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Squamous cell carcinoma of buccal mucosa: a 40-year review☆,☆☆,★

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Abstract

Purpose: The aim of this study was to analyze the outcome of surgical therapy for buccal squamous cell carcinoma (SCCA) at a single tertiary care institution during a 40-year period.

Materials and methods: A retrospective review was performed by examining the records and pathology of 48 patients with buccal SCCA treated at a single tertiary care institution from 1970 to 2009.

Results: Treatment entailed surgery alone in 18 patients (37.5%) and surgery followed by radiation therapy in 30 patients (62.5%). Composite resection was performed in 17 patients (35.4%), and ipsilateral neck dissections were performed in 37patients (77.1%). One-year observed actuarial disease-free survival rates were 60%, 46%, 0%, and 40% for T1 through T4, respectively. Univariate analysis revealed increased age as a risk factor for disease recurrence ($P = .062$), with skin taken and neck dissection not achieving significance ($P = .24$ and .20, respectively). Multivariate analysis demonstrated age as increasing risk and neck dissection as decreasing risk of recurrence ($P = .029$ and .023, respectively).

Conclusions: We report relatively high disease-free survival rates in patients who underwent aggressive resection and neck dissection. Performance of neck dissection and younger age were associated with a favorable prognosis. Performance of neck dissection may decrease the risk of recurrence in primary SCCA of the buccal mucosa. Although through-and-through resection of skin decreased risk of disease recurrence, this difference is not statistically significant ($P = .24$).

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1. Introduction

The anatomy of the buccal mucosa and buccal space allows for extension of carcinoma unimpeded by any anatomic barriers to neighboring intraoral subsites and structures. This oral cavity subsite is defined as the mucosal lining of the cheeks and lips from the oral commissure anteriorly to the pterygomandibular raphe posteriorly, merging with the alveolar ridges superiorly and inferiorly. Involvement of the maxilla, mandible, cheek skin, and lips leads to varied and morbid resections including through-and-through resection of the skin and composite resections of the mandible and/or maxilla. Tumors of the buccal mucosa may also involve multiple subsites, leading to ambiguity of the site of origin [1].

Buccal squamous cell carcinoma (SCCA) is not uncommon in Southeast Asian and Indian populations because of the prevalence of betel nut use [2]; however, it is a rare tumor in North America, constituting only 10% of all carcinomas of the oral cavity [3]. Owing to the rarity of buccal SCCA and the wide variation in patient presentations and populations,

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there is a paucity of high-level evidence on the recommended management of these patients. Management of this malignancy, therefore, has been guided by case series from single institutions [4].

Buccal carcinoma has traditionally been treated surgically, with postoperative radiation therapy reserved for patients with high-risk histopathologic findings, such asperineural invasion, lymphovascular invasion, bone invasion, extracapsular spread, or close margins [5-8]. Our institution had previously reported our experience of buccal carcinoma treated over a 20-year period. That study concluded that aggressive surgical treatment of buccal carcinoma may result in better survival rates [7]. Our goals in this present study are (1) to further describe our experience with this rare disease over a longer time period (40 years), (2) to focus our analysis on a homogeneous patient population by including only previously untreated buccal SCCA patients whose disease is isolated to or originating from the buccal mucosa, and (3) to evaluate the oncologic necessity of through-and-through resection of cheek skin.

2. Materials and methods

The current retrospective study was approved by the institutional review board of the University of California at Los Angeles. Our study was Health Insurance Portability and Accountability Act compliant.

2.1. Data collection

The medical records of all patients diagnosed with SCCA of the buccal mucosa at a single academic institution between June 1972 and January 2010 were reviewed. Data regarding diagnosis, treatment and follow-up were all obtained from the clinical record notes.

2.2. Patient characteristics

A computer-assisted search of the institutional pathology database was used to identify patients with biopsy-proven buccal SCCA from January 2000 to January 2010. Our institutional pathology database was established in January 2000. To identify patients before January 2000, a previously maintained tumor database was used to identify patients from June 1972 to April 1990. Because we lacked a systematic mechanism to identify patients treated for buccal carcinoma for the time period of May 1990 to December 1999, we did not include any cases from these years. Inclusion criteria were patients diagnosed with primary and previously untreated SCCA of the buccal mucosa that was surgically treated. Primary buccal carcinoma was defined as a malignant neoplastic process originating from the buccal mucosa. In cases of buccal tumors that included other oral subsites, the case was only included if it was clear from the clinical record that the tumor originally arose from buccal mucosa. Other oral cavity tumors with secondary extension to the buccal mucosa or prior surgical treatment were excluded. Patients with prior treatment of their disease were excluded. The medical charts were retrospectively reviewed to determine patient age, sex, tumor site, pathologic staging, tobacco use, alcohol use, presence of perineural invasion, differentiation, margin status, resection of skin, presence of neck dissection, T-stage, and N-stage.

2.3. Statistical analysis

Time to first recurrence (local, regional, or distant) was the primary outcome measure. Cox proportional hazards regression was used to assess the relationships between each individual patient characteristic and time to first recurrence. In addition, a multiple Cox proportional hazards model was constructed to assess the association of the combined effects of age, T-stage and neck dissection with time to first recurrence. Statistical analysis was performed using S-plus version 6 (Insightful). $P < .05$ was considered significant, and values less than 0.1 were considered trending toward significance.

3. Results

The initial search of the 2 pathology databases (from 1972 to 2009) yielded 199 cases of carcinoma involving the buccal mucosa. Lesions originating from adjacent intraoral structures with extension into the buccal mucosa were excluded. In addition, verrucous and basaloid squamous carcinoma subtypes were excluded. These exclusion criteria resulted in 48 patients with primary SCCA of the buccal mucosa who underwent surgical resection for primary disease and postoperative radiation therapy when indicated. The mean age was 69 (range, 40–93), and there were 28 women (58%). The mean follow-up time for all patients was 45 months (range, 1–305) and the median follow-up time was 17 months. Risk factors for buccal carcinoma included a history of smoking in 63%, alcohol use in 38%, and betel nut use in 4% of patients. A summary of the patients staging and demographics can be found in Tables 1 and 2, respectively.

Fourteen patients had tumors that were treated with through-and-through resection of the skin. Of these patients, 7 (50%) had T4 tumors with gross invasion of the skin, 2 had T2 tumors where an intraoperative clinical decision to take skin was made by the surgeon in order to obtain negative margins, and the remaining 5 patients had unavailable operative reports as the surgeries were before 1985. Sixteen

Table 1
Distribution of TNM stage

T	N0	N1	>N1	Total
T1	5	1	1	7
T2	12	4	9	25
T3	1	2	2	5
T4	4	2	5	11
Total	22	9	17	48

Table 2
Patient demographics by stage

Stage	Age		Smoking (%)	Alcohol (%)
	Range	Mean		
I (n = 17)	47–85	69	35	35
II (n = 5)	64–73	70	40	40
III (n = 3)	69–81	74	33	33
IV (n = 23)	40–93	67	57	39

patients (33%) had bone involvement identified intraoperatively and underwent resection of either the mandible or maxilla. In 9 (56%) of the 16 cases of bone resection, bone involvement was also identified on pathologic staging. Thirty-eight patients underwent neck dissection, yielding 24 patients with nodal positivity on final pathology (63%). Eighteen of the patients who underwent neck dissection (47%) received ipsilateral elective neck dissections for advanced-stage disease (T3 or T4), and in 4 patients (11%) with early-stage disease (T1 or T2) who required free flap reconstruction, neck dissections were performed for donor vessel harvest. Elective neck dissections were modified radical neck dissections in all cases except for one supraomohyoid dissection.

A total of 30 patients (63%) received postoperative external beam radiotherapy. Four patients had positive margins found on final pathology (8%). All patients with positive margins had resections before 1985 with frozen section analysis results no longer available for review. Pathology also showed 9 (18%) well-differentiated, 23 (48%) moderately differentiated, and 10 (21%) poorly differentiated tumors. Level of differentiation was unavailable on 6 patients (13%). Perineural invasion was demonstrated in 14 specimens (29%). A summary of treatments and pathology by staging can be found in Tables 3 and 4, respectively.

Of the 48 patients, 21 (44%) had recurrences. Of these 21 recurrences, 13 (62%) recurred locally, 6 (29%) regionally and 2 (10%) had distant metastases. Two of the local recurrences (15%) occurred in patients with positive margins on final pathology while the remainder of recurrences had negative surgical margins. Median time to recurrence was 9 months (range, 1–108). Of the 14 patients who underwent a through-and-through resection of the skin, 6 patients had recurrent disease (3 locally, 2 regionally, and 1 distantly).

Table 3
Summary of treatment

Stage	Postoperative XRT	Neck Dissection	Composite Resection	Skin Taken
I (n = 17)	6	9	2	3
II (n = 5)	2	4	1	2
III (n = 3)	1	2	2	0
IV (n = 23)	21	22	12	9

XRT indicates external beam radiotherapy.

Table 4
Summary of pathological findings by stage

Stage	Differentiation			Perineural invasion	Positive margins
	Well	Moderately	Poorly		
I (n = 17)	6	7	1	3	1
II (n = 5)	2	1	2	0	0
III (n = 3)*	0	2	0	0	2
IV (n = 23)	1	13	7	11	1

* Pathologic results not available for all specimens.

Treatment and pathologic characteristics were initially evaluated with univariate analysis to determine risk factors for time to first recurrence (local, regional, or distant metastases). In the univariate model, increasing age trended toward an increased risk of recurrence ($P = .062$), with skin taken and neck dissection demonstrating decreased risk of disease recurrence without achieving significance ($P = .24$ and $P = .20$, respectively) (see Table 5). Multivariate analysis was also performed, identifying performance of neck dissection and decreasing age as protective against disease recurrence ($P = .023$ and $P = .019$, respectively), and increasing T-stage trending toward a risk for recurrence ($P = .075$) (see Table 6).

4. Comment

Primary SCCA of the buccal mucosa is a relatively rare but aggressive tumor. The literature on treatment of this tumor is dominated by studies emerging from betel nut endemic regions of the world where definitive radiotherapy is advocated [9,10]. In contrast, tobacco associated buccal SCCA has been guided by case series where treatment is primarily surgery followed by postoperative radiation. The current study seeks to supplement the North American literature by describing our experience with this disease and, in particular, examine how aggressive surgical resection influences survival.

Table 5
Time to first recurrence (any type): univariate models

Variable	Hazard ratio (95% confidence interval)	*P*
Female gender	1.2 (0.75–1.8)	.53
Age	1.0 (0.93–1.0)	.062
History of tobacco	1.1 (0.41–3.2)	.80
History of alcohol	0.99 (0.40–2.5)	.99
Postoperative XRT	0.65 (0.27–1.6)	.33
T stage	1.2 (0.78–1.9)	.37
N stage	0.87 (0.52–1.5)	.61
Size	1.1 (0.71–1.6)	.74
Perineural invasion	0.78 (0.22–2.8)	.70
Differentiation	(overall test)	.74
Positive margins	1.1 (0.31–3.8)	.89
Neck dissection	0.55 (0.22–1.4)	.20
Skin resection	1.8 (0.67–5.0)	.24

Table 6
Time to first recurrence (any type): multivariate model

Variable	HR (95% confidence interval)	*P* value
ND	0.29 (0.10–0.84)	.023
Age	0.95 (0.91–0.99)	.019
T	1.5 (0.96–2.3)	.075

HR indicates hazard ratio; ND, neck dissection.

We found that 63% of our study sample had a history of tobacco use and 38% consumed alcohol. This tobacco incidence is consistent with other series and further supports tobacco use as a risk factor for buccal carcinoma [4]. The proportion of females in our study population is high relative to other studies at 58%. The previously reported proportions of females in studies from North America and Europe have been 35% to 45% [5,11]. This may be explained by an increasing prevalence of smoking or simply a sample bias [12].

Our histopathologic findings are comparable to other available data on buccal carcinoma. Our incidence of perineural invasion was 29%. This is comparable to other series that include perineural invasion status of 29% [13]. The differentiation status of the tumors in our study sample was biased towards a more poorly differentiated sample. We found that we had 19% well, 48% moderately, and 21% poorly differentiated tumors.

A significant portion of other available data on differentiation of buccal tumors is in the literature from betel nut endemic areas, which tend to have better differentiated tumors (41.8% well, 51.6% moderately, and 6.6% poorly differentiated) [13]. Furthermore, the lower incidence of regional disease rates (16% pN0) [10] reflects the differences in regional disease in non-endemic regions (28–30%) [4,7]. This supports the theory that buccal carcinoma from betel nut endemic parts of the world is pathologically and clinically different and should not be extrapolated to nonendemic regions [14].

Regional lymph node metastases have previously been thought to be less common in buccal carcinoma than other oral cavity subsites [10]. Reported prevalence of regional disease ranges from 16–37% [4,10,15]. These lower rates of regional disease are somewhat contrary to our own experience where 26 (54%) of 48 patients had pathologic neck disease. Certainly in the case of Dhawan et al [10], the high rate of well-differentiated tumors (61% compared to our experience of 19%) likely contributed to their low regional disease rate. The wide range of neck disease reported for buccal carcinoma speaks to the difficulty of studying such a heterogeneous disease. The high percentage of regional disease in our study population is more consistent with series from North America and Europe [4,15]. In addition, previous studies have recognized the dangers of regional neck disease and advocate aggressive regional treatment [11]. A combination of the high prevalence of neck disease and devastating consequences of an undertreated neck may explain why the current study was able to recognize that neck dissection was protective on multivariate analysis even with a relatively small sample size. It should be noted that the high rate of modified radical neck dissections in elective situations (all but one) is likely secondary to a historical bias, as these cases spanned the previous 4 decades. Presently, our institution performs a supraomohyoid neck dissection when the intervention is for pathologic staging purposes.

Increasing age as a risk factor for recurrence is somewhat unexpected. We can hypothesize that this may be due to a tendency to offer less surgically aggressive interventions to older patients who tend to have higher comorbidities. In addition, it is possible that there is a subset of less aggressive tumors, or more treatable tumors, in younger patients. Certainly, the association of human papillomavirus (HPV) infection and oropharyngeal tumors has led to an identification of a radio-sensitive subset of oropharyngeal tumors that tend to occur in younger patients [16,17]. There has been little investigation of buccal carcinoma and HPV association, likely in part due to the rarity of the disease process. However, there have been studies demonstrating an increased presence of HPV presence in oral cavity tumors in betel nut endemic areas relative to matched controls [18].

Recurrence after primary therapy is often reported soon after primary treatment. Other series report recurrences appearing within 12 months [4] or less than 2 years after initial treatment [15]. In fact, 71% (15/21) of our patients with recurrences presented within 12 months of surgery. The scarcity and precipitate nature of recurrences with this disease justifies presenting our cases with limited follow-up. Furthermore, our recurrence rate of 44% is comparable to other reported series of recurrences of 45% [4,15].

A primary goal of this study was to examine the impact of skin resection on survival because skin resection entails significant morbidity with questionable impact on survival. Although through-and-through resection of skin is associated with decreased risk of disease recurrence, it does not reach significance ($P = .24$). The sample size of the current study was not sufficient to directly answer this question, as only 14 patients required a through-and-through resection. Of these, 6 (43%) had recurrent disease within 12 months. To our knowledge, there are no data available in patients with primary buccal carcinoma in the North American population directly addressing this question. Therefore, turning to the betel nut–endemic literature, through-and-through resection of skin is recommended if tumor is observed within 13 mm of the epidermis on imaging [14]. This distance is based on evidence that 1-cm surgical margins are required to control disease locally, and a 3-mm layer of skin must be preserved in order to maintain the dermal plexus [14]. Five-year local control rates between the patients undergoing through-and-through resection and those with only transoral resection were 94% and 91%, respectively. This high survival rate again highlights the vastly different clinical behavior of buccal carcinoma associated with betel nut use compared to tobacco-related disease and emphasizes the need for further evaluation of indications for through-and-through resection of skin in the North American population.

The current study failed to show a predictive relationship between T- and N-stage and recurrence rates on univariate analysis; however, increasing T-stage was associated with recurrence on multivariate analysis. The inability to demonstrate worsening prognosis with N-stage illustrates the inherent limitations of studying this rare disease. Limited follow-up time and an underpowered sample inherently limit this study and hinder our ability to draw conclusions based on the types of local resections (ie, skin through-and-through resection [$P = .24$] and composite resection). These limitations, however, highlight the benefit of single institutions publishing their own clinical experience so these data can eventually be consolidated and interpreted through meta-analyses.

5. Authorship

Adam S. DeConde: corresponding author, drafting of manuscript, acquisition of data, final approval of the version to be published; Mia Miller: revising the article, acquisition of data, final approval of the version to be published; Beth Palla: acquisition of data; Chi Lai: acquisition of data; David Elashoff: edited and approved manuscript, analysis and interpretation of data, final approval of the version to be published; Dinesh Chhetri: editing and approval of manuscript, acquisition of data, conception and design, final approval of the version to be published; Maie A. St. John: conception and design, interpretation of data, final approval of the version to publish.

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Adam S. DeConde had access to all data and takes responsibility for the integrity of these data and analysis.

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