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ORIGINAL ARTICLE

Patterns of recurrence and second primary tumors in oral squamous cell carcinoma treated with surgery alone

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Abstract The aim of the present study is to review the recurrence patterns and incidence of second primary tumors (SPTs) in patients with oral squamous cell carcinoma (OSCC) who underwent surgery alone without postoperative adjuvant therapy. Data on patients recorded in the head and neck cancer registry of Cathay General Hospital were reviewed. A total of 72 patients with T1-3N0 OSCC who underwent surgery alone were included. Among the 72 patients, 44 had T1 tumors, 22 had T2 tumors, and 6 had T3 tumors. The 5-year overall survival (OS) rate was 77.3%, the recurrence-free survival rate was 74.1%, and the SPT-free survival rate was 73%. Eighteen (25%) patients had disease recurrence (regional recurrence in nine patients, local recurrence in seven patients, and locoregional recurrence in two patients). Most patients with local recurrence alone (6/7 patients, 85.7%) could be salvaged with treatment. However, locoregional control was obtained in only five (45.5%) of 11 patients with neck recurrence after surgical salvage therapy. At the time of analysis, 20 patients developed SPTs, and 15 (75%) of the SPTs were in the oral cavity. The annual incidence of SPT was 5%. Neck recurrence and SPT were associated with 48.4% and 24.4% lower 5-year OS rates, respectively. Multivariate analysis revealed that neck recurrence was a significant risk factor for low OS ($p = 0.008$). Neck recurrence was the most important prognostic factor for OS. The incidence of SPT development was high. Regular and long-term monitoring for recurrence and development of SPTs is necessary to improve the survival rate.

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Introduction

The incidence of oral squamous cell carcinoma (OSCC) is increasing rapidly in Asia and the South Pacific, which includes Taiwan. In addition to smoking and drinking alcohol, betel quid chewing has been identified as a significant etiological factor in this area [1]. Conventional treatment of OSCC includes a combination of surgery, radiotherapy, and chemotherapy. Locoregionally recurrent disease contributes to the majority of cancer-related deaths in patients with OSCC. Another significant problem is the high incidence rate of second primary tumors (SPTs), which has the greatest impact on survival rates in patients with limited initial tumors [2].

Although studies have investigated the survival rate and patterns of recurrence in patients who underwent surgery alone for early stage OSCC [3–6], few studies have analyzed the occurrence of SPTs in OSCC patients treated with surgery alone. In this study, we evaluated the survival rates, recurrence patterns, prognostic factors, and effects of salvage treatment in 72 patients with localized (T1-3N0) oral cancer. The incidence and pattern of SPT development were also analyzed in order to evaluate the impact of recurrent disease and SPTs on survival of OSCC patients treated with surgery alone.

Materials and methods

Data on patients, recorded in the head and neck cancer registry of Cathay General Hospital, who underwent surgical treatment for OSCC from January 1998 to May 2008 were reviewed. One hundred and thirty patients with previously untreated OSCC were treated primarily with surgery. A total of 72 patients (55.4%) were included in our study. This retrospective study was approved by the hospital's institutional review board.

Inclusion criteria included localized (T1-3) squamous cell carcinoma (SCC) of the oral cavity, no palpable cervical nodes on physical examination or radiographic evidence of node enlargement, postoperative pathological examination showing absence of nodal metastases in patients who underwent neck dissection, and treatment with surgery alone without any adjuvant treatment modalities.

Indications for surgery alone for the treatment of SCC of the oral cavity in our institution were as follows: T1, T2, or T3 stage primary tumors, no pathologic evidence of nodal disease (N0), free surgical margins, and absence of perineural invasion (PNI) and lymphovascular permeation.

Oral cancer recurrence refers to an oral cancer that returns following treatment, after a period of time in which the doctor was unable to detect any signs of this complication. We used the criteria published by Hong et al. [7] to distinguish SPTs from recurrences. The definition of SPTs was based on the following criteria: both tumors were malignant with histologic confirmation, the two tumors were geographically distinct (at least 2 cm of normal mucosa between them) or separated in time by 3 or more years, and the possibility that the second primary tumor represented a metastasis was excluded [7]. In this series, three tumors that developed within the anatomic vicinity of the primary tumor were classified as SPTs rather than recurrence after a time interval of 41 months, 42 months, and 83 months.

All statistical analyses were performed with the statistical package SPSS for Windows (Version 17.0, SPSS, Inc., Chicago, IL, USA). Survival distributions were calculated using the Kaplan–Meier method. Significant differences in the survival distributions were tested using the log-rank test. Multivariate survival analysis was conducted using a Cox proportional hazards model. A p-value <0.05 was considered to indicate statistical significance.

Results

Clinicopathological characteristics

The subjects comprised 60 (83.3%) men and 12 women (Table 1). The median age at diagnosis was 53.5 years (range: 22–87 years), and the median duration of follow-up was 49 months (range, 6–136 months). Only 15 patients (20.8%) did

Table 1 Kaplan–Meier survival analysis of 5-year overall survival (OS) rate.

Variables	5-y OS	
	%	p
Age		
≤40 (16)	67	0.157
<40 (56)	80.2	
Gender		
Male (60)	74.8	0.168
Female (12)	88.9	
Betel nut chewing		
Yes (43)	74.3	0.349
No (29)	81.1	
Primary site		
Tongue (31)	65.1	0.126
Buccal area (28)	87.1	
Others (13)	84.6	
Tumor classification		
T1 (44)	82.1	0.317
T2 and T3 (28)	69.4	
Tumor differentiation		
Well (38)	77.3	0.860
Moderate/poor (34)	76.7	
Neck dissection		
Yes (32)	81.8	0.758
No (40)	74	
Positive surgical margins, PNI, or LVP		
Yes (11)	43.8	0.132
No (61)	81.2	
Neck recurrence		
Yes (11)	35.8	<0.001
No (61)	84.2	
Local recurrence		
Yes (9)	63.5	0.347
No (63)	79.4	
SPT		
Yes (20)	60.5	0.046
No (52)	84.9	

LVP = lymphovascular permeation; PNI = perineural invasion; SPT = second primary tumor.

not use tobacco, drink alcohol, or chew betel quid. The majority of patients ($n = 43$, 59.7%) were betel quid chewers. Tumors were graded as well differentiated (52.8%), moderately differentiated (44.4%), or poorly differentiated (2.8%) according to World Health Organization guidelines. T1 tumors were diagnosed in 44 (61.1%) patients, T2 in 22 (30.6%) patients, and T3 in six (8.3%) patients. Based on the 2002 American Joint Committee on Cancer staging system [8], there were 44 individuals with Stage I disease, two individuals with Stage II disease, and six individuals with Stage III disease. The sites of primary tumor included the tongue in 31 patients, buccal mucosa in 28 patients, gingiva in six patients, lip in five patients, floor of the mouth in one patient, and retromolar trigone in one patient. Lip splitting was required to obtain negative surgical margins in five patients. Neck dissection was performed in 32 patients (30 homolaterally, 2 bilaterally). Eleven patients did not meet the criteria for surgery alone and refused any postoperative adjuvant therapy. Among them, seven individuals (9.7%) had positive margins and four individuals (5.6%) had PNI. These 11 patients received surgery alone for initial treatment and were included in this study.

Recurrence patterns and salvage treatment

Recurrent disease developed in 18 patients (25%) during the follow-up period. The median time between surgery and recurrence was 8.5 months (range: 2—30 months). Recurrence occurred within the first 2 years of primary treatment in 13 (72.2%) patients, and all cases of recurrence occurred within the first 3 years. The 1- and 3-year overall recurrence-free survival (RFS) rates were 84.5% and 74.1%, respectively (Fig. 1). A trend was seen toward lower 3-year RFS in those patients with positive surgical margins (51.9%) compared to patients without positive surgical margins or PNI (78%, $p = 0.083$). Seven (38.9%) patients had disease recurrence only at the primary site, nine (50%) patients had recurrence only in the ipsilateral neck, and two (11.1%) patients had simultaneous primary and neck recurrence. Surgical salvage treatment was attempted in all patients with tumor recurrence and was successful in 11 (61.1%) patients (6/7 patients (85.7%) with local recurrence and 5/9 patients (55.6%) with regional recurrence). However, three patients with regional recurrence developed a second primary tumor despite regional tumor control (gingiva, $n = 1$; tongue base, $n = 1$; and larynx, $n = 1$).

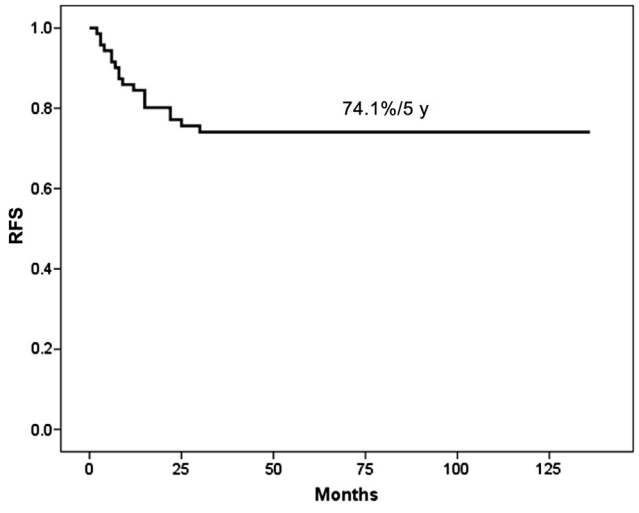

Figure 1. Recurrence-free survival (RFS) for all patients.

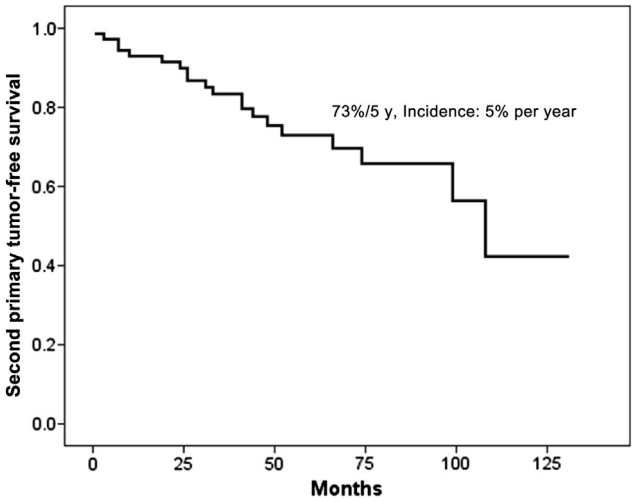

Figure 2. Second primary tumor-free survival for all patients.

Second primary tumors

A total of 20 patients (27.8%) developed SPTs. The median time from initial treatment of the index tumor to the diagnosis of the SPT was 32 months (range: 0.5—108 months). Sixteen (80%) cases were diagnosed within 5 years after treatment of the index tumor. The 3-, 5-, and 7-year overall SPT-free survival rates were 83%, 73%, and 66%, respectively (Fig. 2). There was a trend toward lower SPT-free survival among patients who chewed betel quid ($p = 0.073$). The incidence of SPT was 5% per year and was constant during the follow-up period for at least 7 years. A total of 18 SPTs (18/20 patients, 90%) occurred in the head and neck region, including nine SPTs in the buccal area, two

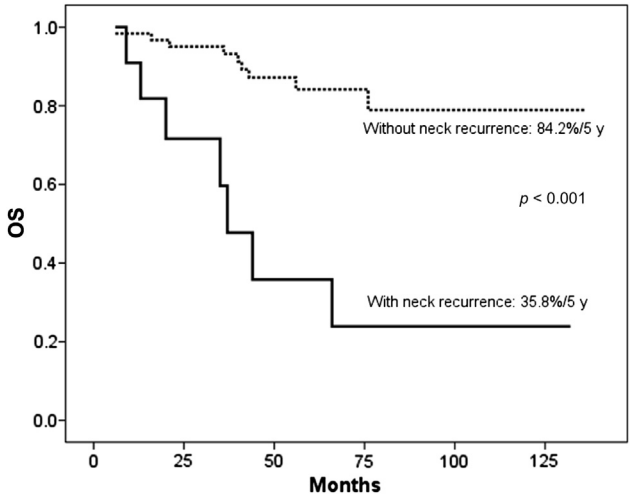

Figure 3. Overall survival (OS) rates for patients with and without neck recurrence.

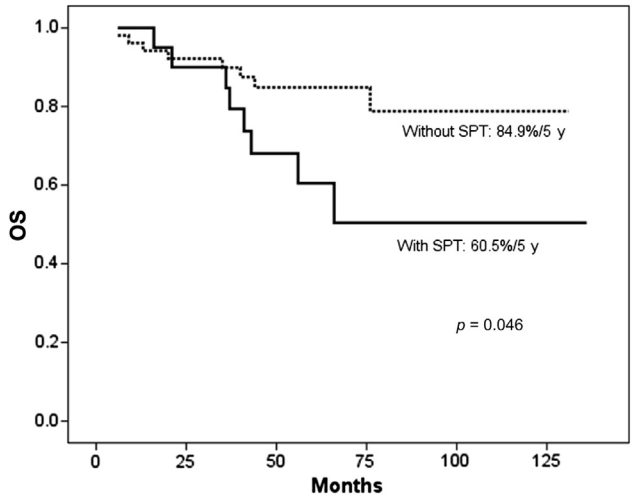

Figure 4. Overall survival (OS) rates for patients with and without second primary tumors (SPT).

in the gingiva, two in the mouth floor, two in the tongue base, and one each in the tongue, hard palate, and larynx. All of those tumors were SCC, and 16 (16/18, 88.9%) of the patients with SPTs presented with an isolated local disease. Two SPTs occurred outside the head and neck region, including one hepatoma and one lymphoma. During the follow-up period, seven of the 20 patients (35%) with SPT died due to SPT-related complications.

Overall survival

The 3-, 5-, and 7-year OS rates were 88%, 77%, and 70%, respectively. Sixteen patients died during the follow-up period. The associations among various clinicopathological variables with 5-year OS are listed in Table 1. Patients with neck recurrence and those with SPT had significantly poorer OS. The Kaplan—Meier OS curves for neck recurrence and SPT are shown in Figs. 3 and 4, respectively. Neck recurrence and SPT were associated with 48.4% and 24.4% lower 5-year OS rates, respectively. Subsequent multivariate Cox regression analyses of the above factors revealed that neck recurrence was the only independent predictor of lower OS ($p = 0.008$, hazard ratio: 2.294, 95% confidence interval: 1.247—4.219).

Discussion

Good locoregional control and survival can be obtained with surgery alone for localized OSCC. In our series, the 3-year OS rate was 77%, the 5-year OS rate was 70%, and the recurrence rate was 21%. These rates were consistent with those previously reported in the literature (Table 2) [3—6]. Radiation therapy is an alternative to surgery for early-stage oral cancers. Although evidence from randomized controlled trials is not available, retrospective series have suggested that surgery and radiation therapy yield similar results in terms of local control and survival. It has been reported that the 5-year locoregional control rate among patients with oral cavity T1-T2 disease treated with radiotherapy alone ranges from 69.5% to 81%, and that the OS rate varies from 46.6% to 81% [9—11]. However, radiotherapy itself can cause both acute and long-term complications, including mucositis, dysphagia, hoarseness, xerostomia, radionecrosis, subcutaneous fibrosis, trismus, loss of taste, thyroid dysfunction, esophageal stenosis, dental decay, and damage to the middle and inner ear [12,13]. Definitive surgical resection is preferred whenever feasible because of the negative impact of radiotherapy-related complications on quality of life.

In the previous published series [3—6], 18% to 28% of oral cancer patients treated with surgery alone developed recurrent disease. Wolfensberger et al. [4] reported on a cohort of 93 patients with early-stage (T1-2, N0-1) oral cancer treated with surgery alone and found that 47% of patients developed local disease recurrence and 41% developed regional recurrence. In our study, the most common recurrence pattern was regional (50%), followed by local (38.9%) and locoregional (13%). This pattern was similar to that reported by Lim et al. [6] who found regional recurrence in 50% of patients and local recurrence in 31%.

Both positive surgical margins and PNI are predictors of disease recurrence [14,15]. In the current study, there was a trend toward lower RFS in patients with positive surgical margins and PNI (51.9% vs. 78%, $p = 0.083$) compared with patients without these conditions. The small sample size and good prognosis of this disease may hinder a statistically significant finding. In addition, an undissected neck [4], poorly differentiated tumors [5], and neck node metastasis [6] have been found to be significant predictors for recurrence in OSCC patients treated with surgery alone.

The prognosis of salvage surgery for recurrent disease in patients treated by surgery alone may be better than that for recurrent disease treated with postoperative radiotherapy [16,17]. According to our results and the literature [3—6], salvage treatment is appropriate for most (69—100%) OSCC patients treated with surgery alone. The average overall success rate of salvage treatment is approximately 60% (range: 36—71%).

Table 2 Literature review of outcomes in oral cancer patients treated with surgery alone.

Authors	Cases	Site	Survival (%)	Recurrence no. (%)	Salvage rate (%)
Hicks [3], 1998	79	Oral tongue	85; 4-y disease-specific	22 (28)	NA
Wolfensberger [4], 2001	93	Oral cavity	94; 4-y disease-specific	17 (18)	71
Iyer [5], 2004	147	Buccal area	91; 3-y overall	39 (27)	69
Lim [6], 2008	76	Oral cavity	69; 5-y overall	16 (21)	36
Present study	72	Oral cavity	77; 5-y overall	18 (25)	61

NA = not available.

Table 3 Reported salvage treatment for local, regional, and locoregional recurrence.

	Local no.	Salvage rate (%)	Regional no.	Salvage rate (%)	Locoregional no.	Salvage rate (%)
Iyer et al. [5], 2004	18	83.3	11	72.7	10	40
Lim et al. [6], 2008	5	75	8	20	2	0
Present study	7	85.7	9	55.6	2	0

Few studies have investigated the success rates of salvage therapy for disease recurrence in patients with oral cancer that was initially treated with surgery alone. As shown in Table 3, [6,7] the majority (75—85.7%) of cases of local recurrence could be salvaged with further treatment. The success rates of surgical salvage therapy for regional recurrence were poorer in our series (55.6%) and in the study by Lim et al. [6] (20%). Iyer et al. [5] reported a high success rate (72.7%) for surgical salvage therapy in patients with regional recurrence. However, salvage therapy could only be performed in 40% of the patients with local or regional recurrence in their series. The results show the value of salvage treatment but also demonstrate that not all patients can be treated with surgical salvage therapy, especially those with neck recurrence, including regional and locoregional recurrence. Furthermore, our study showed that neck recurrence decreased the 5-year OS by 48.4% and that neck recurrence was the only independent prognostic factor for survival.

Few studies have separately analyzed the occurrence of SPTs in patients with OSCC that was treated with surgery alone. In the present study, 72.2% of the recurrent disease appeared within the first 2 years of diagnosis of the index OSCC, and the incidence decreased with time. Conversely, the incidence of SPT remained constant for an extended period, and its development had a long-term effect on survival. During the study period, there were a total of 20 cases of SPT development, which corresponds to an incidence of 5% per year, whereas other groups [18,19] noted an annual incidence of 2.9—3%. A possible explanation for the discrepancy is that we only included patients with localized tumors treated with surgery alone. Recently, some authors reported that SPTs were more likely to occur in patients with limited initial tumors and in those unexposed to radiation [2,20]. In our study, betel quid chewing seemed to be a risk factor for the development of SPTs. The majority of patients ($n = 43$, 59.7%) in our study were betel quid chewers. The percentage of OSCC patients in this study who chewed betel quid (59.7%) was lower than that in southern Taiwan (82% or higher) [15,18], possibly because our hospital is in a metropolis where betel chewing is not so prevalent. Longer follow-up may be necessary, particularly in those patients who are heavy betel quid chewers.

The majority (15/20, 75%) of SPTs were located in the oral cavity, a finding compatible with reports from other betel quid chewing areas (56—70.3%) [18,19]. Most of the patients (15/18, 83.3%) with second primary head and neck tumors presented with an isolated local disease. The high incidence of localized second cancers was probably because of the intense surveillance and the fact that radiation was not used during the first treatment. According to the literature [18,19], the esophagus and lung are two of the most frequent sites of SPTs outside the oral cavity. This study had no cases of esophageal or lung SPT, possibly because of the small number of patients in this study.

In summary, good locoregional control and survival can be obtained with surgery alone for localized OSCC. Neck failure was the most common pattern of recurrent disease and was the only independent prognostic factor for OS. The incidence of SPT development was high. Further studies with appropriate follow-up programs and strategies for preventing the development of SPTs in patients with OSCC are warranted.

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