

# Clinical Analysis of Oral Squamous Cell Carcinoma: A Single-institution Experience

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**Abstract.** *Background/Aim:* There is limited evidence about the significance of head and neck surgical observation at the time of diagnosis and follow-up of oral cancer after treatment. The aim of this study was to elucidate the prognosis and prognostic factors of oral squamous cell carcinoma (OSCC), analyze cases of double cancers, and highlight the importance of examinations during both diagnosis and post-treatment for OSCC. *Patients and Methods:* We performed a retrospective analysis of 272 OSCC cases treated for the first time during a 10-year period from April 2013 to March 2023 at Kyushu University Hospital. Information obtained in the clinical setting, such as age, stage, prognosis, and presence of double cancers, was used in the analysis. *Results:* The mean age of 272 patients was 69 years; 203 patients were males and 69 were females. The most common oral cancer sites were the tongue (54.4%). The 5-year overall survival rate was 63.8%. Double cancer was found in 93 patients (34.2%). Synchronous double cancers were found in 38 patients (14.0%), 50% of whose cancer types were head and neck cancers. *Conclusion:* We analyzed 272 OSCC patients treated at the Kyushu University Hospital, and the results were comparable to those reported by other institutions. Tumor

site, age, and stage were identified as prognostic factors. Half of the patients with synchronous double cancers had head and neck cancer, and 3-10% of patients with double cancers after treatment for OSCC also had head and neck cancer, suggesting the importance of otorhinolaryngological observation at the time of the diagnosis and after treatment.

Oral cancer accounts for approximately 1% of all cancers in Japan (1). Old age, smoking, and alcohol consumption are known risk factors (2). In the eighth edition of the TNM classification of malignant tumors, the Union for International Cancer Control (UICC), the concept of depth of invasion (DOI) was adapted to the T classification, which is a major change in the field of oral cancer field (3). Even in the new TNM classification, early-stage oral cancer has a better prognosis with less function lost with treatment. However, advanced-stage oral cancer is more dysfunctional and does not have a good long-term prognosis. Prevention through risk avoidance and early detection are important in the treatment of oral cancer.

Head and neck surgical observation is not mandatory at the time of diagnosis and follow-up of oral cancer. However, in daily clinical practice, complications of head and neck cancer are often observed before and after oral cancer. We believe that head and neck surgical observation may be routinely necessary at the time of diagnosis and follow-up of oral cancer. Studying the frequency of head and neck cancer complications and double cancers in oral cancer may prove the usefulness of head and neck surgical observation. It is reported that double cancers are observed 18.6% of all head and neck cancers (4). Examinations for head and neck double cancer include imaging tests, such as computed tomography, and endoscopy, such as upper gastrointestinal endoscopy and nasal endoscopy, each of which has different types of double cancer for the purpose of search. Investigating the types of double cancers and the timing of their appearance in oral cancer may be useful in selecting pre- and post-treatment examinations. There are few

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**Key Words:** Oral squamous cell carcinoma, prognosis, double cancer, risk factor.

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coherent reports on double cancers at the time of oral cancer diagnosis and after treatment.

In this study, we analyzed the prognosis and prognostic factors of oral squamous cell carcinoma (OSCC) in our hospital based on the eighth edition of the TNM classification/UICC. In addition, we analyzed the double cancers and discussed the significance of examinations of the head and neck region at the time of the diagnosis and after treatment for OSCC.

### Patients and Methods

**Case selection.** We retrospectively collected clinical information from 272 OSCC patients. All 272 patients were histopathologically diagnosed based on biopsy findings and subsequently treated with surgery or chemoradiation at Kyushu University during the period from April 2013 to March 2023. This study was approved by the institutional review board of Kyushu University (No. 29-43).

**Definitions.** Smoking. Smokers were defined as having a Brinkman Index (BI; Number of cigarettes per day × year of smoking) of ≥400, and those with a BI score of <400 were defined as never smokers.

**Alcohol consumption.** Alcohol consumption was defined as a history of alcohol consumption exceeding the appropriate level (10g/ day), as defined by the Ministry of Health Labour and Welfare in Japan.

**Double cancer.** Double cancer was defined based on the definition of Warren *et al.*: 1) both the first and second cancers were proven to be cancer, 2) the two lesions were separated, and 3) metastasis of the other was ruled out (5). We used the definition of Gluckman *et al.* to define synchronous and heterochronic double cancers. Cancers diagnosed within six months of one cancer were considered synchronous double cancers, and those diagnosed for more than six months were determined to have heterochronic double cancers (6).

**Statistical analysis.** Analysis method. All statistical analyses were performed using the JMP Statistical Discovery Software program (ver. 15.1; SAS, Cary, NC, USA). We used Fisher's exact test and Pearson's correlation coefficient to evaluate the associations between molecular markers. Overall survival (OS) was defined as the time from the first day of therapy until death or the last follow-up examination. Disease-specific survival (DSS) was defined as the time from the first day of therapy to death from OSCC. We used the Kaplan-Meier method for the analyses of OS and DSS, and the differences between the groups were compared using a log-rank test. A Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs). *p*-Values of <0.05 were considered statistically significant.

### Results

**Clinical findings.** The clinicopathological findings of 272 patients with OSCC are summarized in Table I. The average age of the patients was 69 years (range=17-92 years), and most patients were male (n=203, 74.6%). The most common sub-site was the tongue (n=148, 54.4%), followed by oral floor (n=31, 11.4%), lower gum (n=30, 11.0%), buccal

Table I. Clinical findings of 272 cases of oral squamous cell carcinoma included in the study.

|  |               | All (n=272)  |
|--|---------------|--------------|
| Age (y)                                  | Mean (range)  | 69.0 (17-92) |
| Sex (%)                                  | Male          | 203 (74.6)   |
|  | Female        | 69 (25.4)    |
| Tumor site (%)                           | Tongue        | 148 (54.4)   |
|  | Oral floor    | 31 (11.4)    |
|  | Lower gum     | 30 (11.0)    |
|  | Buccal mucosa | 29 (10.7)    |
|  | Upper gum     | 27 (9.9)     |
|  | Hard palate   | 7 (2.6)      |
| T-stage (%)                              | T1/T2         | 99 (36.4)    |
|  | T3/T4         | 173 (63.6)   |
| N-stage (%)                              | N0 (N-)       | 155 (57.0)   |
|  | N1,2,3 (N+)   | 117 (43.0)   |
| Clinical stage, 8 <sup>th</sup> UICC (%) | I             | 45 (16.5)    |
|  | II            | 40 (14.7)    |
|  | III           | 38 (14.0)    |
|  | IV            | 149 (54.8)   |
| History of smoking (%)                   | Yes (BI ≥400) | 163 (59.9)   |
|  | No (BI <400)  | 92 (33.8)    |
|  | Unknown       | 17 (6.3)     |
| History of drinking (%)                  | Yes           | 110 (40.4)   |
|  | No            | 136 (50.0)   |
|  | Unknown       | 26 (9.6)     |
| Double cancer (%)                        | Yes           | 93 (34.2)    |
|  | No            | 179 (65.8)   |

UICC: Union international cancer control.

mucosa (n=29, 10.7%), upper gum (n=27, 9.9%), and hard palate (n=7, 2.6%). Eighty-five (31.2%) patients had early clinical stage (I/II) OSCC tumors, and the others (68.8%) had advanced clinical stage (III/IV) OSCC tumors. Ninety-nine (36.4%) patients had a low-T stage (T1/2) and 173 (63.6%) had a high-T stage (T3/4). Lymph node metastasis was observed in 117 patients (43%). Most patients were smokers (n=163, 59.9%). Only 110 patients (40.4%) had a history of alcohol consumption.

**Outcome.** In total, 63 (23.2%) of the 272 patients because of their tumors. Fourteen of the 272 (5.1%) died from other causes. The remaining 195 patients (71.7%) were alive at the last follow-up examination.

**Prognostic analyses.** Overall survival. The overall 5-year survival rates were 63.8% overall, 94.9% in stage I, 77.5% in stage II, 80.4% in stage III, and 44.2% in stage IV (Figure 1A and Figure 2A). The disease-specific 5-year survival rates were 67.9% overall, 94.9% in stage I, 79.8% in stage II, 82.8% in stage III, and 50.6% in stage IV (Figure 1B and Figure 2B).

**Prognostic factors.** Our univariate analysis revealed that age ≥81 years (*p*=0.0037), sub-sites of the buccal mucosa

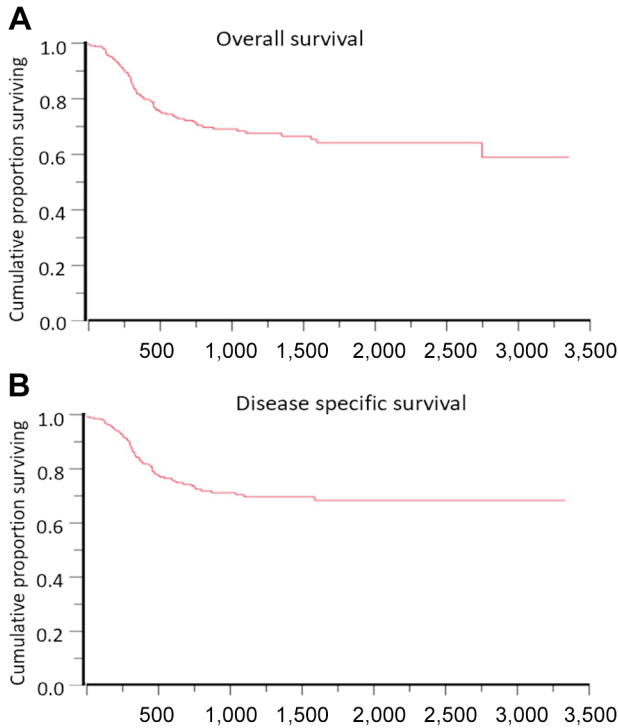


Figure 1. Kaplan-Meier analyses for the OS and DSS. (A) The 5-year OS rate is 63.8%. (B) The overall 5-year DSS rate is 67.9%. OS: Overall survival. DSS: Disease-specific survival.

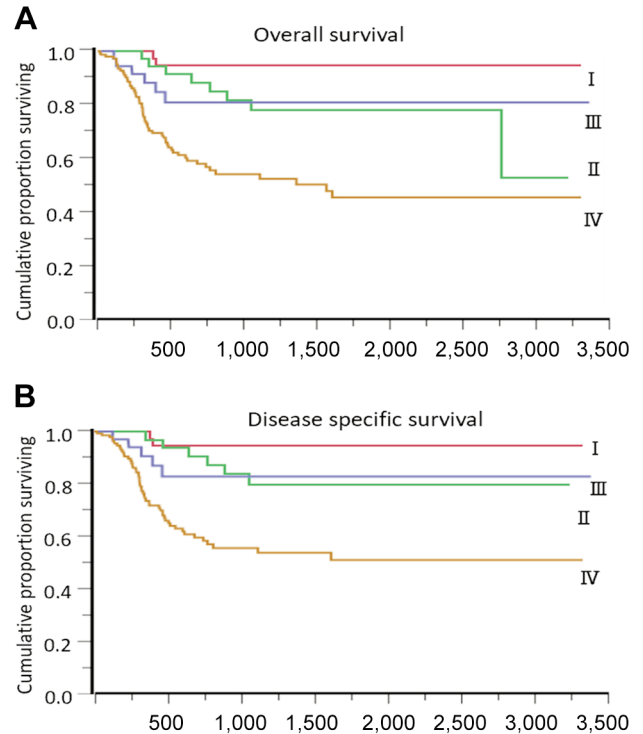


Figure 2. Kaplan-Meier analyses for OS and DSS according to 8<sup>th</sup> UICC clinical stage. (A) The 5-year OS rates in stages I, II, III, and IV are 94.9%, 77.5%, 80.4%, and 44.2%, respectively. (B) The 5-year DSS rates in stages I, II, III, and IV are 94.9%, 79.8%, 82.8%, and 50.6%, respectively. OS: Overall survival. DSS: Disease-specific survival.

( $p=0.0272$ ), lower gum ( $p=0.0288$ ), and advanced-clinical stage ( $p<0.0001$ ) were significantly associated with decreased DSS (Table II). A multivariate analysis revealed that age  $\geq 81$  years ( $p=0.0124$ ), sub-sites of the buccal mucosa ( $p=0.0036$ ,  $0.0019$ ) and oral floor ( $p=0.0278$ ), and advanced clinical stage ( $p<0.0001$ ) were significantly associated with decreased DSS (Table II).

**Double cancers in OSCC.** Observation period. The observation period ranged from 0.3 to 121 months (median, 31.9 months).

**Double cancers.** Of the 272 patients, 93 patients (34.2%) had double cancer (Table I). Total 151 sites and 19 cancer type were detected as double cancers. The most common type of double cancer was esophageal cancer in 33/ 151 sites (22%), followed by oropharyngeal cancer in 22/151 sites (15%), hypopharyngeal cancer in 20/151 sites (13%), colon cancer in 17/151 sites (11%), gastric cancer in 13/151sites (9%), lung cancer in 10/151 sites (7%), laryngeal cancer in 8/151 sites (5%), and other cancers (oral, thyroid, prostate, etc.). Synchronous double cancers were observed in 38/ 272 patients (14.0%), total 44 sites and divided 11cancer types. Half of synchronous double cancers were head and neck cancers.

Double cancer after oral cancer treatment was found in 7.4% of all patients. Of these, 26% had head and neck cancer.

**Statistical analysis of double cancers.** Statistical analyses showed that a smoking history ( $p=0.0002$ ) and drinking history ( $p=0.0068$ ) were significantly correlated with the presence of double cancer (Table III). We analyzed the differences in double cancer between early- and advanced-stage OSCCs. Thirty-four (40.0%) patients with early-stage OSCC had double cancer, and 59 (31.5%) patients with advanced-stage OSCC had double cancer (Table III). Head and neck double cancer accounted for 46% of early-stage OSCC double cancers, and 31% of advanced-stage OSCC double cancers. The number of head and neck cancers prior to OSCC was 13 (15.3%) in patients with early-stage OSCC and 11 (5.9%) in patients with advanced-stage cancer. There was a tendency for early-stage OSCC to have a higher incidence of head and neck cancer.

**Discussion**

**Prognosis.** The 5-year overall survival rate of 63.8% and DSS rate of 67.9% for OSCC at our hospital were higher

Table II. Relationship between disease-specific survival and clinical factors in OSCC.

| Variable                             | n=272   | Univariate analysis |              |          | Multivariate analysis |              |          |
|--------------------------------------|---------|---------------------|--------------|----------|-----------------------|--------------|----------|
|                                      |         | HR                  | 95% CI       | p-Value  | HR                    | 95% CI       | p-Value  |
| Age, years                           |         |                     |              |          |                       |              |          |
| >80/≤80                              | 34/238  | 2.55                | 1.354-4.789  | 0.0037*  | 2.52                  | 1.221-5.200  | 0.0124*  |
| Sex                                  |         |                     |              |          |                       |              |          |
| Male/Female                          | 203/69  | 0.95                | 0.542-1.6497 | 0.8437   | 0.87                  | 0.444-1.707  | 0.6872   |
| Sub-site                             |         |                     |              |          |                       |              |          |
| Buccal mucosa/Tongue                 | 29/148  | 2.20                | 1.093-4.413  | 0.0272*  | 2.97                  | 1.429-6.189  | 0.0036*  |
| Lower gum/Tongue                     | 27/148  | 2.32                | 1.091-4.914  | 0.0288*  | 1.43                  | 0.627-3.283  | 0.3934   |
| Buccal mucosa/Upper gum              | 29/27   | 2.36                | 0.818-6.783  | 0.1121   | 6.43                  | 1.982-20.867 | 0.0019*  |
| Oral floor/Upper gum                 | 31/27   | 2.22                | 0.742-6.633  | 0.9646   | 4.16                  | 1.168-14.813 | 0.0278*  |
| History of smoking                   |         |                     |              |          |                       |              |          |
| Yes/No                               | 163/92  | 1.23                | 0.716-2.132  | 0.4492   | 1.53                  | 0.770-3.030  | 0.2258   |
| Unknown                              | 17      |                     |              |          |                       |              |          |
| History of drinking                  |         |                     |              |          |                       |              |          |
| Yes/No                               | 110/136 | 0.82                | 0.490-1.371  | 0.4493   | 0.86                  | 0.476-1.566  | 0.6287   |
| Unknown                              | 26      |                     |              |          |                       |              |          |
| T-stage                              |         |                     |              |          |                       |              |          |
| T3-4/T1-2                            | 173/99  | 4.06                | 2.114-7.796  | <0.0001* |                       |              |          |
| N-stage                              |         |                     |              |          |                       |              |          |
| N1-3/N0                              | 117/155 | 4.85                | 2.827-8.335  | <0.0001* |                       |              |          |
| Clinical stage, 8 <sup>th</sup> UICC |         |                     |              |          |                       |              |          |
| III-IV/I-II                          | 187/85  | 4.73                | 2.247-9.947  | <0.0001* | 5.68                  | 2.518-12.817 | <0.0001* |
| Double cancer                        |         |                     |              |          |                       |              |          |
| Yes/No                               | 93/179  | 1.24                | 0.457-1.772  | 0.4070   | 1.02                  | 0.581-1.792  | 0.9434   |

OSCC: Oral squamous cell carcinoma; HR: hazard ratio; CI: confidence interval; UICC: Union international cancer control. \*Statistically significant.

than rates reported by the National Cancer Center in Japan (58% and 64%, respectively) (1). The 5-year DSS rates by stage were 94.9% for stage I, 79.8% for stage II, 82.8% for stage III, and 50.6% for stage IV, which were better than those reported in other studies (1).

**Prognostic factors.** In the analysis of prognostic factors, age ≥81 years, buccal mucosa and oral floor location, and advanced clinical stage were independent poor prognostic factors. These results are consistent with previous studies (7, 8).

**Double cancers.** Synchronous double cancers were found in 14% of cases. Half of the synchronous double cancers were head and neck cancers. Other reports indicate that double cancers were found in 2.2-2.7% of OSCC cases, of which 0-30.3% were head and neck cancers (9, 10) (Table IV). Otorhinolaryngological observations are considered necessary at the time of the diagnosis of OSCCs. Double cancer after oral cancer treatment was found in 7.4% of all patients. Of these, 26% had head and neck cancer. Although there are various reports of double cancers after oral cancer treatment, depending on the duration of follow-up, 3-10% of patients had complicating head and neck cancer (9, 11-14)

(Table IV). Therefore, regular observation of the pharynx during follow-up is desirable. The fact that a history of head and neck cancer is common among patients with early-stage double cancers of the OSCC suggests that follow-up observation of the head and neck region after head and neck cancer may have led to the early detection of OSCC.

**Limitations.** It should be noted that this study was conducted at a single institution and is a retrospective approach; therefore, some limitations in the results of the analysis should be acknowledged.

### Conclusion

Prognosis of OSCC at our Hospital was summarized, and the results were comparable to those of other reports. Age, sub-site of the buccal mucosa and oral floor, and advanced-clinical stage were founded to be poor prognostic factors, which is in line with other reports.

Because synchronous double cancers and double cancers after treatment of OSCCs included 3-10% of head and neck cancers, observation of the otorhinolaryngological area is considered desirable at the time of the diagnosis and during the follow-up of patients with OSCC.

Table III. Association between clinical variables and double cancer in 272 OSCCs.

| Variables                            | n=272 | With double cancer | Without double cancer | p-Value |
|--------------------------------------|-------|--------------------|-----------------------|---------|
|                                      |       | 93 (34.2)          | 179 (65.8)            |         |
| Age, years                           |       |                    |                       |         |
| ≤80                                  | 34    | 10 (29.4)          | 24 (70.6)             | 0.5300  |
| >80                                  | 238   | 42 (28.2)          | 107 (71.8)            |         |
| Sex                                  |       |                    |                       |         |
| Male                                 | 203   | 76 (37.4)          | 127 (62.6)            | 0.0528  |
| Female                               | 69    | 17 (24.6)          | 52 (75.4)             |         |
| History of smoking                   |       |                    |                       |         |
| Yes                                  | 163   | 69 (42.3)          | 94 (57.7)             | 0.0002* |
| No                                   | 92    | 18 (19.6)          | 74 (80.4)             |         |
| Unknown                              | 17    |                    |                       |         |
| History of drinking                  |       |                    |                       |         |
| Yes                                  | 110   | 49 (44.6)          | 61 (55.4)             | 0.0068* |
| No                                   | 136   | 38 (27.9)          | 98 (72.1)             |         |
| Unknown                              | 26    |                    |                       |         |
| Clinical stage, 8 <sup>th</sup> UICC |       |                    |                       |         |
| I/II                                 | 85    | 34 (40.0)          | 51 (60.0)             | 0.1733  |
| III/IV                               | 187   | 59 (31.5)          | 129 (68.5)            |         |

OSCC: Oral squamous cell carcinoma; UICC: Union international cancer control. \*Statistically significant.

Table IV. The reports of double cancer with oral squamous cell carcinoma.

|                | Author                         | Type of carcinoma     | Observation period  | Frequency         | Type of DC               |
|----------------|--------------------------------|-----------------------|---------------------|-------------------|--------------------------|
| Synchronous DC | Schwartz <i>et al.</i> (9)     | HNSCC (OSCC 32%)      | 42 m (0-169 m)      | 66/851 (7.7%)     | HNC 20/66 (30.3%)        |
| Synchronous DC | Valentin A <i>et al.</i> (10)  | OSCC                  | -                   | 4/194 (2.1%)      | Lung, Esophagus, Stomach |
| Secondary DC   | Schwartz LH <i>et al.</i> (9)  | HNSCC (OSCC 32%)      | 42 m (0-169 m)      | 96/851 (11.3%)    | HNC 30/96 (31.2%)        |
| Secondary DC   | Koo K <i>et al.</i> (11)       | T1, T2 OSCC           | 71.7 m (3.6-238 m)  | 11/112 (9.7%)     | HNC 9/11 (84.7%)         |
| Secondary DC   | Min SK <i>et al.</i> (12)      | Oral cavity carcinoma | 4.94 y              | 1096/15261 (7.2%) | -                        |
| Secondary DC   | Mroueh R <i>et al.</i> (13)    | OSCC                  | -                   | 640/6602 (10%)    | -                        |
| Secondary DC   | Petersen LO <i>et al.</i> (14) | OSCC                  | 10.2 y (2.2-18.3 y) | 219/936 (23%)     | HNC 97/219 (44%)         |

DC: Double cancer; HNSCC: head and neck squamous cell carcinoma; OSCC: oral squamous cell carcinoma; m: months; y: years; HNC: head and neck carcinoma.

## Conflicts of Interest

The Authors have no financial or non-financial interests to disclose.

## Authors' Contributions

All Authors contributed to the study conception and design. Materials preparation, data collection and analysis were performed by Rina Jiromaru. The first draft of the manuscript was written by Rina Jiromaru and all Authors commented on previous versions of the manuscript. All Authors read and approved the final manuscript.

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