SPANDIDOS PUBLICATIONS

MOLECULAR AND CLINICAL ONCOLOGY 1: 531-534, 2013

Squamous cell carcinoma of the buccal mucosa: Analysis of clinical presentation, outcome and prognostic factors

QI-GEN FANG[1,2], SHUANG SHI[3], ZHEN-NING LI[1,2], XU ZHANG[1,2], FA-YU LIUA[1,2], ZHONG-FEI XU[1,2] and CHANG-FU SUN[1,2]

Departments of [1]Oromaxillofacial-Head and Neck Surgery, [2]Oral and Maxillofacial Surgery and [3]Pediatric Dentistry, School of Stomatology, China Medical University, Heping, Shenyang, Liaoning 110002, P.R. China

Received December 5, 2012; Accepted February 27, 2013

DOI: 10.3892/mco.2013.86

Abstract. Squamous cell carcinoma (SCC) of the buccal mucosa is a common malignancy in Southeast Asia. The purpose of this study was to present our clinical experience with buccal SCC over a period of 7 years and to analyze the factors associated with surgical outcome. We conducted a retrospective review on 67 buccal SCC patients (between September, 2005 and May, 2011) with tumors restricted to or originating from the buccal mucosa. In a univariate model, nodal stage, degree of tumor differentiation and composite resection were associated with recurrence, while in a multivariate model, the degree of differentiation was the only factor affecting locoregional control. In a survival analysis, recurrence, nodal stage and degree of differentiation were considered as significant factors. Buccal SCC is an aggressive malignant tumor and the degree of differentiation is the most significant factor affecting prognosis and survival. An adequate systemic treatment is required in the case of poorly differentiated tumors. Neck dissection (ND) exerts a positive effect on the locoregional control of buccal SCC staged as cT1-2N0. In the case of identification of positive lymph nodes during surgery, postoperative radiation is recommended in order to improve locoregional control.

Introduction

Squamous cell carcinoma (SCC) of the buccal mucosa is a common malignant tumor in the Chinese mainland, Taiwan and India; however, it is rarely encountered in Europe and North America. Risk factors associated with SCC include betel quid chewing, tobacco and alcohol consumption (1-3). Due to the differences in etiology and species, there are significant differences in pathology, clinical presentation, treatment outcomes and survival between Western and Southeastern countries. Several studies on buccal SCC have been conducted in Western countries (4), India (5) and Taiwan (6). However, available data on the treatment and survival outcome of buccal SCC patients in the Chinese mainland are limited.

Surgery or radiotherapy as a single modality is currently considered a suitable method for the treatment of early-stage buccal SCC, whereas postoperative radiation combined with surgical excision is recommended for advanced tumors (7).

The aim of this study was to present our clinical experience with this tumor over a 7-year period and to focus our analysis of clinical presentation, outcome and prognostic factors on a homogeneous patient population, by including only previously untreated buccal SCC patients with tumors restricted to or originating from the buccal mucosa. We also evaluated the role of neck dissection (ND) in the treatment of buccal SCC staged as cT1-2N0.

Materials and methods

This retrospective chart review was authorized and approved by the China Medical University Review Board.

Patient selection. A search was conducted for medical records of patients diagnosed with buccal SCC between September, 2005 and May, 2011. A total of 67 patients (33 male and 34 female) were included in our study. The mean age was 65 years (range, 25-86 years). Exclusion criteria included lesions originating from adjacent intraoral structures with extension into the buccal mucosa and a pathological diagnosis of adenoid cystic carcinoma.

Statistical analysis. Follow-up time was defined as the time period between the first appointment at the Oral Maxillofacial Head and Neck Tumor Center and the date of last contact or death. The Kaplan-Meier method was used to analyze the factors affecting survival. The Cox logistic regression model (uni- and multivariate) was used to analyze the risk factors for recurrence. $P<0.05$ was considered to indicate a statistically significant difference and $P<0.1$ indicated a trend toward significance (4).

Correspondence to: Dr Chang-Fu Sun, Department of Oral and Maxillofacial Surgery, School of Stomatology, China Medical University, 117 Nanjing North Street, Heping, Shenyang, Liaoning 110002, P.R. China
E-mail: changfusun@hotmail.com

Key words: buccal squamous cell carcinoma, survival analysis, neck dissection, prognostic factor

Table I. Patient characteristics.

	Age						Tumor differentiation		
Stage	Mean	Range	ND	PR	CR	Skin resection	High	Moderate	Poor
I (n=8)	73.5	55-86	5	0	2	0	4	4	0
II (n=21)	64.7	25-83	18	3	6	1	13	4	4
III (n=20)	65.2	44-84	19	7	9	1	11	7	2
IV (n=18)	63.2	43-79	17	6	13	5	8	8	2

ND, neck dissection; PR, postoperative radiation; CR, composite resection.

Results

Patients and treatments. A total of 67 patients (33 male and 34 female) were included in our study. The mean age was 65 years (range, 25-86 years) the mean follow-up time was 34 months (range, 7-84 months). Forty-one (61.3%) out of the 67 patients had a history of smoking and 26 (38.8%) had a history of alcohol consumption. pTNM stage, tumor and nodal stage were classified according to UICC, 2002. Fifty-nine patients underwent a selective or modified radical ND, whereas the remaining patients refused the ND due to their concerns regarding the complications associated with this procedure. Sixteen patients received postoperative radiation, 30 patients presented with bone involvement and underwent resection of either the maxilla or the mandible, while through-and-through skin resection was performed in 7 patients. Thirty-six tumors were pathologically confirmed as well-differentiated, 23 were moderately differentiated and 8 were poorly differentiated. There were no positive resection margins in any of the patients (Table I).

Recurrence occurred in 32 (47.8%) out of the 67 patients. The longest and shortest time period to first recurrence was 43 and 3 months, respectively (average, 14.7 months).

Recurrence risk factors. Statistical analysis was performed to determine the recurrence risk factors. In the univariate model, regional lymph node metastasis was associated with an increased risk of recurrence (P=0.067), whereas high tumor differentiation and composite resection were associated with a decreased risk of recurrence (P<0.001 and P=0.073, respectively). Multivariate analysis identified high tumor differentiation as being protective against disease recurrence (P<0.001). The Kaplan-Meier method demonstrated that poorly differentiated tumors, regional lymph node metastasis and recurrence may exert a negative effect on survival (P<0.001, P=0.082 and P<0.001, respectively) (Table II, Figs. 1-3).

Table II. Recurrence risk factors.

Variable	P-value (UVA)	P-value (MVA)
Gender	0.210	0.439
Age	0.194	0.602
Postoperative radiation	0.912	0.202
Tumor stage	0.303	0.240
Nodal stage	0.067	0.299
History of tobacco	0.555	0.965
History of alcohol	0.105	0.969
Neck dissection	0.863	0.680
Differentiation	<0.001	<0.001
Skin resection	0.857	0.195
Composite resection	0.073	0.470
Clinical stage	0.105	0.313

UVA, univariate analysis; MVA, multivariate analysis.

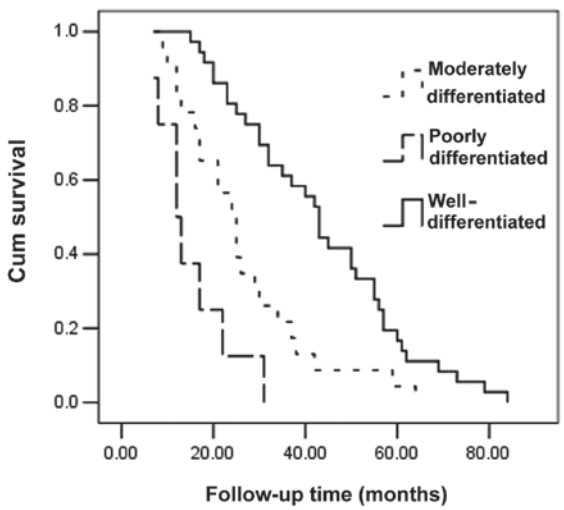

Figure 1. Comparison of survival time among patients according to tumor differentiation (P<0.001).

Discussion

Alcohol, tobacco and betel quid chewing are well-recognized risk factors for buccal SCC development (1,2). Markopoulos (8) reported that older males, ethnic minority groups and lower socioeconomic groups were more commonly affected by buccal SCC. In the present study, we demonstrated that 38.8% of the patients had a history of alcohol consumption, 61.3% had a history of tobacco product consumption and all patients belonged to low socioeconomic groups.

Buccal SCC commonly occurs in people aged 50-80 years. The findings of a previous study conducted by Diaz *et al* (9)

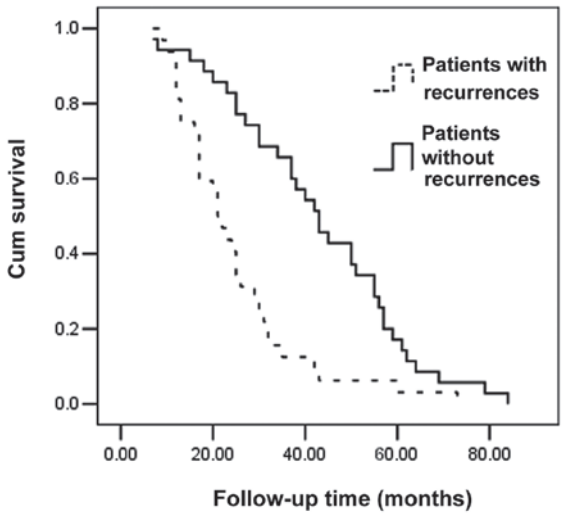

Figure 2. Comparison of survival time between patients with and those without recurrences (P<0.001).

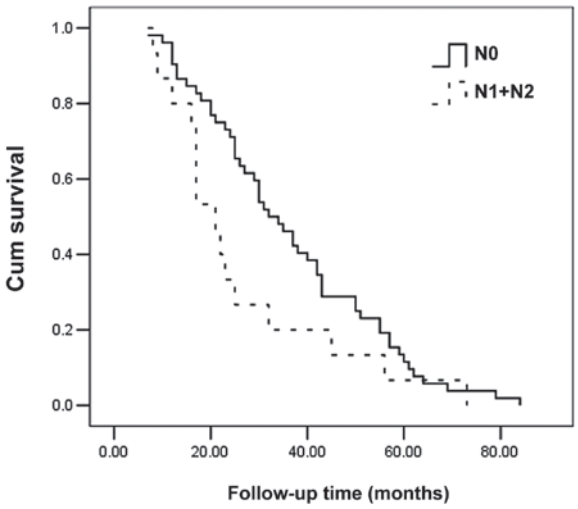

Figure 3. Comparison of survival time between patients with and those without lymph node metastasis (P=0.082).

demonstrated that the mean age of the patients was 66.0 years. In the present study, the mean age was 65.0 years; however, one patient was diagnosed at the age of 25 years. This is a rare finding, which may be partially attributed to HPV infection and unhealthy life habits. In addition, we demonstrated that the male:female ratio was ~1:1, which was not consistent with the findings of Lin *et al* (6) and Huang *et al* (1). A possible explanation is that the main cause of the disease in Taiwan is betel quid chewing, which is more commonly encountered among men (1,10). Of note, there is an increasing prevalence of smokers among the female population in China.

Previous studies demonstrated that regional lymph node metastases in buccal carcinoma occurred less commonly compared to other oral cavity subsites. Coppen *et al* (7) reported that the prevalence of neck lymph node metastasis was 25.0%, whereas Diaz *et al* (9) suggested that the prevalence was 27.8%. In our study, the prevalence was 23.4%. However, in a study published by DeConde *et al* (4), 54% of the patient sample was positive for neck lymph node metastasis. These findings may be explained by the differences in distribution according to tumor differentiation.

The recurrence rate of buccal SCC was relatively high according to previously published studies (4,9,11). Diaz *et al* (9) reported that 54 (45%) out of 119 patients with buccal SCC presented with recurrences, whereas DeConde *et al* (4) reported tumor recurrence in 21 (44%) out of 48 patients. In the present study, out of the 67 patients with negative resection margins, 32 (47.8%) presented with recurrences. Possible explanations are as follows: first, the only barrier to the spread of buccal malignant tumor was the buccinator muscle and its overlying fascia (9) and there was no reliable anatomic barrier to prevent invasion once the carcinoma encroached upon the buccal fat pad; second, radiation therapy may improve locoregional control (12), however, only 16 (23.2%) patients received postoperative radiation in our study; third, during our follow-up, the majority of the patients with recurrences remained addicted to tobacco and/or alcohol. Several recurrent tumors were advanced and unresectable and only a few patients could be successfully salvaged (10). We demonstrated that recurrence exerted a significant negative effect on survival, which was consistent with the findings of Yanamoto *et al* (13). Therefore, aggressive treatment of the tumor in its early stages is critical. Thirty patients underwent resection of either the mandible or the maxilla and in the univariate model we identified composite resection as a positive prognostic factor. Pathak *et al* (14) reported that involvement of the maxillary bone was a prognostic factor affecting disease-free survival. Ghoshal *et al* (2) concluded that most locoregional recurrences of buccal SCC occurred within the first 2 years. In our study, the rate of recurrence within 2 years after surgical resection was 94.1%. Therefore, we recommend that the follow-up time not be shorter than 2 years and it should be at least 5 years in patients treated for SCC of the head and neck; however, the value of routine follow-up is controversial, since a previous study published by Coppen *et al* (7) reported that continuous follow-up visits had little value in the detection of local recurrences after 5 years and even less value after 3 years. However, the patient sample included in that study was small and there were differences among different species; thus, a follow-up period of at least 5 years remains our recommendation.

Neck lymph node metastasis was considered as a negative factor for recurrence, which was inconsistent with the findings of previous studies (1,15). We attributed this inconsistency to our limited patient sample. In the case of pathologically proven lymph node metastasis, a selective or radical ND is necessary. There remains the issue of contralateral neck treatment. Koo *et al* (16) reported that 2 out of 8 patients staged as T3 presented with contralateral neck metastasis and suggested prophylactic neck treatment if the lesion was staged as higher than T3. However, Lin *et al* (6) reported that bilateral treatment was performed on patients staged as N2, but provided no additional benefit compared to unilateral treatment; therefore, the authors concluded that there was little lymphatic drainage in the neck that crossed the midline and metastasis of buccal cancer to the contralateral side was a rare finding. In our clinical experience, there has been no report of contralateral neck disease recurrence and ipsilateral ND should suffice, unless the tumor crosses the midline.

It remains debatable whether to perform an ND on cN0 patients, particularly cT1-2N0 patients. In the present study, 29 patients were staged as cT1-2N0 and 23 underwent ND, following which no patients were pathologically confirmed as N1 or N2. During follow-up, 2 out of 23 patients with ND and 3 out of 6 patients without ND presented with neck recurrence and although our patient sample was relatively small, we considered the difference as significant (P=0.046). Diaz *et al* (9) demonstrated that the rate of neck recurrence in cN0 patients with or without ND was 10 and 25%, respectively. Liao *et al* (15) reported that the rate of neck recurrence in cN0 patients with or without ND was 5 and 18%, respectively. In a risk-benefit evaluation regarding the indication of ND, factors that need to be considered include the possible prognostic influence of delayed diagnosis of metastasis during follow-up, the probability of neck metastasis and the probability of complications associated with ND. In the case of low probability of neck node metastasis, certain studies (17) suggested ND would be an overtreatment; however, there are no reliable methods, such as palpation, CT and MRI, which may predict the risk of metastasis. Therefore, it remains our policy to perform an ND in order to improve locoregional control.

In this study, we demonstrated that tumor differentiation was intimately associated with recurrence in univariate and multivariate models and affected survival time. We hypothesized that tumor differentiation was inversely correlated with aggressiveness. Seven out of 8 patients with poorly differentiated tumor presented with recurrences, which may be related to the fact that these patients remained addicted to tobacco and alcohol postoperatively and only 1 patient received postoperative radiation therapy. Lin *et al* (6) conducted a retrospective study including 145 patients diagnosed with buccal SCC and demonstrated that tumor differentiation was the most significant prognostic factor. The authors suggested that in the case of a poorly differentiated carcinoma, an effective systemic treatment was required in order to achieve a better outcome. Pathak *et al* (14) demonstrated that the degree of tumor differentiation was a prognostic factor affecting the disease-free survival. However, Fang *et al* (10) assessed the prognostic factors on locoregional control of buccal SCC and reported that histological grading was of no prognostic value.

In conclusion, buccal SCC is an aggressive malignant tumor, with its degree of differentiation being the most important factor affecting prognosis and survival. In case of poorly differentiated tumors, an adequate systemic treatment is necessary. ND exerts a positive effect on the locoregional control of buccal SCC staged as cT1-2N0. In the case of identification of positive lymph nodes during surgery, postoperative radiation is recommended in order to improve locoregional control.

References

1. Huang CH, Chu ST, Ger LP, Hou YY and Sun CP: Clinicopathologic evaluation of prognostic factors for squamous cell carcinoma of the buccal mucosa. J Chin Med Assoc 70: 164-170, 2007.
2. Ghoshal S, Mallick I, Panda N and Sharma SC: Carcinoma of the buccal mucosa: analysis of clinical presentation, outcome and prognostic factors. Oral Oncol 42: 533-539, 2006.
3. Freedman ND, Abnet CC, Leitzmann MF, Hollenbeck AR and Schatzkin A: Prognostic investigation of the cigarette smoking-head and neck cancer association by sex. Cancer 110: 1593-1601, 2007.
4. DeConde A, Miller ME, Palla B, Lai C, Elashoff D, Chhetri D and St John MA: Squamous cell carcinoma of buccal mucosa: a 40-year review. Am J Otolaryngol 33: 673-677, 2012.
5. Pandey M, Bindu R and Soumithran CS: Results of primary versus salvage surgery in carcinomas of the buccal mucosa. Eur J Surg Oncol 35: 362-367, 2009.
6. Lin CY, Lee LY, Huang SF, *et al*: Treatment outcome of combined modalities for buccal cancers: unilateral or bilateral neck radiation? Int J Radiat Onco Biol Phys 70: 1373-1381, 2008.
7. Coppen C, de Wilde PC, Pop LA, van den Hoogen FJ and Merkx MA: Treatment results of patients with a squamous cell carcinoma of the buccal mucosa. Oral Oncol 42: 795-799, 2006.
8. Markopoulos AK: Current aspects on oral squamous cell carcinoma. Open Dent J 6: 126-130, 2012.
9. Diaz EM Jr, Holsinger FC, Zuniga ER, Roberts DB and Sorensen DM: Squamous cell carcinoma of the buccal mucosa: one institution's experience with 119 previously untreated patients. Head Neck 25: 267-273, 2003.
10. Fang FM, Leung SW, Huang CC, *et al*: Combined-modality therapy for squamous carcinoma of the buccal mucosa: treatment results and prognostic factors. Head Neck 19: 506-512, 1997.
11. Liao CT, Huang SF, Chen IH, *et al*: Tongue and buccal mucosa carcinoma: is there a difference in outcome? Ann Surg Oncol 17: 2984-2991, 2010.
12. Bumpous J: Metastatic cutaneous squamous cell carcinoma to the parotid and cervical lymph nodes: treatment and outcomes. Curr Opin Otolaryngol Head Neck Surg 17: 122-125, 2009.
13. Yanamoto S, Yamada S, Takahashi H, *et al*: Clinicopathological risk factors for local recurrence in oral squamous cell carcinoma. Int J Oral Maxillofac Surg 41: 1195-1200, 2012.
14. Pathak KA, Mathur N, Talobe S, *et al*: Squamous cell carcinoma of the superior gingival-buccal complex. Oral Oncol 43: 774-779, 2007.
15. Liao CT, Wang HM, Ng SH, *et al*: Good tumor control and survivals of squamous cell carcinoma of buccal mucosa treated with radical surgery with or without neck dissection in Taiwan. Oral Oncol 42: 800-809, 2006.
16. Koo BS, Lim YC, Lee JS and Choi EC: Management of contralateral N0 neck in oral cavity squamous cell carcinoma. Head Neck 28: 896-901, 2006.
17. Weiss MH, Harrison LB and Isaacs RS: Use of decision analysis in planning a management strategy for the stage N0 neck. Arch Otolaryngol Head Neck Surg 120: 699-702, 1994.