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Treatment Results and Prognostic Factors for Locally Advanced Buccal Cancer

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Abstract

Objective: The aim of this study was to retrospectively analyze locally advanced buccal cancer in order to determine tumor characteristics and any other prognostic factors that may influence the survival of patients with the disease.

Patients and Methods: The records of 54 patients with stage III to IV locally advanced buccal cancer (TNM system) who were seen from August 2000 to June 2008 at one institution were reviewed. The patients received radical surgery and then adjuvant treatment. The adjuvant treatment included concurrent chemoradiotherapy or radiotherapy alone. The chemotherapy protocol consisted of two 4-weekly courses of concurrent cisplatin and 5-fluorouracil followed by another two 4-weekly courses after radiotherapy, with regimens of cisplatin (60–100 mg/m^2/day) on day 1 and 5-fluorouracil (1000 mg/m^2/day) on days 1–5.

Results: The 3-year cumulative overall survival, disease-specific survival, disease-free survival, locoregional control, and distant metastasis-free survival rates were 66%, 69%, 58%, 65%, and 92%, respectively. Univariate analysis indicated that the pN classification, the surgical margin, and the presence of extracapsular spread were significantly associated with overall survival. On multivariate analysis, pN classification and surgical margin significantly affected disease-free survival. The pN classification (pN0 *vs.* pN1–3) and the surgical margin (<1 *vs.* ≥ 1 mm) were the two most significant factors affecting clinical outcome.

Conclusion: The presence of lymph node involvement, the presence of extracapsular spread and a surgical margin <1 mm were strong prognostic factors that were associated with tumor control. More aggressive postoperative therapy is suggested for patients with buccal mucosa carcinoma if these factors exist. (*Tzu Chi Med J* 2010;22(2):96–102)

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1. Introduction

Buccal mucosa cancer is one of the major oral malignancies. The incidence of buccal mucosa carcinoma has rapidly increased in Taiwan in recent decades; major risk factors for this disease are smoking, alcohol drinking, and betel nut chewing [1–5]. Nearly half of these patients will present with advanced disease and regional lymph node metastases [6]. Buccal cancer is locally aggressive with recurrence rates of 30–80% reported in the literature [7–9]. Moreover, locoregional recurrence remains the most frequent type of recurrence in patients with buccal cancer, and its incidence depends mainly on the site of the tumor, its clinical stage and its pathological characteristics. Numerous predictive factors in relation to the primary site and the neck, such as bone invasion or extension, resection margin, perineural invasion, vascular invasion, the presence of lymph node involvement and extracapsular extension of the lymph node involvement, are associated with locoregional recurrence [10]. Surgical excision combined with postoperative radiation has been recommended for advanced stage tumors [11]. Many studies have demonstrated superior locoregional control in advanced head and neck cancer when postoperative radiotherapy is used compared to treatment with surgery or radiation alone [12–16].

More recently, two large-scale randomized trials by the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research Treatment of Cancer (EORTC) have demonstrated the benefits of adjuvant concurrent chemoradiotherapy (CCRT) after radical surgery in high-risk head-and-neck cancer patients; this infers that adjuvant CCRT should be used when there is extracapsular spread (ECS) and/or an unclear margin [17,18]. However, these two trials included head and neck tumors from all sites, which may have blurred the differences in survival at different sites. This study was a retrospective case analysis of locally advanced buccal cancers and the aim was to determine tumor characteristics, treatment patterns or any other prognostic factors that influence disease survival.

2. Patients and methods

The records of 60 patients with stage III to IV locally advanced buccal cancer (TNM system) [19] seen from August 2000 to June 2008 at one institution were reviewed. Six patients were excluded from analysis because they were either lost during follow-up (4 patients) or had a synchronous second primary (2 patients). All were diagnosed histologically with buccal cancer by pathologists and none had suffered from a previous cancer. All patients were informed about their disease treatment, including potential benefits and possible side effects. All patients were treated by a multidisciplinary group that included a head and neck surgery team, radiation oncologists, medical oncologists and dieticians.

2.1. Treatment

Radical surgery consisted of wide excision with or without flap reconstruction of the primary tumor and of unilateral or bilateral radical neck dissection for neck disease management. Pathology reports were reviewed for evidence of the size, grade, type, surgical margins, lymph node involvement, perineural invasion, vascular permeation, lymphatic permeation and ECS of the tumor. Subclavian venous-access catheters were placed for nutritional support and the administration of chemotherapy. Adjuvant treatments were started 4–6 weeks after surgery. Adjuvant CCRT was indicated for a positive margin, extracapsular nodal spread, or any combination of two other risk factors, including perineural invasion, vascular permeation, pT3, pT4 and N(+) nodal disease. Adjuvant radiotherapy (RT) was indicated for a single risk factor except for positive margin and extracapsular nodal spread.

Radiation therapy was delivered using the intensity-modulated radiation technique via an inverse planning system (PLATO; Nucleotron Inc., Veenendaal, The Netherlands). The radiation field encompassed the primary tumor bed and neck lymph nodes. Treatment was delivered with a 6-MV multileaf collimator system (Precise; Elekta Ltd., Crawley, UK) using a step-and-shoot method with 7 coplanar beams.

The critical normal structures used for optimization included the brainstem, spinal cord, parotid glands, optic nerves, chiasm, lenses and eyeballs. Verification of the treatment plan and dose was carried out before treatment and a weekly machine-check film involving electronic portal imaging was carried out to ensure set-up accuracy during treatment. The prescribed doses delivered by external beam RT were as follows: 70–72 Gy to the gross tumor volume; 60–66 Gy to the high risk nodal region; and 50–60 Gy to the low risk nodal region. Conventional RT fractionation was carried out, namely 1.8–2.0 Gy per day and 5 days per week for 6–7 weeks. The spinal cord dose was limited to 45 Gy.

Chemotherapy was given concurrently with and after RT. The chemotherapy protocol consisted of two 4-weekly courses of concurrent cisplatin and 5-fluorouracil (5-FU) followed by another two 4-weekly courses after RT, with regimens of cisplatin (60–100 mg/m^2/day) on day 1 and 5-FU (1000 mg/m^2/day) on days 1–5. We evaluated treatment toxicity using the common toxicity criteria of the National Cancer Institute, V2.0 [20].

2.2. Patient follow-up and patterns of failure

Patients were assessed at 3, 6 and 12 months and then every 6–12 months (or more often if clinically indicated) for 5 years. Survival was calculated from the date of diagnosis to the most recent follow-up or date of recurrence or death. The pattern of failure was defined according to the first site of failure. Local failure was defined as recurrence of the primary tumor. Locoregional failure was defined as recurrence of metastasis associated with the regional lymph nodes. Distant failure was metastasis to any site beyond the primary tumor and the regional lymph nodes. After recurrence or metastasis, patients were given salvage therapy as determined by their physicians.

2.3. Statistical analysis

Baseline characteristics were analyzed using *t* test for continuous variables and χ^2 test for categorical variables. The Kaplan-Meier method was used for survival and control analysis [21]. The difference between the various groups was determined using the log-rank test [22]. Cox proportional hazard regression was used to perform multivariate analysis for hazard ratio (HR) assessment. For estimating the effective size, HR was provided with a 95% confidence interval (CI) in addition to a conventional *p* value. SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) was used for the analysis of all data. A statistically significant difference was defined as a *p* value of less than 0.05.

3. Results

3.1. Patient characteristics

Of the 54 patients evaluated, 11 were stage III and 43 were stage IV. The patient characteristics and stages are presented in Tables 1 and 2. The mean age was 53.2 years (range, 35–76 years). Most patients were men (92.6%, 50/54), and 48 patients (88.9%, 48/54) had a history of betel nut chewing.

Table 1 — Characteristics of the 54 patients with buccal mucosa cancer*

Age	
≤50 yr	24 (44.4)
>50 yr	30 (55.6)
Sex	
Male	50 (92.6)
Female	4 (7.4)
Tumor stage	
T1–2	14 (25.9)
T3–4	40 (74.1)
Nodal stage	
N0	28 (51.9)
N1–3	26 (48.1)
Stage	
III	11 (20.4)
IV	43 (79.6)
Histological differentiation	
Well	4 (7.4)
Moderate	41 (75.9)
Poor	7 (13.0)
Unknown	2 (3.7)
Surgical margin	
<1 mm	13 (24.1)
≥1 mm	41 (75.9)
Treatment	
S	6 (11.1)
S+RT	18 (33.3)
S+CCRT	30 (55.6)
Smoking	
No	9 (16.7)
Yes	45 (83.3)
Betel nut chewing	
No	6 (11.1)
Yes	48 (88.9)

*Data presented as *n* (%). S=surgery alone; S+RT=surgery+radiotherapy; S+CCRT=surgery+concurrent chemoradiotherapy.

Table 2 — Stage distribution of the 54 patients with buccal mucosa cancer*

Stage		N0	N1	N2	N3
	T1	–	1 (2)	1 (2)	0 (0)
III (20.4%)	T2	–	0 (0)	12 (22)	0 (0)
	T3	9 (17)	1 (2)	4 (7)	0 (0)
IV (79.6%)	T4	19 (35)	2 (4)	5 (9)	0 (0)

*Data presented as *n* (%).

3.2. Treatment outcome

The median patient follow-up at the commencement of the analysis was 25 months (range, 4–104 months). Six patients had refused adjuvant treatment. There were 48 patients who received RT. The patients who received RT had doses ranging from 3960 to 8100 cGy of radiation (median, 6660 cGy). Forty-one of the 48 patients received the full planned dose of radiation and seven received an incomplete radiation dose because of treatment-induced complications. Fifteen of the 30 patients who received chemotherapy completed the full course of chemotherapy and the others received less than 4 cycles at a reduced dose. When the patients received reduced doses of or a limited cycle of chemotherapy, this was due to poor compliance because of side effects induced by the chemotherapy. Among the six patients without adjuvant treatment, two patients, one pT4N2M0 and the other pT4N0M0, had locoregional recurrence at 2 and 7 months and distant metastases at 10 and 11

Table 3 — The 3-year clinical outcomes according to prognostic factors

Risk factor	Overall survival (%)	*p*	Disease-specific survival (%)	*p*	Disease-free survival (%)	*p*	Locoregional control rate (%)	*p*	Distant metastasis-free survival (%)	*p*
Age										
≤50 yr	61	0.79	61	0.45	62	0.90	74	0.47	86	0.25
>50 yr	70		75		56		59		96	
Sex										
Male	70	0.07	72	0.28	60	0.18	67	0.40	94	0.22
Female	25		33		0		0		67	
Tumor stage										
T1–2	38*	<0.01	38*	<0.01	39*	0.01	44*	0.008	90	0.80
T3–4	75		79		66		73		92	
Nodal stage										
N(–)	92*	<0.001	96*	<0.001	82*	<0.001	82*	0.001	100*	0.015
N(+)	33		34		32		46		79	
Stage										
III	82	0.3	90	0.16	81	0.23	81	0.43	100	0.27
IV	59		61		50		57		89	
Grade										
1	75	0.9	100	0.38	100	0.19	100	0.25	100	0.58
2+3	64		66		54		61		91	
Surgical margin										
<1 mm	45*	0.04	49	0.06	42	0.20	48	0.21	84	0.18
≥1 mm	73		75		63		70		94	
Extracapsular spread										
Positive	25*	<0.01	33	0.08	50	0.32	75	0.98	75	0.18
Negative	54		54		59		63		91	
Perineural invasion										
Positive	67	0.87	67	0.70	56	0.62	67	0.93	89	0.79
Negative	57		59		57		62		90	
Bone invasion										
Positive	63	0.59	84	0.59	50	0.90	50	0.59	100	0.37
Negative	68		68		62		76		94	
Skin invasion										
Positive	74	0.83	80	0.86	82	0.42	100	0.46	82	0.20
Negative	79		79		70		70		100	

*Statistically significant difference ($p<0.05$) on univariate analysis.

months. The other four patients were all pT3N0M0 and had no recurrence or metastases. The 3-year cumulative overall survival, disease-specific survival, disease-free survival, locoregional control, and distant metastasis-free survival rates for all patients were 66%, 69%, 58%, 65%, and 92%, respectively.

Univariate analysis for all 54 patients indicated that pN classification, surgical margin, and ECS were significantly associated with overall survival (Table 3, Figs. 1–3). The pN classification also significantly affected the locoregional control rate and distant metastasis-free survival. For the pN0 and pN+ classifications, the 3-year overall survival, disease-specific survival, disease-free survival, locoregional control, and distant metastasis-free survival rates were 92%/33%, 96%/34%, 82%/32%, 82%/46%, and 100%/79%, respectively (Table 3). On multivariate analysis for all patients, pN classification and surgical margin significantly affected disease-free survival. The pN classification also significantly affected overall survival and disease-specific survivals (Table 4). The pN classification (pN0 *vs.* pN1–3) and surgical margin (<1 *vs.* ≥1 mm) were the two most significant factors affecting clinical outcome. Straifying pN+ into pN1 and pN2–3, it was found that pN1 patients had poorer 3-year locoregional control rates than pN0 patients (82% *vs.* 50%, $p=0.039$) but had the same distant metastasis-free survival rates as pN0 patients. There was no significant difference between pN1 and pN2–3 in terms of locoregional control rate (50% *vs.* 46%, $p=0.896$) and distant metastasis-free survival rate (100% *vs.* 72%, $p=0.268$).

4. Discussion

Of the 54 patients, most were men (92.6%, 50/54). There were 48 (88.9%) patients who had the habit of chewing betel nuts. This epidemiological result is similar to other studies carried out in Taiwan.

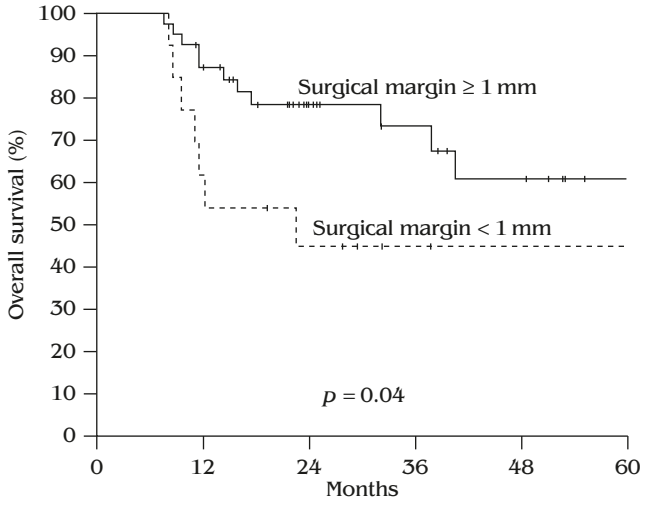

Fig. 1 — Kaplan-Meier estimates of overall survival according to the cut-off surgical margin.

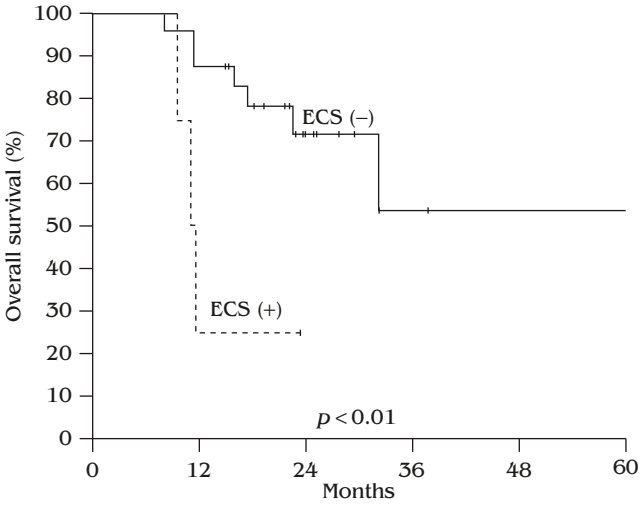

Fig. 3 — Kaplan-Meier estimates of overall survival according to the prognostic factor of extracapsular spread (ECS).

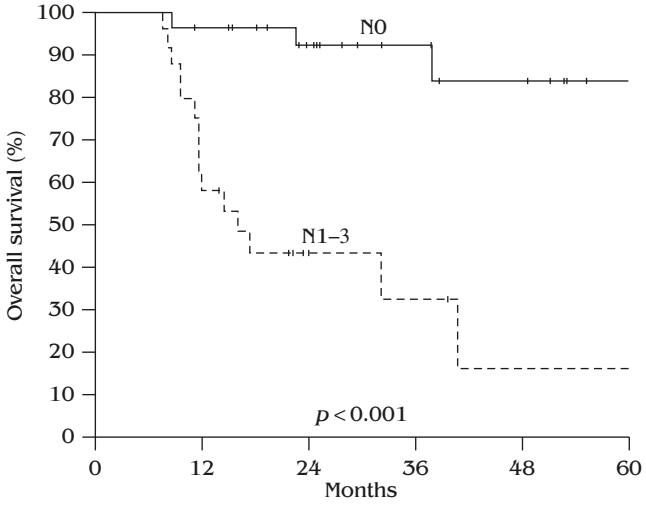

Fig. 2 — Kaplan-Meier estimates of overall survival according to the pN classification.

Table 4 — Significant prognostic factors identified by multivariate Cox regression analysis

	p
Overall survival	
Nodal stage	0.02
Disease-specific survival	
Nodal stage	0.03
Disease-free survival	
Nodal stage	0.005
Surgical margin	0.04
Locoregional control rates	
Nodal stage	0.09
Distant metastasis-free survival (–)	

The discrepancy in sex reflects the fact that the prevalence of betel quid chewing is much higher among men than among women in Taiwan [3,4,23].

Buccal cancer is often locally aggressive, with recurrence rates of 30–80% reported in the literature [7–9,24,25]. Locoregional failure is the major cause of death for buccal cancers managed with surgery and RT. Several studies have demonstrated that the status of the surgical margins reported is correlated with tumor control [24–26]. Fang et al showed that a positive surgical margin and tumor invasion of the skin of the cheek were associated with poor prognosis [24]. Bernier et al demonstrated that surgical margin was an indicator for the adjusted postoperative strategy [17]. In our series, we found that surgical margins within 1 mm were correlated with overall survival. This factor was also significant in the multivariate analysis for disease-free survival. The 3-year overall survival for tumors distal to the nearest resection margin < 1 mm and ≥ 1 mm were 45%/73% (p=0.04). So, we suggest that surgical margin within 1 mm of a buccal cancer should receive stronger postoperative treatment.

Several other postoperative prognostic factors were evaluated in our study. In addition to surgical margin, the pN classification also played an important role in our study. We found that pN classification was the most important prognostic factor for both survival and locoregional control. Compared with other studies, Diaz et al demonstrated that the 5-year survival rate for patients with pN0 and pN+ neck were 70% and 49%, respectively (p=0.0116) [27]. In addition, Huang et al had similar results when pN0 and pN+were compared (78% *vs*. 41%, p<0.001) [28]. In this study, the significant results for overall survival and locoregional control rate among patients with pN0 and pN+disease

suggest that intense postoperative adjuvant therapy should be given to patients with pN+disease, and CCRT with or without targeted therapy in a clinical trial setting should be considered.

ECS of involved lymph nodes has been found to be a poor prognostic factor. Diaz et al documented that cervical metastasis with and without ECS had 5-year survival rates of 24% and 69%, respectively (27). In our study, the 3-year overall survival for ECS(–) and ECS(+) status were 54% and 25%, respectively. However, ECS was significantly associated with poor survival only in univariate analysis but not in multivariate analysis. The reason for this may be the limited case numbers or confounding by other factors. ECS is often present when multiple lymph nodes are involved and its contribution to outcome may have been masked by the N stage (29).

In the literature, the incidence of systemic dissemination in buccal cancer has been found to range from 0% to 23% (9,16,24,27,28). In our study, only four (7.4%) patients developed distant metastases, with the lungs being the most common site. Locoregional failure was the major cause of death and remains the main challenge clinically. Thus, how local control can be improved is important when following a multimodal treatment strategy.

Since this was a retrospective study, a number of factors in terms of patients and tumor characteristics could not be controlled for and may have biased the results. However, the presence of lymph node involvement, ECS and a surgical margin < 1 mm were found to be strong prognostic factors associated with tumor control. More aggressive postoperative therapy is suggested for patients with buccal mucosa carcinoma if these factors exist.

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