Clinicopathologic Evaluation of Prognostic Factors for Squamous Cell Carcinoma of the Buccal Mucosa

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Background: The purpose of this research was to evaluate the prognostic significance of clinicopathologic variables on the survival rate for squamous cell carcinoma of the buccal mucosa (BMSCC). We analyzed the outcomes of surgical therapy for this aggressive cancer and compared these results with those in the literature.

Methods: We reviewed the medical charts of 172 patients treated in our institution between 1990 and 2005. There were 22 patients excluded from our studies: 20 patients with advanced tumors who received no treatment or palliative treatment, and 2 patients who had received preoperative radiotherapy (RT). The remaining 150 patients were treated with surgeries and among them, 56 patients had undergone postoperative RT. The influence of clinicopathologic factors on the survival rate was analyzed with the Kaplan–Meier method and log-rank test. Multivariate analysis was assessed with Cox's regression model.

Results: There were 148 males and 2 females, with a mean age of 53.5 years. The prevalence rate of habitual betel quid chewing documented in charts among 113 patients was 75%. The 5-year overall survival rate and disease-specific survival rate for all patients were 64% and 69%, respectively. For patients with stages I, II, III, and IV disease, the 5-year disease-specific survival rates were 90%, 77%, 52%, and 47%, respectively ($p < 0.001$). According to the multivariate analysis, the pathologic staging and histologic grading of the tumor were independently the important prognostic factors affecting survival rate. There were 80 patients who developed locoregional recurrence in lymph nodes in the follow-up diagnoses. Distant metastases occurred in 14 patients, with 11 of them also having locoregional recurrence. The distant metastases were found in the lungs (8/14), T-spine (3/14), liver (2/14) and brain (1/14).

Conclusion: Pathologic stage and histologic grade are the most important prognostic factors. [*J Chin Med Assoc* 2007; 70(4):164–170]

Key Words: buccal squamous cell carcinoma, survival, treatment outcome

Introduction

Squamous cell carcinoma of the buccal mucosa (BMSCC) is the most common form of oral cancer in South Asia, including India and Taiwan.[1–7] BMSCC is a rare clinical entity, accounting for approximately 10% of all oral cancers in the United States and Western Europe.[8] BMSCC accounts for 26.5–37.4% of all intraoral cancers in Taiwan and buccal mucosa seems to be the site at greatest risk of contracting malignancy in betel quid chewers.[3,7,9] Tobacco and alcohol use are considered the major risk factors for buccal carcinoma in the United States. Betel quid chewing is the main risk factor for buccal cancer in Taiwan.[10–13] The high incidence of carcinoma of the buccal mucosa in Taiwan is due to habitual betel quid chewing, which exposes the buccal mucosa to high doses of carcinogens.[14]

In 2002, oral carcinoma was the 4th in cancer incidence of males and the 5th leading cause of cancer death of males in Taiwan.[9] BMSCC tends to act more aggressively than those originating in other subsites in the oral cavity because limited anatomic barriers

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within the buccal space provide essentially no resistance to tumor spread.[15] Therefore, it presents lower 3- and 5-year disease-specific survival rates of 62–91% and 37–76%, respectively.[2,4–6,16–22] Locoregional recurrence after surgery or even after combined surgery and radiotherapy (RT) is the main cause of death in these patients. BMSCC is aggressive and associated with a poor prognosis of the high incidence of locoregional recurrence rates of 26–80% reported in the literature.[2,4,5,17–22] Available data suggest that recurrent disease is most often locoregional, with distant metastases affecting a relatively small percentage of 0–23% of patients.[2,4–6,16,18,20]

Traditionally, treatment for stage I and II lesions has been either surgery or radiation therapy as a single modality.[1] Surgical excision combined with postoperative RT has been recommended for advanced-stage tumors.[5,23,24]

Since there are few reports in the literature analyzing the clinicopathologic aspects of the disease and surgical treatment results of current therapy, the aim of this study was to evaluate the prognostic factors for survival rate and compare them with data reported in the literature. This study represents the largest series of previously untreated patients with BMSCC who received curative surgeries with or without postoperative RT in Southern Taiwan, where the habit of betel quid chewing is prevalent.[3,13]

Methods

We reviewed the charts of 172 patients histopathologically diagnosed with primary BMSCC at Kaohsiung Veterans General Hospital between November 1990 and May 2005. Of the 172 patients, 22 were excluded: 20 patients with advanced tumors who received no treatment or palliative treatment, and 2 patients who had received preoperative RT. The remaining 150 patients had undergone wide excisions for buccal cancer. If the tumor was near or had invaded the mandible and/or maxilla, marginal or segmental mandibulectomy and/or partial or hemimaxillectomy was performed for adequate margins. When treating clinically negative neck lymph nodes, neck dissection was not performed except for intensive follow-up. In addition, modified radical neck dissection was used when there were clinically positive neck lymph nodes, unless lymph nodes were involved in the posterior triangle of the neck and/or the spinal accessory nerve, in which case radical neck dissection was performed.

Tumors were staged retrospectively according to the TNM staging system as proposed by the 2002 American Joint Committee on Cancer (AJCC).[25] Of 150 patients, 66 patients (43.7%) were alive at the time of last follow-up diagnosis. The histologic diagnosis and report of well, moderately, or poorly differentiated SCC were graded according to World Health Organization guidelines. Surgical margin status was determined on final histopathologic evaluation.

All patients had undergone surgeries, and 56 (37.3%) among them had received postoperative RT. It should be noted that RT was not given preoperatively to any of these patients. Postoperative RT was performed on patients with pathologic T4 tumors, multiple positive neck lymph nodes, positive surgical margins, and extracapsular spread (ECS). Irradiation was started as soon as feasible after surgery, usually within 3–8 weeks. The prescribed dose was 1.8–2.0 Gy per fraction per day, given 5 days a week. Radiation dosage ranged from 50 to 66 Gy and was delivered in daily fractions over 6–7 weeks. In addition, preoperative or postoperative chemotherapy was not used, except for palliative treatment.

The survival time was measured from the time of histologic diagnosis in all 150 patients who had undergone surgeries. The period of follow-up was calculated as the duration between the date of initial diagnosis to the date of death or last follow-up when alive. For disease-specific survival, patients dying from intercurrent disease were censored at the time of death. Survival curves were calculated by the Kaplan–Meier product-limit method. The prognostic significance of 14 clinicopathologic factors on survival in the multivariate analysis was assessed using Cox's regression model with forward selection. SPSS version 10.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. A p value < 0.05 was considered to be significant. In addition, p values were for a 2-sided hypothesis.

Results

A total of 150 patients with a diagnosis of BMSCC met the inclusion criteria for this study. The patients were not evenly distributed by gender (148 males, 2 females). The overall male-to-female ratio was 74:1 in this study. At the time of diagnosis, the mean age was 53.5 years (range, 24–85 years). The mean age of male patients was 53.2 years (range, 24–77 years). The prevalence rate of habitual betel quid chewing documented in charts among 113 patients was 75%.

The distribution according to the AJCC staging system was: 50 (33.3%) patients with pathologic stage I, 37 (24.7%) with stage II, 18 (12.0%) with stage III,

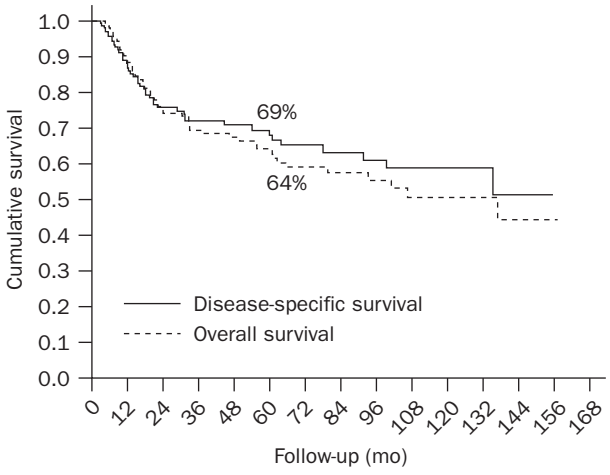

Figure 1. The 5-year disease-specific survival in a recent cohort of 150 patients with squamous cell carcinoma of the buccal mucosa treated at Kaohsiung Veterans General Hospital. Survival rate is demonstrated with the use of the Kaplan–Meier product limit method.

and 45 (30%) with stage IV disease. The histopathology of tumor differentiation showed that most patients ($n=93$, 62%) had moderately differentiated SCC. In addition, 50 cases (33%) showed well-differentiated tumor, and 7 cases (5%) had poorly differentiated SCC.

The median overall survival rate was 136.9 months (range, 1.5–157.0 months). The 1-year, 3-year, 5-year, 10-year, and 12-year overall survival rates for all patients were 88%, 70%, 64%, 50%, and 44%, respectively. The 1-year, 3-year, 5-year, 10-year, and 12-year disease-specific survival rates for all patients were 89%, 72%, 69%, 59%, and 51%, respectively. There were no perioperative deaths. Death occurred in 84 patients during follow-up. The Kaplan–Meier overall and disease-specific survival curves are shown in Figure 1. The 5-year survival rates for patients with N0 and N+ neck disease were 78% and 41%, respectively ($p<0.001$). In addition, distant metastases occurred in 14 patients (9.3%) during the follow-up period, 11 (78.6%) of whom also showed locoregional recurrence. Distant metastases were found in the lung (8/14), T-spine (3/14), liver (2/14) and brain (1/14).

The median time between initial treatment and locoregional recurrence was 41.1 months (range, 1.5–119.7 months). Locoregional recurrence developed in 80 patients (53.3%) during follow-up. Among them, 50 (33.3%) had disease recurrences only at the primary sites, 16 (10.7%) had recurrences only in the ipsilateral neck, and 14 (9.3%) patients had simultaneous primary and neck recurrences during follow-up. Locoregional failure was one of the main causes of subsequent death. In the stratification analysis, we found that the 5-year disease-specific survival rate for patients with locoregional recurrent disease was 58%. However, by using the log-rank test, the disease-specific survival rate of those with no evidence of locoregional recurrence was found to be 84% ($p<0.001$). In addition, 47 (58.8%) out of 80 patients with recurrences were suitable for salvage surgeries with wide excisions or neck dissections. The incidence rate of second primary cancer was 19% (28 patients), and all of them were SCCs involving the upper aerodigestive tract.

Univariate analysis of the prognostic factors for disease-specific survival is outlined in Table 1. The disease-specific survival curves according to gender, age group, betel quid chewing, second primary cancer, buccinator muscle invasion, and surgical margin demonstrated no statistical differences by univariate analysis. However, the disease-specific survival curves were significantly correlated with pathologic stage, T-stage, N-stage, treatment modality, histologic grade, mandibular bone invasion, perineural invasion, and vascular invasion in univariate analysis. The Kaplan–Meier disease-specific survival curves for pathologic stage and histologic grade are shown in Figures 2 and 3, respectively.

The Cox regression model was constructed with a forward selection in which significant variables, from 14 clinicopathologic factors, were added 1 at a time to assess their effect on the fit of the model. Finally, only the statistically significant prognostic factors, including pathologic stage and histologic grade, were included in the model (Table 2). Each of these prognostic factors was considered to have an independent association with death. Patients with stage IV tumors had a 6.56 greater risk of death when compared with those having stage I tumors. In addition, patients with moderately or poorly differentiated cancer had a 2.35 higher risk of death compared with patients with well-differentiated cancer.

Discussion

BMSCC is rare in the United States and Western Europe, where the major risk factors of oral cancers are thought to be alcohol drinking and tobacco smoking. In contrast, BMSCC occurs frequently in India, Southeast Asia (including Taiwan) and numerous other countries where chewing of betel quid is popular.[10–12]

Of the 150 patients in this study, only 1.3% were females. The selection effect of sex in our hospital cannot be ruled out. This rate was slightly less than the 4–7% in Taiwanese,[2,5,6] but was significantly less than the 13–86% in Indians, or 38–87% in Americans.[4,16,18–22,26,27] The discrepancy in sex ratio

Table 1. Univariate analysis of clinicopathologic prognostic factors on disease-specific survival in BMSCC patients

	Survival ($n=150$)			
	5-year disease-specific survival rate	p*	RR (95% CI)	$p^{\dagger}$
Gender				
Female (2)	–	0.531	1.00	
Male (148)	0.69		0.05 (0.00–70285.3)	0.677
Age (yr)				
≤40 (18)	0.66	0.754	1.00	
41–50 (45)	0.66		1.12 (0.41–3.10)	0.822
51–60 (43)	0.69		1.09 (0.39–3.07)	0.871
>60 (44)	0.75		0.83 (0.26–2.18)	0.600
Betel quid chewing				
No (37)	0.80	0.056	1.00	
Yes (113)	0.66		2.26 (0.95–5.35)	0.064
Pathologic stage				
I (50)	0.90	<0.001	1.00	
II (37)	0.77		2.61 (0.95–7.21)	0.063
III (18)	0.52		4.62 (1.59–13.38)	0.005
IV (45)	0.47		7.41 (2.91–18.87)	<0.001
T-stage				
T_1 (54)	0.89	<0.001	1.00	
T_2 (48)	0.68		3.20 (1.31–7.82)	0.011
T_3 (8)	0.31		8.98 (2.78–29.02)	<0.001
T_4 (40)	0.52		5.97 (2.40–14.85)	<0.001
N-stage				
N_0 (115)	0.78	<0.001	1.00	
N_1 (21)	0.61		1.77 (0.82–3.82)	0.147
N_2 (14)	0.00		14.83 (6.33–34.71)	<0.001
Secondary primary				
No (122)	0.70	0.902	1.00	
Yes (28)	0.68		1.05 (0.50–2.18)	0.902
Treatment modality				
Surgery alone (94)	0.78	0.005	1.00	
S+RT (56)	0.57		2.28 (1.25–4.14)	0.007
Histologic grading of differentiation				
Well (50)	0.87	<0.001	1.00	
Moderate (93)	0.65		2.51 (1.19–5.31)	0.016
Poor (7)	0.00		7.02 (2.30–21.39)	<0.001
Invasion of buccinator muscle				
No (93)	0.68	0.620	1.00	
Yes (57)	0.71		0.85 (0.46–1.59)	0.616
Mandibular invasion				
No (134)	0.73	<0.001	1.00	
Yes (16)	0.43		3.26 (1.56–6.84)	0.002
Perineural invasion				
No (135)	0.72	0.006	1.00	
Yes (15)	0.44		2.96 (1.30–6.76)	0.010
Vascular invasion				
No (139)	0.72	<0.001	1.00	
Yes (11)	0.00		4.82 (1.98–11.72)	0.001
Surgical margins				
Negative (120)	0.74	0.054	1.00	
Positive (30)	0.52		1.88 (0.98–3.62)	0.058

**p estimated by log-rank test; †p estimated by Cox's regression. BMSCC=squamous cell carcinoma of the buccal mucosa; RR=relative risk of death; CI=confidence interval; S=surgery; RT=radiotherapy.*

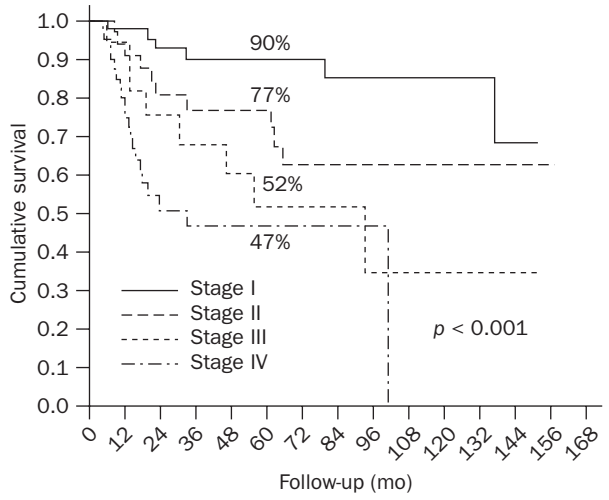

Figure 2. Effect of pathologic stage on survival. Survival curves were calculated based on all deaths by using the Kaplan–Meier life table method.

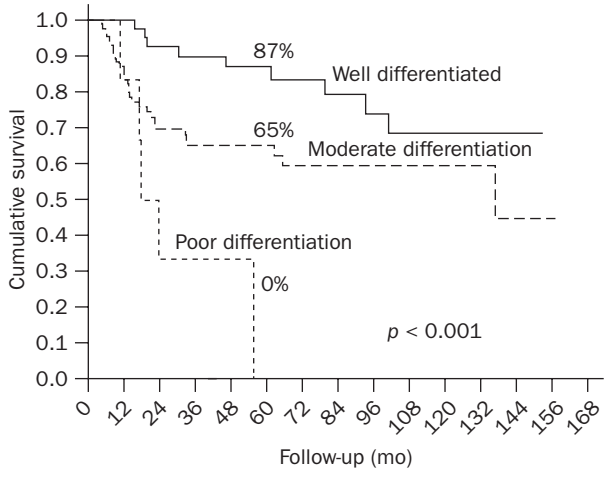

Figure 3. Effect of histologic grading of differentiation on survival rate.

reflects the fact that the prevalence of betel quid chewing is much higher among males than females in Taiwan (20.9% *vs.* 1.2%).[28]

The 3-year disease-specific survival rate (72%) in this study was lower than those in the other studies (range, 78–91%).[4,6] Yet, the 5-year disease-specific survival rate (69%) was moderate as compared with those in the other studies (range, 37–76%).[5,6,16–22] The different clinicopathologic characteristics of patients and treatment modalities received by patients may explain the various survival rates between studies. For example, there were 2 studies with obviously higher survival rates than ours. One is the study of Iyer et al,[4] with a 3-year disease-specific survival rate of 91% for 147 patients with early-stage BMSCC who underwent peroral wide excisions. The other is the study of Liao et al,[6] with a 5-year disease-specific survival rate of 76% for 232 patients treated with radical surgeries with or without neck dissection. Compared to our study, more patients with early-stage disease in Iyer et al's[4] study and those in Liao et al's[6] underwent extra aggressive radical surgery and neck lymph node dissection, which explains their higher survival rates. In addition, there was a recent study from Taiwan by Lin et al[5] with relatively lower survival rates than ours. That study showed that the 5-year disease-specific survival rate was only 37% for 121 patients who received different treatment modalities (surgery alone, RT alone, and surgery with postoperative RT). The most likely reason was that more patients in their study were in the advanced stages than in our study (63.6% *vs.* 42%). Additionally, 1-third of their patients (30%) only received RT alone, which had a very poor survival in either the early- or the advanced-stage disease.[1,5] Furthermore, there were 2 studies with survival rates comparable to ours. One is the study of Diaz et al,[21] which reported a 5-year disease-specific survival rate of 63% for 119 patients treated at a single institution. The other is a study by Fang et al[2] from Southern Taiwan, which found that

Table 2. Cox's regression of prognostic factors on survival for squamous cell carcinoma of the buccal mucosa

Factor (no. of patients)	ARR (95% CI)	*p*
Pathologic stage		
I (50)	1.0	
II (37)	2.59 (0.94–7.15)	0.066
III (18)	4.76 (1.63–13.85)	0.004
IV (45)	6.56 (2.55–16.86)	<0.001
Histology		
Well (50)	1.0	
Moderate + poor (100)	2.35 (1.11–4.96)	0.026

Cox's regression analysis for relative risk of death after adjusting for variables in each other. ARR = adjusted relative risk of death; CI = confidence interval.

the 3-year disease-specific survival rate for 57 patients treated by surgery and postoperative RT was 62% (60% in our 56 patients).

Multivariate analysis permitted stratification of all 150 patients into different death risk categories based on pathologic staging and histologic grading. Diaz et al[21] reported the MD Anderson experience for 119 patients with BMSCC treated with surgery alone (84 patients) or surgery combined with adjuvant radiation therapy (35 patients) between 1974 and 1993. The 5-year disease-specific survival rate was 63%; and by stages, the disease-specific survival rates were: 78% in stage I, 66% in stage II, 62% in stage III, and 50% in stage IV ($p=0.030$). In our series, for patients with stages I, II, III and IV disease, the 5-year disease-specific survival rates were 90%, 77%, 52% and 47%, respectively ($p<0.001$). This indicated that the patients who were treated in their early stages had better prognoses and survival rates.[1,4,6,21]

The presence of regional metastasis was an important factor for the prognosis.[6,16,21] Diaz et al[21] demonstrated that the 5-year survival rate for patients with N0 and N+ neck were 70% and 49%, respectively ($p=0.0116$). Our study result was comparable with the above results (78% *vs.* 41%, $p<0.001$).

The prognostic value of histologic grading has been controversial, with conflicting evidence in the literature.[29,30] Patients with moderately/poorly differentiated cancer in our study had a poor survival rate. Liao et al[6] found that poor differentiation of cancer (HR, 1.050; 95% CI, 1.016–1.084; $p=0.034$) was a significant factor for disease-specific survival in multivariate analysis. In our series, the mortality rate in patients with moderately/poorly differentiated cancer was 2.35 times higher compared with that in patients with well-differentiated cancer in multivariate analysis. A probable reason was that the moderately/poorly differentiated cancers tended to present more often with N+ disease than well-differentiated tumors ($p=0.02$). Iyer et al[4] suggested that these patients with poorly differentiated carcinoma should be treated more aggressively (i.e. selective neck dissection and postoperative RT).

The 53.3% rate of locoregional recurrence encountered in this study is just slightly lower than the range of 56–80% reported by others.[5,18,19] The recurrence rate of our study was higher than the range of 26–47% reported in the literature.[2,4,17,20–22,27] Many previous surveys demonstrated that local recurrence rates are quite high, ranging between 45% and 80%.[17–19] The rate of local recurrence is relatively high due to the lack of anatomic barriers to spread in the buccal space.[15] Failure of locoregional control negatively affects survival in patients with BMSCC. Sieczka et al[19] found that the 5-year survival rate was 100% for those with no evidence of locoregional recurrence and declined to 50% for patients with recurrent disease ($p=0.001$). Our findings were comparable with the above results, 84% *vs.* 58% ($p<0.001$).

Our study supports the findings of others that oral cavity carcinomas are notorious for development of second primary cancer.[31] There is a 14–37% incidence of second primary cancers; these mainly involve the upper aerodigestive tract.[4,8,18,20,26] Our study found that the incidence rate of second primary cancer was 19% (28 patients), which was comparable with reports in the literature. In addition, they were all SCCs involving the upper aerodigestive tract. It was noteworthy that the majority of these tumors were SCC and involved the upper aerodigestive tract, suggesting a mucosa field change.[31] For example, Chhetri et al[20] reported a 37% incidence of second primary neoplasms, 90% of which were SCC involving the upper aerodigestive tract.

In the literature, the incidence of systemic dissemination for BMSCC ranges from 0% to 23%.[2,4–6,16,18,20,21,26] In our study, 14 patients (9%) developed distant metastases, and lungs were the most common sites. Fang et al[2] found a 7% rate of distant metastasis for 57 patients with BMSCC treated by surgery and postoperative RT. Distant metastases occurred in 19 patients (15.7%), 14 of whom also had locoregional recurrence in the study by Lin et al.[5] Liao et al[6] reported that the 5-year distant metastasis rate was 14%; lungs and bones were the most frequent sites for distant metastases.[32]

In conclusion, the strong influence of disease stage on prognosis emphasizes the importance of early diagnosis of BMSCC and aggressive treatment for patients with poorly/moderately differentiated cancer.

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