



Primary oral squamous cell carcinoma: an analysis of 703 cases in southern Taiwan

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Abstract

We retrospectively analyzed the records of 703 cases of oral squamous cell carcinoma (SCC) collected from 1 January 1985 to 31 December 1996 at a teaching hospital in southern Taiwan, to identify the characteristics of patients and factors associated with survival. There was an overwhelming male predominance (male:female = 15:1). The mean age of the patients was 52. The peak age of oral SCC patients declined from 50 to 59 years in the first six years (1985–1990) and 40–49 years in the last six years (1991–1996). The most common site of oral SCC was the buccal mucosa with 263 patients (37.4%). Most patients (346/703 patients; 49.2%) had stage III cancer. The most common site of occurrence of SCC was the buccal mucosa (263/703 patients; 37.4%), both overall and in patients who chewed betel quid alone or in combination with cigarette smoking and/or alcohol consumption; the tongue was the most common site among patients without any oral habits (18/48 patients; 37.5%). Furthermore, the age of occurrence was on average 6–12 years younger among patients who chewed betel quid than in those who did not. Of the 703 patients, 496 received treatment with surgery, chemotherapy, and/or radiation therapy. Of these, 209 (42.1%) died. The cancer stage significantly influenced mortality: the 5-year survival rate in patients treated from 1985 to 1991 was 72% in those with stage I, 38.9% in those with stage II, 26.7% in those with stage III, and 11.8% in those with stage IV cancer. Six variables were found to significantly affect survival: tumor size, lymph node involvement, surgery, betel quid chewing, staging, and histological differentiation (all $p < 0.05$, Kaplan–Meier analysis with log rank test). Of these, surgery and cancer stage independently affected survival in a proportional hazards model (both $p < 0.0001$). Therefore, the early surgical intervention, and the withdrawal from oral habits, especially betel quid chewing, will be advantageous to patients' survival. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Oral squamous cell carcinoma; Survival; Betel quid

1. Introduction

Cancers of the oral cavity represent a major health problem, as indicated by their high incidence in many parts of the world. The worldwide annual incidence of oral cancers was estimated to be 412,000 in 1985, representing the fifth most common cancer in the world [1]; the global annual mortality from oral cancers in 1985 was 262,000 deaths [2].

Oral cancers account for approximately 4% of all cancers [3]. In some Southeast Asian countries such as Bangladesh, India, Pakistan, and Sri Lanka, oral cancers are the most common forms of cancer and constitute about a third of all cancers [4]. Epidemiologic data suggest that the high incidence of oral cancer in these countries may be closely related to the high

prevalence of betel quid chewing [5]. In Taiwan, oral cancers rank as the seventh most prevalent cancer in both sexes, and constituted the fifth most common cancers in males [6].

The treatment of oral cancer is conventionally a combination of surgery, radiotherapy, and chemotherapy. However, the overall survival rates have not improved substantially in the last two decades [7]. This highlights the necessity for continued efforts to improve the treatment modalities.

Squamous cell carcinoma (SCC) is the most common type of oral carcinoma. It accounts for about nine of every ten oral malignancies, and is a major cause of cancer morbidity and mortality. In the current study, we reviewed the records of all patients who received a diagnosis of primary oral SCC in a teaching hospital in southern Taiwan during a 12-year period. Our purpose was to define the characteristics and treatment of those patients, and the factors that affect prognosis.

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2. Materials and methods

We reviewed the records of all cases of SCC diagnosed at Kaohsiung Medical College, Taiwan from 1985 through 1996. Lesions were classified according to primary site as described in the International Classification of Diseases for Oncology (World Health Organization, Geneva, 1988) [8]. The anatomical sites reviewed in this study included (a) the lips (ICD140); (b) buccal mucosa (ICD142); (c) alveolus and gingiva (upper and lower) (ICD143); (d) palate (ICD145); (e) tongue (ICD141); and (f) floor of the mouth (ICD144). Tumors involving more than one anatomical site were designated as multiple sites, which may represent an extensive tumor involving several sites or multiple simultaneous primary tumors. Patients with tumors of the salivary glands, sarcomas, or verrucous carcinomas were excluded. Patient follow-up data were also obtained by the Tumor Registry, Kaohsiung Medical College Teaching Hospital, Taiwan. The hospital records of these patients were traced, and from them complete details, including first visit delays, surgical pathology reports, operation records, radiation schedule, and chemotherapeutic regimens were obtained. A database containing 14 variables for each patient was compiled (Table 1). All data of patients and tumor variables were then transferred to a Window-based PC and statistical analysis was carried out using the SYSTAT statistical package [9], including the SURVIVAL supplementary module [10].

Survival probabilities of who received treatment at our hospital were estimated with the Kaplan–Meier method [11]; survival curves were compared with the log-rank test (Mantel–Haenszel method) [12]. Multivariate analysis was used to determine the independent

prognostic value of selected variables, using Cox's proportional hazards linear regression model with forward stepwise regression [13]. The 5-year survival rate was calculated for SCC patients managed between 1985 and 1991.

3. Results

From 1985 to 1996, a total of 9672 biopsy specimens were collected in the Oral and Maxillofacial Pathology Department of Kaohsiung Medical College, of which 1167 (12.1%) were histologically proven to be oral SCC. These 1167 specimens were from 703 patients, including 659 males and 44 females; the male to female ratio was 15:1. Male oral SCC patients ranged in age from 17 to 89 years, while female patients were from 23 to 86 years. The majority of patients were from 40 to 59 years old. The peak age from 1985 to 1990 was 50 to 59 years, while the peak age from 1991 to 1996 was 40–49 years (Fig. 1). The majority of patients with multi-site occurrence had extensive tumors involving several anatomical areas; only twelve patients presented with multiple primary lesions. The most common site of occurrence was the buccal mucosa, followed by the tongue, and multiple sites (Table 2). Nearly 50% of oral SCC patients were designated as having stage III cancer ($n=346$, 49.2%), followed by stage II ($n=137$, 19.5%), stage I ($n=123$, 17.5%), and stage IV cancer ($n=97$, 13.8%). The mean delay to the first visit was an approximately 7.6 months. Fifty-one tumors were on the alveolar mucosa. Additionally, 35 tumors of multi-site occurrence involved the edentulous mucosa. Therefore, a total of 86 tumors (12.2%) involved the edentulous ridges.

Table 1
The variables used for survival analyses

Variables	Description
1. Age	10–19; 20–29; 30–39; 40–49; 50–59; 60–69; 70–79; 80–89
2. Sex	Male; female
3. Tumor size (T)	T1 (≤ 2 cm); T2 (2–4 cm); T3 (≥ 4 cm); T4 (tumor invades adjacent structures)
4. Lymph node (N)	N0 (no palpable node); N1 (palpable, ipsilateral node); N2 (palpable, contralateral/bilateral node); N3 (palpable fixed node)
5. Metastasis (M)	M0 (no distant metastasis); M1 (clinical/radiologic evidence of metastasis)
6. Stage ^a	I; II; III; IV
7. Differentiation	Well; moderate; poor
9. Site	Buccal mucosa; tongue; lip; gingiva/alveolus; mouth floor; palate
10. Multiple sites	Yes/No
11. Surgery	Wide excision + ^b SND/RND; wide excision only; ^c no surgery
12. Therapy	Radiotherapy; chemotherapy; radio-chemotherapy; no radio- or chemotherapy
13. Betel quid chewing	Yes/No
14. Cigarette smoking	Yes/No
15. Alcohol drinking	Yes/No

^a Clinical staging: I (T1,N0,M0); II (T2,N0,M0); III (T3,N0,M0/T1,N1,M0/T2,N1,M0/T3,N1,M0); IV (any T or N with M1).

^b SND/RND: suprahyoid dissection/radical neck dissection.

^c Patients received neither wide excision nor SND/RND.

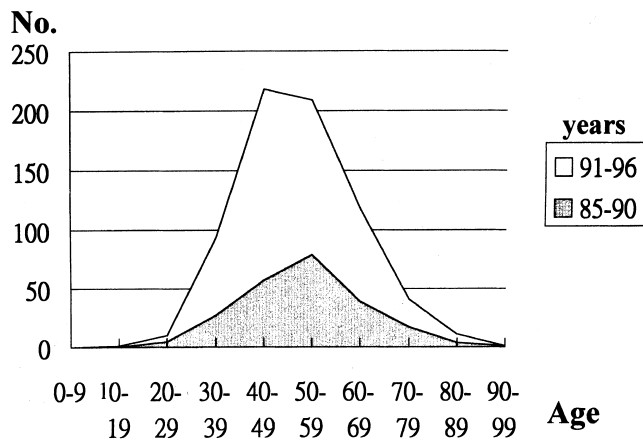


Fig. 1. Peak age of oral squamous cell carcinoma patients shifted from 50–59 year-old in 1985–1990 to 40–49 year-old of 1991–1996.

Most oral SCC patients in this study were betel quid chewers (82.7%). Among betel quid chewers, the predominant lesion site was the buccal mucosa; however, among those without any oral habits, the most common site was the tongue. Furthermore, oral SCC patients who chewed betel quid, smoked cigarettes, and drank alcohol were on average 12 years younger than those without any of these habits (Table 3). Patients who did not chew betel quid, regardless of whether they drank or smoked, were not on average younger than patients with no habits.

Of these 703 patients, 496 were treated at Kaohsiung Medical College. The other 207 patients were not treated at our hospital. The main treatment modality for these 496 patients was surgery with or without radio-chemotherapy. Three hundred and twenty-four patients received either surgery only or surgery combined with radiotherapy and/or chemotherapy (Table 4).

A total of 209 patients died of/with SCC after treatment; the others were survived with or without recurrence disease. Among patients who died, the most common lesion site was the buccal mucosa, followed by multiple sites, and the tongue (Table 5). The highest death rate according to histologic differentiation was among patients with moderately differentiated SCC (51/100, 51%), followed by poorly differentiated SCC

(10/22, 45.5%), and well differentiated SCC (148/374, 39.6%). On the other hand, with respect to cancer staging, the highest mortality rate was among patients with stage IV disease (41/70, 58.6%), followed by stage III (115/260, 44.2%), stage II (33/86, 38.4%), and stage I (20/80, 25%). The five-year survival rates for patients treated between 1985 and 1991 were 72.7% (24/33) for patients with stage I, 38.9% (14/36) for those with stage II, 26.8% (26/97) for those with stage III, and 11.8% (2/17) for those with stage IV cancer. The overall 5-year survival rate was 36.1% (66/183).

Log-rank test analysis of Kaplan–Meier survival curves identified six of the 14 variables as significantly affecting survival ($p < 0.05$) (Table 6). Two out of these six variables, namely surgery and staging, affected the survival significantly in the proportional hazards model ($p < 0.0001$) (Fig. 2(a,b), Table 7). If stage I patients and those with radical neck dissection were used as the baseline group (relative risk, RR = 1), stage IV patients without surgery were predicted to have the highest risk of mortality, an RR of 4.72. On the other hand, if patients without any oral habits were used as the baseline group (RR = 1), the RR of mortality of patients with the habits of betel quid chewing, cigarette smoking, and alcohol drinking was 5.32 (Table 8).

4. Discussion

Oral cancer occurs predominantly among males, with a male to female ratio ranging from 2 to 10 [14,15]. However, the male to female ratio in the current study was much higher (15:1). The ratio in our study was also much higher than in a previous report from Taiwan [16]. This phenomenon is quite alarming and deserves special epidemiological caution. The possible cause of the marked male predominance is the majority of betel quid chewers in Taiwan were male. However, it may also be due to a bias in the catchment area or patterns of referral of SCC patients.

The peak age of occurrence of SCC declined during the study period (Fig. 1). Furthermore, eleven oral SCC patients were below 30 years of age, including one 17-year-old boy. These facts indicate a trend of younger age of occurrence of oral SCC in southern Taiwan. A similar phenomenon has also been reported in a number of international publications [17–20].

In this study, 12.2% SCC lesions involved the edentulous ridges. It has been reported that edentulous ridges have a higher risk of SCC [21]. However, previous studies indicated that denture use is not an independent risk factor for alveolar ridge SCC [22], and does not contribute to the elevated risk of SCC on edentulous ridges [23]. Therefore, further studies are needed to compare the risk of SCC in edentulous patients with or without denture use.

Table 2
Sites of occurrence of oral squamous cell carcinomas

Site	Number (%)
Buccal mucosa (ICD 142)	263 (37.4)
Tongue (ICD 141)	147 (20.9)
Lip (ICD 140)	30 (4.3)
Gingiva/alveolus (upper/lower) (ICD 143)	84 (11.9)
Mouth floor (ICD 144)	13 (1.8)
Palate (ICD 145)	24 (3.4)
Multiple sites ^a	142 (20.3)
Total	703 (100)

^a Tumors involving multiple anatomical sites.

Table 3
Sites of occurrence, habits, and mean age at diagnosis of oral squamous cell carcinoma (SCC)

Habit(s)	Site							Total (%)	Mean age at time of diagnosis of SCC (yr)	Relative age ^b , (yr)
	Buccal mucosa, No.	Tongue, No.	Lip, No.	Gingiva, No.	Mouth floor, No.	Palate, No.	Multi-site, No.			
No habit	9	18	4	11	0	0	6	48 (7.6)	60	–
B + C + A	118	52	11	37	6	9	63	296 (47.1)	48	–12
B	28	9	0	8	0	0	9	54 (8.6)	50	–10
B + C	67	22	5	14	1	3	29	141 (22.4)	51	–9
B + A	8	6	4	4	0	0	7	29 (4.6)	54	–6
C + A	3	11	0	0	2	3	6	25 (4.0)	60	0
C	6	10	0	4	2	1	8	31 (4.9)	60	0
A	2	1	1		0	0	0	5 (0.8)	62	+2
Total	241	129	25	79	11	16	128	629 ^a (100)	52	
%	38.3	20.5	4.0	12.6	1.7	2.5	20.3	100		

A: alcohol drinking; B: betel quid chewing; C: cigarette smoking.

^a 74 patients with oral habits not recorded were excluded.

^b Relative to group with no habits.

Table 4
Types of surgery and therapy for oral squamous cell carcinoma patients

Surgery	Therapy				Total
	Radiotherapy only	Chemotherapy only	Radio-chemotherapy	None	
WD only	25	30	42	52	149
WD + SND/RND	34	41	67	33	175
No surgery	39	77	56	0	172
Total	98	148	165	85	496 ^a

WD: wide excision; SND: suprahyoid neck dissection; RND: radical neck dissection.

^a The remaining 207 patients were not treated at our hospital.

Table 5
Deaths among oral squamous cell carcinoma patients according to sites and stage of cancers

Site	Stage				Total
	I	II	III	IV	
Buccal mucosa	5	16	41	11	73
Tongue	3	7	19	11	40
Lip	1	0	4	2	7
Gingiva/alveolus	3	5	12	5	25
Mouth floor	0	0	1	0	1
Palate	0	0	3	2	5
Multiple sites	8	5	35	10	58
Total (%)	20 (25)	33 (38.4)	115 (44.2)	41 (58.6)	209

#: number of deaths of the stage/total number of deaths of the stage.

The most prevalent site of oral SCC in the present study was the buccal mucosa. This is in contrast to data from other countries such as Australia, the USA, and Denmark, which all reported the tongue to be the most frequent site of SCC [15,24,25]. The buccal mucosa is, however, the most common site of SCC in countries

where betel quid chewing is common, such as India, Malaysia, and New Guinea [26–28]. In earlier reports from southern Taiwan [16,29], lingual SCC was the most frequent. In our study, while buccal SCC was more common than lingual SCC, the tongue was the most common site for patients without any oral habits.

Table 6
p-values of 14 variables on Kaplan–Meier survival analysis

Variables ^a	Log rank test	Degrees of freedom	p-value
1. Age	4.53	7	0.7166
2. Sex	0.49	1	0.4842
3. Tumor size (T)	13.07	3	0.0045 ^b
4. Lymph node (N)	29.63	3	< 0.0001 ^b
5. Metastasis (M)	1.23	1	0.2626
6. Stage	35.54	3	< 0.0001 ^b
7. Differentiation	70.12	2	0.0285 ^b
8. Site	8.57	6	0.1993
9. Multiple sites	0.03	1	0.8555
10. Surgery	42.62	2	< 0.0001 ^b
11. Therapy	7.28	3	0.0636
12. Betel quid chewing	5.18	1	0.0229 ^b
13. Cigarette smoking	2.18	1	0.1399
14. Alcohol drinking	0.72	1	0.3955

^a For definition to each variable, refer to the descriptions in Table 1.

^b $p < 0.05$.

These findings imply that the higher rate of buccal SCC may be associated with an increasing number of betel quid chewers in Taiwan [5].

The genesis of SCC is a complex process involving multiple genetic and epigenetic alterations, as indicated by the fact that 7.1% of our SCC patients had no oral habits. Alcohol consumption and cigarette smoking are both recognized risk factors for SCC in developed countries. In high-risk regions of the world, however, other causative factors appear to play important roles. Interestingly, our study patients who drank alcohol or smoked cigarettes, or both drank and smoked, were not younger than patients without any oral habits. In fact, there were more patients without any habits than with a smoking or drinking habit alone, or with both a drinking and smoking habit. The age at the time of diagnosis of SCC began to decrease only when betel quid chewing was added to the equation.

Several lines of evidence from the present and previous studies point to a link between betel quid chewing and the development of SCC. The vast majority of our patients chewed betel quid, drank alcohol, and smoked cigarettes. Moreover, patients who chewed betel quid were on average 6–12 years younger than those without any habits. Previous epidemiologic study [5] has also found that betel quid chewing may be closely linked with the risk of oral SCC, and experimental evidence suggests that Taiwan betel quid has cancer-promoting effects [30–32]. Taken together, there appears to be strong evidence that betel quid chewing increases the risk of SCC.

In the current study, the five-year survival rate of oral SCC patients was associated with the severity of clinical staging. A similar finding of the higher the staging, the lower the five-year survival rate was also noted in previous reports [24,33–35]. The overall five-year survival rate was only 36.1% in the present study. The five-year

survival rate in developed countries is also consistently below 50%, with no sign of improvements in recent years [36–38]. According to the patient follow-up data of the Tumor Registry of our hospital, all the patients died after treatment were due to the SCC or the various

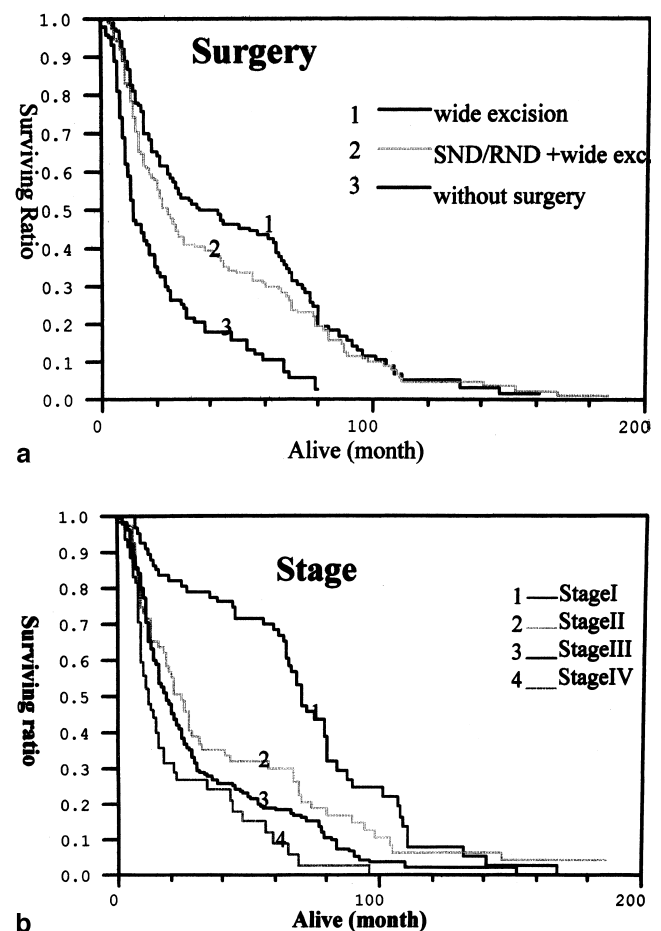


Fig. 2. Two variables, surgery (a), and stage (b), were prominent factors affecting survival in the proportional hazards model ($p < 0.0001$).

Table 7
Variables most significantly affecting survival in proportional hazards model

Variables ^a	Estimate	Standard error	Relative risk	<i>p</i> -values
WD only	0.022	0.138	1.02	0.8732
Without surgery	0.666	0.144	1.95	<0.0001 ^b
Stage II	0.424	0.193	1.53	0.0280 ^b
Stage III	0.666	0.166	1.95	<0.0001 ^b
Stage IV	0.882	0.214	2.42	<0.0001 ^b

^a For definition to each variable, refer to the descriptions in Table 1.

^b *p* < 0.05; WD: wide excision; baseline group: stage I patients and patients received WD & SND/RND (relative risk = 1).

associated fatal complications such as massive bleeding, or multiple organs failure upon distant metastasis. Therefore, the figure obtained in this study may represent the actuarial (disease-specific) survival rates.

Of these 703 patients, 496 were treated at our hospital. The remaining 207 untreated patients were those who had inoperable diseases, or those who were reluctant to have further treatment in our hospital for various reasons such as visiting other hospitals for reconfirmation of the disease or self-using of Chinese herb.

The mean delay from the time of symptom onset to presentation in the current study was more than 7 months; this is consistent with the results of the study of Wang et al. [39], but much higher than in previous reports from two Western countries [40,41]. The long delay may suggest that the degree of self-alertness of oral SCC patients in Taiwan is inadequate and needs to be promoted, and may also at least partly explain why the majority of patients in this study had stage III cancer. An earlier report from Taiwan reported most oral SCC patients had stage IV cancer [42]. However, two previous studies from Brazil [43], and Denmark [44] revealed no association between patient delays and disease stage; further epidemiological investigations are necessary to substantiate the possible association between treatment delay and disease stage. It is generally accepted that cancer mortality may be reduced if lesions are detected, diagnosed and treated at an earlier stage; however, investigation of such an association was not included in the present study. A previous study from USA indicated no association between patient

delays and prognosis in a sample of 149 oral and oropharyngeal cancer patients [45].

Oliver et al. [25] reported the highest death rate in oral SCC patients was among stage III patients with well-differentiated carcinoma and multi-site occurrence. This is different from our findings. The reasons may be related to the high prevalence of betel quid chewing, and the insufficient awareness of the various symptoms of mouth of oral SCC patients in Taiwan.

Of the 14 variables used for survival analysis in this study, six were determined to be related to survival. Furthermore, two of them (surgery and staging) significantly affected survival in a proportional hazards model. Survival is strongly influenced by the stage of disease and surgical treatment. Stage IV patients without surgery were estimated to have the highest RR of mortality. This may indicate that patients with earlier clinical staging who are treated surgically have a greater chance of survival. The prerequisite for successful management is early intervention.

The combined effect of chewing, smoking, and drinking was apparent in this study. Patients who smoked cigarette, drank alcohol, and chewed betel quid experienced a 5.32-fold increased likelihood of death compared with those without any oral habits. Thus, another possibly advantageous approach to increasing the survival rate of oral SCC patients would be to reduce the prevalence of these habits through public awareness programs.

In summary, the early surgical intervention, and the withdrawal from oral habits, especially betel quid chewing, are beneficial to patients' survival.

Table 8
Relative risk of death among oral squamous cell carcinoma according to oral habits

Habit(s)	Relative risk
No habit	1.00
B + C + A	5.32
B + C	2.00
B + A	1.99
B	1.19
C + A	1.13
C	1.14

A: alcohol drinking; B: betel quid chewing; C: cigarette smoking.

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