Prognostic Factors in Patients with Buccal Squamous Cell Carcinoma: Ten-year Experience

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ABSTRACT

Purpose: Squamous cell carcinoma (SCC) of the buccal mucosa accounts for 23 to 37% of all intra-oral cancer cases in Taiwan. Due to the high recurrence rate and invasive tumor behavior, the prognosis is generally poor. The aim of this study was to evaluate the prognostic significance of clinicopathologic factors on the survival rates for patients with buccal SCC in a medical center in central Taiwan.

Patients and Methods: From March 1995 to December 2002, patients admitted to hospital and diagnosed as having buccal SCC were enrolled in the study. In total, there were 415 patients (406 males and 9 females) ranging in age from 25 to 84 (mean 51.1± 11.4) years. The chart records were retrospectively reviewed. Relevant clinical features in each patient such as primary tumor size, tumor stage, initial treatment modalities, surgical margin status, cervical nodal metastasis status, and histopathological grade, were compared for survival analysis.

Results: Three hundred and ninety-four patients received surgical intervention. Univariate analysis of relevant prognostic factors revealed that positive surgical margin, positive cervical nodal metastasis, positive extra-capsular spread, greater tumor size, and advanced tumor stage were associated with poor prognosis. Multivariate analysis identified the factors that independently influenced the survival rate as advanced stage disease [stage III relative risk (RR): 3.09, p=0.006, stage IV
RR: 4.64, \( p<0.001 \)], positive surgical margin (RR: 2.02, \( p=0.001 \)), and extra-capsular spread of cervical lymph node metastasis (RR: 6.89, \( p<0.001 \)).

**Conclusions:** This study represents the largest series in the literature and highlights the importance of tumor stage, surgical margin status, and extra-capsular spread of cervical nodal metastasis as the most important prognostic factors in patients with buccal SCC.

**Key Words:** buccal cancer, squamous cell carcinoma, prognostic factors
**INTRODUCTION**

Squamous cell carcinoma (SCC) of the buccal mucosa is one of the most common forms of oral cavity cancer in Taiwan, accounting for 23 to 37% of all intra-oral cancer cases.\(^{(1-3)}\) However, buccal SCC is relatively rare in North America and Western Europe, accounting for about 10% of all oral cavity malignancies.\(^{(4)}\) The high incidence of buccal SCC in Taiwan is believed to stem from the highly prevalent habit of betel quid chewing, which exposes the buccal mucosa to high doses of carcinogens.\(^{(5)}\)

Buccal SCC is associated with poor prognosis because of a high rate of recurrence and invasive tumor behavior.\(^{(6-10)}\) The treatment of choice in buccal SCC is conventionally a combination of surgery, radiotherapy, and chemotherapy.\(^{(7)}\) However, the overall survival rates have not improved substantially over the past decades.\(^{(11)}\) Therefore, identification of poor prognostic factors has become an important issue in the management of buccal SCC. Although some clinical studies have attempted to disclose the prognostic factors for buccal SCC, these reports have been limited by the small study populations and sample sizes. Moreover, buccal SCC is often grouped with other oral cavity malignancies in clinical studies, further confounding conclusions that may influence prognostic factor analysis.

Among the assessment of the prognosis in patients with buccal SCC, one of the
most favorable methods is the cancer staging system proposed by the International Union Against Cancer (UICC) TNM system. Poor prognosis is well known in the advanced stage. Other prognostic factors have also been proposed in the literature, such as tumor volume, tumor thickness, neck nodal metastasis, surgical margin, and histopathological grading.\textsuperscript{(12-14)} However, the significance of these prognostic factors remains controversial through the results of different studies.\textsuperscript{(10,14)}

Furthermore, there are some differences between Caucasians and Asians in buccal SCC, such as incidence, presenting age, and etiologic factors. The relevant predictive factors in Caucasians that have been published in previous reports are not necessarily suitable for Asians or Taiwanese.

From the published literature,\textsuperscript{(1,15)} the incidence of oral cancer is relatively high in central Taiwan. In addition, the buccal mucosa is the most common site of oral malignancy in this area.\textsuperscript{(15)} Therefore, the aim of this study was to analyze survival rates and investigate relevant prognostic factors in patients with buccal SCC in central Taiwan. In addition, since differences exist between Caucasians and Taiwanese in ethnicity, geography, and life style, we also intended to clarify whether there were any differences in prognostic factors for buccal SCC in different populations and provide information for the design of a better therapeutic strategy.
MATERIALS AND METHODS

Enrolled Patients

We retrospectively reviewed the records of all buccal cancer patients who had been admitted to a 1515-bed tertiary medical center in central Taiwan between March 1995 and December 2002. The observation end point was set at December 31, 2004. Only patients with histologically confirmed primary SCC of the buccal mucosa were included for study. Patients with SCC originating from adjacent areas with subsequent spread to the buccal mucosa were excluded. If the patients had been previously treated elsewhere and were seen with recurrence or residual tumors at Taichung Veterans General Hospital (TCVGH), they were not considered for the study. Patients who had distant metastases at presentation, did not complete the therapeutic protocol in our hospital, or had inadequate chart records were also excluded. After these exclusions, a total of 415 patients fulfilled the requirements and were included for further analyses. They were followed up at TCVGH. The last follow-up was recorded on the basis of the last outpatient visit or the date of death. Approval for this hospital-based study was granted by the Institutional Review Board of Taichung Veterans General Hospital.

Data Collections

Concerning the published literature, in our series, the data included the patients’
demographic data, treatment-related factors, and tumor-related factors. The patients’ demographic data comprised age, gender, blood type, personal history, and habitual history. Treatment-related factors included initial therapeutic modalities, surgical margin status, post-operative complication, and post-operative reconstruction. Tumor-related factors included tumor size, histopathological grading, cervical lymph node metastasis, and tumor stage. All of these variables were studied for impact on survival.

All patients were re-staged (pathological stage) according to the 2002 UICC cancer staging system for the oral cavity. The size or maximum diameter of primary tumors was determined based on gross pathologic measurements and descriptions. Surgical margin status was determined on final histopathological evaluation. Close margins were deemed positive in all analyses, whereas negative margins were considered to be greater than or equal to 5 mm from resection margin after tissue fixation.

**Statistical Analysis**

Statistical analysis was performed by using the commercial SPSS software system for Windows (version 10.1; SPSS, Chicago, IL). Variables that might influence survival status were analyzed by the chi-square test and the logistic
regression method. Survival analysis was investigated by the Kaplan-Meier method.

Data were evaluated as possible prognostic factors using univariate (log-rank test) and multivariate (Cox proportional hazards regression model) analyses. All $p$ values presented were two-sided and a $p$ value $< 0.05$ was considered statistically significant.

**RESULTS**

**Demographic Data**

Four hundred and fifteen patients with buccal SCC were enrolled in this study. There were 406 males and 9 females ranging in age from 25 to 84 years (mean $51.1 \pm 11.4$ years). The majority of the patients (60%, $n=248$) were in the 5th and 6th decades of life (Table 1). Among the 415 patients, tobacco use (93%), alcohol use (82%), and betel quid chewing (91%) were prevalent. Of the 406 males, 373 cases (92%) had a history of habitual betel quid chewing, compared with the female group, where only 3 out of 9 cases (33%) had this habit. Regarding the distribution of ABO blood groups among these patients, 122 cases (30%) were type A, 89 cases (21%) were type B, 186 cases (45%) were type O, and 18 cases (4%) were type AB.

In total, 117 patients (28%) had died by the end of follow-up. The average follow-up period was $43.9 \pm 31.7$ months. Most patients (95%, $n=394$) received
surgical management as their initial treatment. Among these patients, 210 cases (53%) underwent surgery alone as definitive therapy, whereas 184 cases had adjuvant radiotherapy or chemotherapy. Occurrence of post-operative complications was noted in 92 patients (23%), and the most common type of complication was wound infection (92%, n=85). Of the 415 patients, 341 patients (87%) received post-operative reconstruction. Three hundred and thirteen patients (79%) had negative surgical margins on pathological examination, whereas 81 cases (21%) had positive margins. On histopathological evaluation, tumors were graded as well (25%), moderately (70%), or poorly (5%) differentiated. Regarding cervical lymph node assessment, 113 patients (29%) had nodal metastases confirmed by pathological examinations. Furthermore, extra-capsular spread of lymph nodes was found in 42 out of 113 patients (37%). In regard to pathological tumor stage, 72 patients (17%) had stage I disease, 138 patients (33%) had stage II disease, 69 patients (17%) had stage III disease, and 136 patients (33%) had stage IV disease. Table 1 shows the results in detail.

**Factors Influencing the Patients’ Mortality**

Concerning the treatment modalities that may influence the survival status (Table 1), we further divided all the patients into two groups based on whether they received
surgery or not. Due to the small sample size of the non-surgical group (5%), we analyzed prognostic factors in surgically-treated patients. Comparison of the clinicopathological characteristics between non-survivors (n=105) and survivors (n=289) disclosed no significant differences in gender ($\chi^2$ value = 0.49, $p = 0.444$), age ($\chi^2$ value = 0.83, $p = 0.661$), blood type ($\chi^2$ value = 3.10, $p = 0.377$), initial treatment modalities ($\chi^2$ value = 4.19, $p = 0.053$), post-operative reconstructions ($\chi^2$ value = 0.14, $p = 0.835$), and histopathological grade ($\chi^2$ value = 3.01, $p = 0.222$). The only statistically significant differences between the non-survival group and the survival group were in surgical margin status ($\chi^2$ value = 16.52, $p < 0.001$), cervical lymph node metastasis ($\chi^2$ value =30.41, $p < 0.001$), existence of extra-capsular spread of lymph node metastasis ($\chi^2$ value =17.38, $p < 0.001$), and tumor stage ($\chi^2$ value = 33.36, $p < 0.001$). In addition, the non-survival group had a higher proportion of primary tumors greater than 4 cm in size ($\chi^2$ value = 12.39, $p = 0.001$). A comparison of variables between the two groups is listed in Table 2.

Locoregional recurrence was also noted in 228 patients (55%) during the follow-up period, while only 9 patients (2%) were identified as developing distant metastases. The average recurrent period was 28.2 ± 17.4 months. As shown in Table 3, there was a higher proportion of patients with positive surgical margins as well as those with extra-capsular spread of cervical lymph node metastasis in the recurrent
Using multivariate logistic regression analysis, we found that only tumor stage, surgical margin status, and cervical nodal metastasis status were independent prognostic factors. The detailed results are shown in Table 4.

**Survival Analysis**

Based on Kaplan-Meier survival analysis, the overall one-year, three-year, and five-year survival rates in surgically-treated patients were 87%, 78%, and 71%, respectively. In addition, the five-year survival rates for stage I (n=72), stage II (n=132), stage III (n=68), and stage IV (n=122) were 88%, 79%, 69%, and 53%, respectively.

Log-rank test analysis of Kaplan-Meier survival curves identified tumor stage as significantly affecting survival (log rank: 40.6, \( p < 0.001 \)). In addition, there was a significant difference in the overall five-year survival rate in initial treatment modalities (log rank: 4.3, \( p = 0.038 \)), surgical margin status (log rank: 24.3, \( p < 0.001 \)), primary tumor size (log rank: 16.0, \( p < 0.001 \)), and cervical nodal metastasis status (log rank: 105.2, \( p < 0.001 \)). Conversely, there was no significant difference in the overall five-year survival rate in age (log rank: 1.5, \( p = 0.468 \)), gender (log rank: 0.7, \( p = 0.416 \)), blood type (log rank: 4.6, \( p = 0.204 \)), post-operative reconstructions (log
rank: 0.1, \( p = 0.749 \), and histopathological grade (log rank: 5.2, \( p = 0.075 \)). The data are presented in Table 2 and illustrated in Figures 1-3.

Using the Cox proportional hazards model, we found that patients with positive surgical margins had a higher probability of mortality than those with negative surgical margins [relative risk (RR): 2.02, 95% confidence interval (CI): 1.33 – 3.07, \( p = 0.001 \)]. In addition, those with extra-capsular spread of cervical lymph node metastasis had a poorer prognosis than those without cervical nodal metastasis (RR: 6.89, 95% CI: 4.24 – 11.19, \( p < 0.001 \)). Patients with advanced stage disease also had a higher mortality rate compared with those with stage I disease (stage III RR: 3.09, 95% CI: 1.38 – 6.96, \( p = 0.006 \); stage IV RR: 4.64, 95% CI: 2.20 – 9.79, \( p < 0.001 \)). Each of these prognostic factors was considered to have an independent association with mortality. The results are shown in Table 5 in detail.

**Discussion**

In this hospital-based study conducted in central Taiwan, over 500 patients with buccal SCC were analyzed. To the best of our knowledge, this is the largest study focusing on survival rates and prognostic factors of survival in patients with buccal SCC in the literature. Although Paymaster\(^{(16)}\) reported 650 buccal cancer patients in
1956, most of the patients received either no treatment or incomplete treatment, only 300 patients with primary SCC received treatment.

Our results showed that surgical margin status, extra-capsular spread of cervical nodal metastasis, and tumor stage are the best independent prognostic factors, and this finding is in line with previous studies.\(^{(9,13,17-19)}\) Although Sieczka et al.\(^{(10)}\) retrospectively analyzed prognostic factors in 27 patients with buccal SCC and found that negative margins are not predictors of local control, the small population size of their study may limit interpretation of their results. As shown in Table 3, surgical margin status and extra-capsular spread of cervical nodal metastasis were significantly correlated with locoregional recurrent status. It is evident that advanced tumor stage or failure of locoregional control negatively influences survival in patients with buccal SCC. The 55% rate of locoregional recurrence in this study is in parallel to the rates in other studies.\(^{(7,10,13)}\)

Pandey et al.\(^{(14)}\) reviewed 142 patients with buccal SCC treated by primary surgery or salvage surgery and found that the stage of primary tumor did not demonstrate an influence on survival, which is probably due to fewer patients with T1 and T2 tumors in their study.

Buccal cancer occurs predominately among males, with a male to female ratio ranging from 15 to 74:1.\(^{(2,3,13,20)}\) Pathak et al.\(^{(20)}\) also reported that oral cancer shows a
predilection for males of 75–98% in Asian countries, compared with North America, where men account for only 14–55%. In the current study, the ratio of males to females was 45:1. One possible cause of the marked male predominance is that the majority of betel quid chewers in Taiwan are males.\(^{(21)}\) In addition, the selection effect of gender in our hospital cannot be ruled out. As expected, our study showed a discrepancy in the proportion of betel quid chewers among males and females, of 92% and 33%, respectively. This is similar to a previous report by Lee et al.\(^{(22)}\) Although the risk factors for buccal SCC in females are not clear, the pathogenesis of buccal SCC among genders may be different. Further investigations with a prospective cohort study are required to define the possible causes and prognostic factors.

Among the 415 patients with buccal SCC, the average presenting age of onset was 51 years, which is compatible with previous reports\(^{(7,13,17,22)}\) and data in the Taiwan Cancer Registry system. The majority of patients received surgical treatment and nearly half of them had multimodal therapies. The post-operative complication rate in this study was 23%, and most of these cases had wound infection (85 cases), accounting for 22% of all surgically-treated patients. This rate is acceptable as compared to published literature.\(^{(23)}\) Regarding the resection margin status, 21% of cases had positive margins, and this is also comparable with previous studies.\(^{(10,24)}\)

In the current study, multimodality treatment failed to improve prognosis. This is
due to the fact that most early staged patients received surgery alone, whereas, surgery combined with adjuvant radiotherapy or chemotherapy was reserved for patients with advanced stage disease. However, our study supports the findings of others that inadequate surgical margin and extra-capsular spread of cervical lymph node metastasis correlated with poorer prognosis and locoregional recurrence. A previous report on 121 patients concluded that multimodality treatment improved locoregional control.\(^7\) Thus, for patients with positive surgical margins or extra-capsular spread of cervical nodal metastasis, combined-multimodal treatment modalities may improve survival. Lin et al.\(^3\) reported that for patients with more than two lymph nodes or positive ECS, cisplatin-based concomitant chemo-radiation therapy (CCRT) improved locoregional control \((p = 0.02)\). Two large randomized trials also demonstrated that CCRT improved tumor control in patients with positive surgical margins and/or ECS.\(^{25,26}\) In addition, tumor stage also strongly affects the prognosis of patients with buccal SCC. Therefore, early detection and diagnosis of buccal SCC is warranted for improving survival. Yeole et al.\(^{27}\) reported that detecting oral cancer in the early stages, when amenable to single modality therapies, offers the best chance of long-term survival. It has been suggested that those who are habitual cigarette smokers, alcohol consumers, and betel quid chewers should receive oral mucosal screening regularly, so that potential oral cancer can be detected as early as
possible.\textsuperscript{(28,29)} However, primary prevention by control measures for tobacco, alcohol, and betel quid is the most important factor in the long-term perspective.

Even though there are some differences between Caucasians and Taiwanese in buccal SCC, the prognostic factors demonstrated in this study are comparable to previous reports from Western countries. Although there are discrepancies in etiologic factors between these different areas, the tumor biology for buccal SCC may be identical. That is, buccal SCC in Western countries and Taiwan does not represent two diverse disease processes but the same disease in different populations, thus, they share the same predictive factors. Therefore, despite buccal SCC representing an uncommon disease entity in Western countries, the experience regarding buccal SCC in Taiwan may apply to Western countries.

There were some limitations to this study. First, this was a retrospective study, not cohort research. It was sometimes difficult to obtain accurate information during the period of patient follow-up. Second, patients enrolled in this study were those admitted to a cased hospital, not those from out patient clinics. In addition, they were admitted for potentially curative attempts rather than palliative treatment. Furthermore, this study was conducted at a single institution. Thus, external validity of the findings from this study may be limited. Third, although all surgical specimens were sent for pathologic examination, individual differences among pathologists inevitably exist.
Finally, individual differences among surgeons may also exist. Further investigations with prospective cohort designs are required to clarify the impact of these prognostic factors on survival in patients with buccal SCC.

**CONCLUSION**

This hospital-based study reviewing 415 patients with buccal SCC represents the largest series to focus on survival and prognostic factors in surgically treated patients. It highlights the importance of tumor stage, surgical margin status, and extra-capsular spread of cervical nodal metastasis as the most important prognostic factors in predicting survival in patients with buccal SCC. Therefore, the achievement of adequate surgical resection by surgeons’ best efforts is warranted for better outcomes in treatment of patients with buccal SCC.

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REFERENCES


8. Lee KH, Veness MJ, Pearl-Larson T, Morgans GJ: Role of combined modality


16. Paymaster JC: Cancer of the buccal mucosa; a clinical study of 650 cases in Indian patients. Cancer. 9:431, 1956


