer treated with cisplatin-based neoadjuvant chemotherapy and radical cystectomy: a single-centre experience. BJU Int. 2019;123(6):1011-1019. doi: https://doi.org/10.1111/bju.14612

44. Nishioka T, Luo LY, Shen L, et al. Nicotine increases the resistance of lung cancer cells to cisplatin through enhancing Bcl-2 stability. Br J Cancer. 2014;110:1785-1792. doi: https://doi.org/10.1038/bjc.2014.78

45. Chang X, Ravi R, Pham V, Bedi A, Chatterjee A, Sidransky D. Adenylate kinase 3 sensitizes cells to cigarette smoke condensate vapor induced cisplatin resistance. PLoS One. 2011;6(6):e20806. doi: https://doi.org/10.1371/journal.pone.0020806

46. Simon F, Schwenk-Zieger S, Becker S, Unger K, Gires O, Baumeister F. Cigarette smoke reduces the efficacy of cisplatin in head and neck cancer cells - role of ABCG2. Anticancer Res. 2020;40(3):1277-1284. doi: https://doi.org/10.21873/anticancerres.14069

47. Fibrinogen Studies Collaboration. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. JAMA. 2005;294(14):1799-1809. doi: https://doi.org/10.1001/jama.294.14.1799

48. Zhang J, Lu CY, Chen HM, Wu SY. Neoadjuvant chemotherapy or endocrine therapy for invasive ductal carcinoma of the breast with high hormone receptor positivity and human epidermal growth factor receptor 2 negativity. JAMA Netw Open. 2021;4(3):e211785. doi: https://doi.org/10.1001/jamanetworkopen.2021.1785

49. Chang SC, Hsu CH, Lin YC, et al. Effects of 1-year hospital volume on surgical margin and biochemical-failure-free survival in patients undergoing robotic versus nonrobotic radical prostatectomy: a nationwide cohort study from the National Taiwan Cancer Database. Cancers (Basel). 2021;13(3):488. doi: https://doi.org/10.3390/cancers13030488

50. Zhang J, Lu CY, Qin L, Chen HM, Wu SY. Breast-conserving surgery with or without irradiation in women with invasive ductal carcinoma of the breast receiving preoperative systemic therapy: a cohort study. Breast. 2020;54:139-147. doi: https://doi.org/10.1016/j.breast.2020.09.010

51. Lin KC, Chen TM, Yuan KS, Wu ATH, Wu SY. Assessment of predictive scoring system for 90-day mortality among patients with locally advanced head and neck squamous cell carcinoma who have completed concurrent chemoradiotherapy. JAMA Netw Open. 2020;3(3):e1920671. doi: https://doi.org/10.1001/jamanetworkopen.2019.20671

52. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck. 2005;27(10):843-850. doi: https://doi.org/10.1002/hed.20279

53. Amin MB, Edge S, Greene F, et al, eds. American Joint Committee on Cancer Staging Manual. 8th ed. Springer International Publishing; 2017

54. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. 1994;47(11):1245-1251. doi: https://doi.org/10.1016/0895-4356(94)90129-5

55. Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. Stat Med. 2013;32(16):2837-2849. doi: https://doi.org/10.1002/sim.5705

56. Nguyen TL, Collins GS, Spence J, et al. Double-adjustment in propensity score matching analysis: choosing a threshold for considering residual imbalance. BMC Med Res Methodol. 2017;17:78. doi: https://doi.org/10.1186/s12874-017-0338-0

57. Zhang Z, Kim HJ, Lonjon G, Zhu Y. Balance diagnostics after propensity score matching analysis: choosing a threshold for considering residual imbalance. BMC Med Res Methodol. 2017;17:78. doi: https://doi.org/10.1186/s12874-017-0338-0

58. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Stat Med. 2014;33(7):1242-1258. doi: https://doi.org/10.1002/sim.5984

59. Verschuur HP, Irish JC, O’Sullivan B, Goh C, Gullane PJ, Pintilie M. A matched control study of treatment outcome in young patients with squamous cell carcinoma of the head and neck. Laryngoscope. 1999;109(2):249-258. doi: https://doi.org/10.1097/00005537-199902000-00015
60. Rosenquist K, Wennerberg J, Annertz K, et al. Recurrence in patients with oral and oropharyngeal squamous cell carcinoma: human papillomavirus and other risk factors. *Acta Otolaryngol.* 2007;127(9):980-987. doi: https://doi.org/10.1080/00016480601110162

61. Lopez RV, Zago MA, Eluf-Neto J, et al. Education, tobacco smoking, alcohol consumption, and IL-2 and IL-6 gene polymorphisms in the survival of head and neck cancer. *Braz J Med Biol Res.* 2011;44(10):1006-1012. doi: https://doi.org/10.1590/S0100-879X2011007500097

62. Cavailles A, Brinchault-Rabin G, Dixmier A, et al. Comorbidities of COPD. *Eur Respir Rev.* 2013;22(130):454-475. doi: https://doi.org/10.1183/09059180.00008612

63. Sharp I, McDevitt J, Carsin AE, Comber H. Smoking at diagnosis is an independent prognostic factor for cancer-specific survival in head and neck cancer: findings from a large, population-based study. *Cancer Epidemiol Biomarkers Prev.* 2014;23(11):2579-2590. doi: https://doi.org/10.1158/1055-9965.EPI-14-0311

64. Zhang JQ, Cheng TM, Lin WC, Chiu KC, Wu SY. Impact of smoking-related chronic obstruction pulmonary disease on mortality of invasive ductal carcinoma patients receiving standard treatments: propensity score-matched, nationwide, population-based cohort study. *Cancers (Basel).* 2021;13(15):3654. doi: https://doi.org/10.3390/cancers13153654

65. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities. *Eur Respir J.* 2006;28(6):1245-1257. doi: https://doi.org/10.1183/09031936.00133805