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ORIGINAL ARTICLE

Malignant development in patients with oral potentially malignant disorders detected through nationwide screening: Outcomes of 5-year follow-up at a single hospital

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Abstract

Background: Although survival rate and quality of life are improved if patients with oral carcinoma can be detected early, however, such lesions are usually asymptomatic; therefore, it is hard to raise awareness. Screening has proved to be cost-effective for early detection.

Methods: Sixty-two patients with oral carcinomas and 555 patients with oral potentially malignant disorders (OPMDs) who were detected through screening were examined the relationship between clinicopathological features and follow-up outcomes.

Results: The 5-year cumulative cancer-free interval rate was 94.1%, and the annual malignant transformation rate was 1.16%. The rate of interval carcinoma development from Candida hyperplasia, oral submucous fibrosis, homogeneous leukoplakia, non-homogenous leukoplakia, and verrucous hyperplasia, was 13.6%, 5.7%, 4.6%, 12.1%, and 21.3%, respectively. Significant independent risk factors for interval carcinoma development were heavy betel quid chewing, verrucous hyperplasia, and surgery refusal.

Conclusions: Well-designed risk assessment, treatment, and surveillance program could lead to earlier cancer detection and thereby reduce mortality and morbidity.

KEYWORDS
high-risk, interval carcinoma, oral carcinoma, oral potentially malignant disorders, screening, surgery refusal

1 | INTRODUCTION

Despite advances in treatment modalities and diagnosis, outcomes of oral squamous cell carcinoma (OSCC) remain poor.[1,2] Survival rates for OSCC are highly stage-dependent, with patients treated at early stages having higher quality of life and lower cost of care.[1,3,4] Although oral cancer can arise de novo, it is not uncommon for carcinomas to arise from a precancerous background. Therefore, patients with precancerous lesions or conditions are widely accepted to have a significantly higher risk of developing oral cancer. The WHO workshop in 2005 proposed the term "oral potentially malignant disorder" (OPMD) to define any lesion or condition of the oral mucosa with the potential for malignant transformation. Another new term, "potentially premalignant oral epithelial lesion", has been used to broadly define

TABLE 1 The results of Cox's regression analysis to identify independent clinicopathological factors associated with malignant transformation in patients with oral potentially malignant disorders

		Univariate analysis		Multivariate analysis	
Variables	**No. of patients (%)**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Tobacco smoking				NA	
Never	28 (5.0%)	Reference			
0-200 spd·yrs	240 (43.2%)	0.73 (0.21-2.52)	.61		
>200 spd·yrs	287 (51.8%)	1.75 (0.29-3.10)	.92		
Betel quid chewing					
Never	95 (17.1%)	Reference		Reference	
0-200 qpd·yrs	231 (41.6%)	4.44 (1.02-19.39)	.05	3.83 (0.85-17.14)	.08
>200 qpd·yrs	229 (41.3%)	6.89 (1.63-29.21)	.009	5.90 (1.38-25.15)	.02
Alcohol drinking				NA	
Never	429 (77.3%)	Reference			
Yes	126 (22.7%)	1.38 (0.74-2.58)	.31		
Subsite of main tumor[a]				NA	
Buccal pouch	326 (70.9%)	Reference			
Tongue and mouth floor	76 (16.5%)	1.35 (0.62-2.94)	.45		
Others	58 (12.6%)	0.44 (0.14-1.45)	.18		
Multiple primary tumors[a]				NA	
No	376 (81.7%)	Reference			
Yes	84 (18.3%)	0.91 (0.40-2.04)	.81		
Hepatitis C				NA	
No	534 (96.2%)	Reference			
Yes	21 (3.8%)	1.14 (0.28-4.68)	.86		
Metabolic syndrome				NA	
No	456 (82.2%)	Reference			
Yes	99 (17.8%)	1.60 (0.84-3.04)	.16		
Accompanying OSF				NA	
No	410 (73.9%)	Reference			
Yes	145 (26.1%)	1.21 (0.64-2.30)	.56		
Main diagnosis					
Homogeneous leukoplakia	317 (57.1%)	Reference		Reference	
Lichen planus	7 (1.3%)	0 (0.00-0.00)	.98	NA	
Candida hyperplasia	22 (4.0%)	2.29 (0.67-7.83)	.19	NA	
OSF alone	87 (15.7%)	0.83 (0.28-2.44)	.73	0.88 (0.11-6.84)	.90
Nonhomogenous leukoplakia	33 (5.9%)	2.23 (0.76-6.60)	.15	1.27 (0.39-4.21)	.69
Oral verrucous hyperplasia	89 (16.0%)	3.86 (2.02-7.36)	<.001	2.45 (1.13-5.34)	.02
Dysplasia				NA	
No	241 (94.1%)	Reference			
Yes	15 (5.9%)	3.61 (1.37-9.49)	.009		
Management[a]					
Surveillance	238 (51.7%)	Reference		Reference	
Excision	202 (43.9%)	2.67 (1.31-5.42)	.007	1.41 (0.59-3.37)	.45
Surgery refusal	20 (4.4%)	7.16 (2.59-19.79)	<.001	4.51 (1.36-14.96)	.02

(Continues)

TABLE 1 (Continued)

Variables	No. of patients (%)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Follow-up status				NA	
Symptomatic	321 (57.8%)	Reference			
Periodic (≤2 years)	101 (18.2%)	1.03 (0.41-2.57)	.96		
Periodic (>2 years)	133 (24.0%)	3.18 (1.73-5.83)	<.001		

Abbreviations: CI, confidence interval; HR, hazard ratio; MID, maximal interincisal distance; NA, not applicable; OSF, oral submucous fibrosis; spd·yrs, sticks per day·years; qpd·yrs, quids per day·years.
[a]N = 460.

lesions whose histological or clinical features have malignant potential.[5] OPMDs encompass a number of oral lesion types, such as leukoplakia, erythroplakia, lichen planus, Candida hyperplasia, oral verrucous hyperplasia (OVH), oral submucous fibrosis (OSF), and epithelial dysplasia. For people who smoke tobacco or chew betel quid, periodic screening with visual and tactile examination followed by ablation of OPMDs or early-stage OSCCs can effectively reduce OSCC mortality.[6,7]

Although OPMDs do not invariably progress to malignancy, it is reasonable for clinicians to evaluate the risk of malignant development using workable predictors to determine treatment planning and follow-up strategy. Clinicopathological risk factors including the OPMD clinical type, site, grade of epithelial dysplasia, smoking, and alcohol intake have been proposed on the basis of outcome studies in Western countries. Given the high prevalence of OPMDs in southern and eastern Asia, cancer prevention represents a critical public health problem in this region.[8] Effective screening programs for high-risk people should be the preferred means of management. In Taiwan, population-based oral cavity screening with visual and tactile examination for people who smoke tobacco or chew betel quid has been conducted since 2009. In connection with such screening, this study aimed to examine the distribution of OPMDs and follow-up outcomes using the screening outcomes from a single hospital in an area with a high betel quid chewing prevalence.

2 | PATIENTS AND METHODS

Following approval by the Institutional Review Board of Chi Mei Medical Center in Taiwan (approval no. 10612-L02), patients who smoked tobacco or chewed betel quid and were deemed to have suspicious lesions in primary screenings between 2010 and 2012 were enrolled in this study. The final diagnosis was made by oral and maxillofacial surgeons or

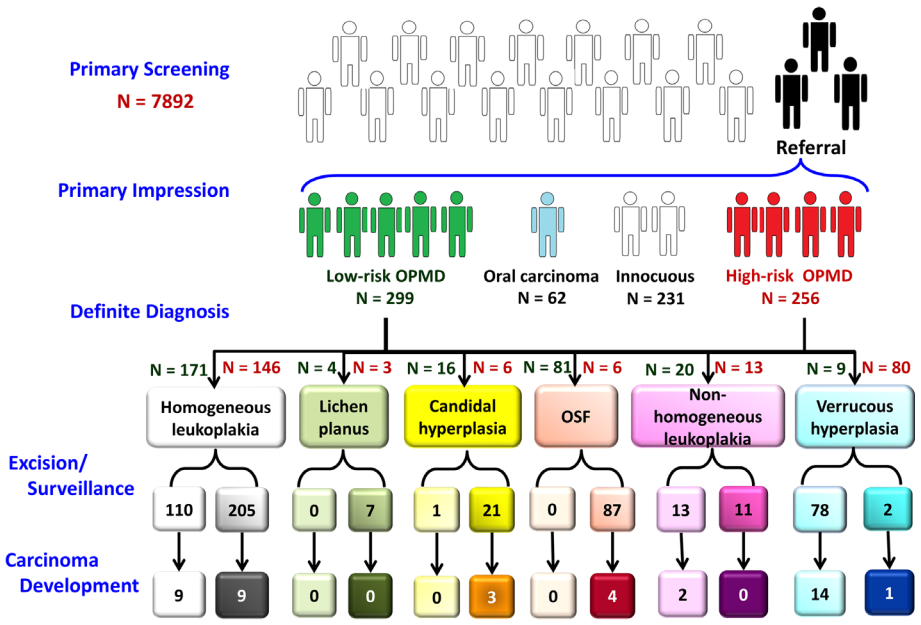


FIGURE 1 The flow diagram of screening, diagnosis, and follow-up of people who smoked tobacco or chewed betel quid in this study. The definite diagnosis of oral potential malignant disorder (OPMD) was judged according to clinical features or pathology. After excluding 20 patients refusing surgical excision, 25 (12.4%) and 12 (3.6%) developed interval carcinoma in 202 patients who underwent excision and 333 patients who adopted surveillance, respectively. OSF, oral submucous fibrosis [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 The clinical factors of 48 interval carcinoma that arising from oral potentially malignant disorders

Case	Clinical diagnosis at screening	Histopathology	Treatments	Accompanying OSF	Duration of carcinoma development	Seventh AJCC stage
1	Verrucous tumor	Verrucous hyperplasia	Surveillance	0	20	I
2	Homo OL	NA	Surveillance	0	23	IV
3	Homo OL	NA	Surveillance	1	25	I
4	Homo OL	NA	Surveillance	0	51	II
5	Homo OL	NA	Surveillance	0	50	II
6	Homo OL	NA	Surveillance	0	14	I
7	Homo OL	NA	Surveillance	0	71	I
8	Homo OL	NA	Surveillance	0	51	I
9	Homo OL	NA	Surveillance	1	12	III
10	Homo OL	NA	Surveillance	1	15	IV
11	non-homo OL	Mild dysplasia	Surgery	0	35	IV
12	non-homo OL	Mild dysplasia	Surgery	1	51	I
13	Verrucous tumor	Verrucous hyperplasia	Surgery	0	70	IV
14	Verrucous tumor	Verrucous hyperplasia	Surgery	0	73	I
15	Verrucous tumor	Verrucous hyperplasia	Surgery	0	73	II
16	Verrucous tumor	Verrucous hyperplasia	Surgery	1	61	III
17	Verrucous tumor	Verrucous hyperplasia	Surgery	1	81	I
18	Verrucous tumor	Verrucous hyperplasia	Surgery	0	20	II
19	Verrucous tumor	Verrucous hyperplasia	Surgery	0	65	II
20	Verrucous tumor	Verrucous hyperplasia	Surgery	0	21	III
21	Verrucous tumor	Verrucous hyperplasia	Surgery	0	73	II
22	Verrucous tumor	Verrucous hyperplasia	Surgery	0	44	III
23	Verrucous tumor	Verrucous hyperplasia	Surgery	0	51	I
24	Verrucous tumor	Verrucous hyperplasia	Surgery	0	44	IV
25	Verrucous tumor	Verrucous hyperplasia	Surgery	0	53	I
26	Verrucous tumor	Verrucous hyperplasia	Surgery	0	52	I
27	Homo OL	Acanthosis	Surgery	0	85	I
28	Homo OL	Hyperkeratosis	Surgery	1	49	II
29	Homo OL	Hyperkeratosis	Surgery	0	58	IV
30	Homo OL	Parakeratosis	Surgery	0	16	I
31	Homo OL	Acanthosis	Surgery	0	78	I
32	Homo OL	Acanthosis	Surgery	1	43	I
33	Homo OL	Hyperkeratosis	Surgery	0	41	I
34	Homo OL	Hyperkeratosis	Surgery	0	19	IV
35	Homo OL	Acanthosis	Surgery	0	57	II
36	Non-homo OL	NA	Surgery refusal	0	70	I
37	Non-homo OL	Mild dysplasia	Surgery refusal	0	25	I
38	Verrucous tumor	VH	Surgery refusal	0	17	I
39	Verrucous tumor	NA	Surgery refusal	1	79	I
40	Verrucous tumor	NA	Surgery refusal	0	19	I
41	Verrucous tumor	Verrucous hyperplasia	Surgery refusal	0	15	II

(Continues)

TABLE 2 (Continued)

Case	Clinical diagnosis at screening	Histopathology	Treatments	Accompanying OSF	Duration of carcinoma development	Seventh AJCC stage
42	Candidiasis	Candidal hyperplasia	Surveillance	1	32	I
43	Candidiasis	Candidal hyperplasia	Surveillance	0	71	I
44	Candidiasis	NA	Surveillance	0	73	IV
45	OSF alone	NA	Surveillance	NA	30	I
46	OSF alone	NA	Surveillance	NA	6	I
47	OSF alone	NA	Surveillance	NA	60	II
48	OSF alone	NA	Surveillance	NA	32	IV

Abbreviations: AJCC, American Joint Committee on Cancer; Homo OL, homogeneous leukoplakia; OSF, oral submucous fibrosis; NA, not applicable; non-homo OL, non-homogenous leukoplakia.

otolaryngologists according to the clinical features or pathological findings. Detailed clinicopathological factors and follow-up status were included as independent variables (Table 1). If a patient had more than one OPMD, the main diagnosis was determined according to the following sequence: OVH, nonhomogeneous leukoplakia or OSF with accompanying leukoplakia, Candida hyperplasia, lichen planus, and homogeneous leukoplakia. Patients with nonhomogeneous leukoplakias, homogeneous leukoplakias accompanied by OSF and OVH were advised to undergo excision under the impression of risky lesions. All patients with OPMD were advised to receive at least one screening annually from an oral and maxillofacial surgeon or otolaryngologist. Cancer-free survival was assessed according to medical records up to June 2018.

For patients with a suspicious lesion during follow-up, a tissue biopsy was performed to confirm interval carcinoma development. Those patients with OSCCs at screening or within 6 months after the primary screening were categorized as having screening-detected carcinomas. The cancer-free interval was defined from the date of initial diagnosis to the date of confirmed interval carcinoma. Using the SPSS 19.0 software package (SPSS Inc, Chicago, Illinois), univariate logistic regression analysis was performed to calculate the hazard ratio and assess the ability of 12 variables to predict the risk of interval carcinoma. Possible index factors in interval carcinoma development were submitted to forward-selection multivariate logistic regression analysis. When the 95% confidence interval of a given factor's relative risk was not included, the value was considered significant ($P < .05$). The cancer-free rate was estimated using the Kaplan-Meier survival analysis, and significant difference was determined using a log-rank test.

3 | RESULTS

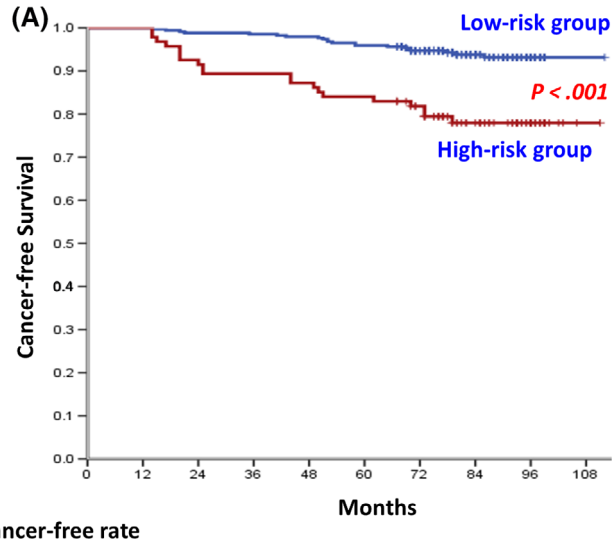
Suspicious lesions detected in screening activity were reexamined by specialists and diagnosed as 62 OSCCs, 590 OPMDs, and 231 innocuous lesions; the prevalence rate of screening-detected OSCCs and OPMDs was thus 0.8% and 7.5%, respectively (Figure 1). According to the 7th American Joint Committee on Cancer (AJCC) staging system, distribution of the 62 screening-detected OSCCs was as follows: stage I (30.7%), stage II (14.5%), stage III (12.9%), and stage IV (41.9%). A total of 35 OPMD cases were excluded because of incomplete clinical information or loss of follow-up.

The demographic and clinicopathological data for the remaining 555 patients with OPMDs are listed in Table 1. The male to female ratio was 138. The mean age of patients with OPMD at the time of diagnosis was 49.0 ± 10.9 years (range, 30-91 years). The prevalence of betel quid chewing, tobacco smoking, and alcohol drinking in this cohort was 82.9%, 95.0%, and 22.7%, respectively. The incidence of metabolic syndrome, hepatitis C virus infection, and accompanying OSF was 17.8%, 3.8%, and 26.1%, respectively. The distribution of OPMD types in this study was as follows: lichen planus (n = 7), Candida hyperplasia (n = 22), OSF alone (n = 87), homogeneous leukoplakia (n = 317), nonhomogenous leukoplakia (n = 33), and OVH (n = 89). A total of 256 patients with high-risk OPMDs underwent biopsy, and the percentage of epithelial dysplasia in cases of homogeneous leukoplakia, nonhomogeneous leukoplakia, and OVH was 0.6%, 21.2%, and 6.7%, respectively. For 144 patients with high-risk OPMDs, 34 patients (23.6%) did not undertake surgery because 14 patients having serious systemic disease that could have high risk of postoperative morbidities and 20 patients refusing surgery.

The mean follow-up period was 80.9 months, and the annual follow-up adherence rate was 42.2%. By the end of this study, 48 patients had developed interval carcinomas, with a malignant transformation rate of 8.7%, whereas the malignant development rate for Candida hyperplasia, homogeneous leukoplakia, OSF alone, nonhomogeneous leukoplakia, and OVH was 13.6%, 5.7%, 4.6%, 12.1%, and 21.3%, respectively

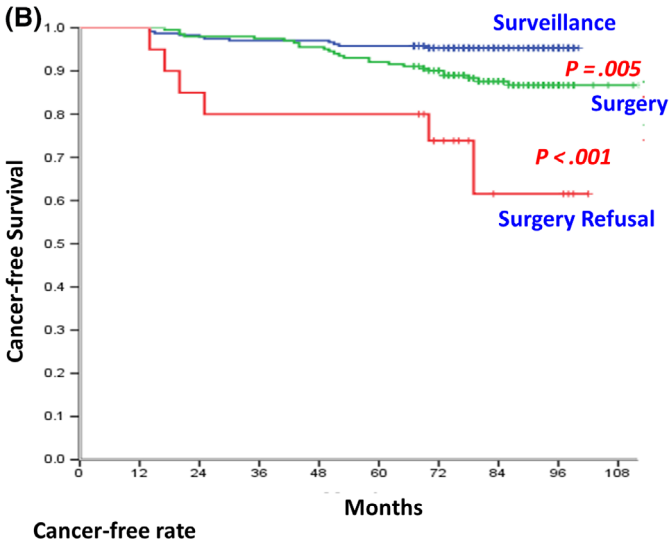
(Table 2). The clinicopathological factors of diagnosis at screening, treatments, accompanying OSF, the duration of carcinoma development, and 7th AJCC stage for the 48 patients with interval carcinoma development are listed in Table 2. The AJCC stage distribution for interval carcinoma was as follows: stage I (53.2%), stage II (16.2%), stage III (8.5%), and stage IV (19.1%). Of these interval carcinomas, 69.4% were detected in the early stage, whereas 45.2% of screening-detected carcinomas were diagnosed in the early stage.

The 5-year cumulative cancer-free interval rate was 94.1%, and the annual malignant transformation rate was 1.16% (Figure 2). Excluding the 20 patients who refused surgery, the annual malignant development rate of Candida hyperplasia, homogeneous leukoplakia, OSF alone, nonhomogeneous leukoplakia, and OVH was 2.11%, 0.84%, 0.68%, 1.22%, and 2.78%, respectively. Multivariate analysis with Cox proportional regression indicated that high accumulation dose of betel quid chewing, OVH, and surgery refusal were significantly correlated with the risk of malignant development in patients with OPMDs (Table 1). The risk stratification for interval carcinoma using betel quid chewing, alcohol drinking, clinical diagnosis, and management was shown in Table 3. Patients with homogeneous leukoplakia with heavy accumulation dose of betel quid chewing and alcohol drinking habit, patients with risky lesions having alcohol drinking habits, and patients with risky lesions having high accumulation dose of betel quid



Cancer-free rate

Month	12	24	36	48	60
Low-risk	100	98.8	98.6	98.0	95.9
High-risk	100	91.5	89.4	87.2	84.4



Cancer-free rate

Month	12	24	36	48	60
Surveillance	99.2	97.9	96.6	96.6	95.3
Surgery	99.5	97.5	97.0	95.0	91.6
Refusal	95.0	80.0	73.8	73.8	73.8

FIGURE 2 (A) Kaplan-Meier survival curve of cancer-free survival curve stratified by four clinical factors. The high-risk group had a significant worse survival rate. (B) Patients who refused surgery had significantly poorer cancer-free survival than those who underwent surgery or received surveillance [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Risk stratification assessment of malignant development for patients with oral potential malignant disorder using accumulation dose of betel quid chewing, alcohol drinking, clinical diagnosis, and management

	Light BQ chewing and alcohol (−) HR (95% CI)	Light BQ chewing and alcohol (+) HR (95% CI)	Heavy BQ chewing and alcohol (−) HR (95% CI)	Heavy BQ chewing and alcohol (+) HR (95% CI)
Homogenous leukoplakia, excision	Reference	0	0.64 (0.07-6.116)	5.69 (0.95-34.06)
Homogenous leukoplakia, observation	0.75 (0.08-7.24)	2.03 (0.21-19.53)	1.82 (0.19-17.51)	9.34 (2.08-41.79)*
Risky lesions	4.35 (0.45-42.26)	5.64 (1.53-20.84)*	7.58 (2.05-28.05)*	5.40 (1.09-26.76)*

Abbreviations: CI, confidence interval; heavy BQ chewing, betel quid chewing >200 qpd·yrs; HR, hazard ratio; light BQ chewing, betel quid chewing ≤200 qpd·yrs; risky lesions, oral submucous fibrosis with accompanying leukoplakia, non-homogenous leukoplakia, and verrucous hyperplasia.
*$P < .05$.

chewing were categorized as high-risk group. The cancer-free survival rate of high-risk group was significantly worse than low-risk group (Figure 2A). The annual malignant development rate for surgery refusal was 3%. The cancer-free survival rate of the 20 patients who refused surgery was significantly worse than in those who underwent surgery or received surveillance (Figure 2B). The mean malignant development interval for patients under surveillance and or undergoing surgery was 39.1 and 52.5 months, respectively.

4 | DISCUSSION

In Europe, the prevalence of OPMDs has been reported to be as low as 0.2% or as high as 14.4%, with numerous estimates falling between these extremes.[9] The OPMD detection rate in community-based screening activities in the Indian subcontinent has ranged between 2.7% and 9.9%.[10,11] An international study of 8922 subjects recruited from Asia-Pacific countries where betel quid chewing is common indicated that the prevalence of OPMDs among chewers ranged between 0.9% and 31.2%.[12] A meta-analysis of 22 studies demonstrated a pooled OPMD prevalence of 4.47%, with the highest prevalence rate (10.54%) found in the Asian population.[8] For high-risk individuals with a habit of betel quid chewing or tobacco smoking, a population-based screening activity conducted in Malaysia indicated that the incidence rate OPMDs and OSCCs was 1.4% and 0.04%, respectively.[13] In Taiwan, nationwide population-based screening of tobacco smokers or betel quid chewers indicated that the incidence rate of OPMDs and OSCCs was 4.7% and 1.8%, respectively.[14] As part of this screening program, this study retrospectively reviewed patients at a single hospital located in a rural district of southern Taiwan, for whom a higher OPMD detection rate of 7.5% was found, similar to the 7.3% OPMD detection rate from a screening activity in rural India.[15]

For the high-risk individuals, screening is a cost-effective means of reducing morbidities and mortality, provided they are educated in oral cavity self-examination, undertake proper treatment, and are subject to periodic follow-up.[6,11] Education and periodic surveillance as part of a screening activity can raise awareness and thereby lead to detection of asymptomatic lesions.[16] Early detection of carcinoma depends not only on raising awareness but also on the vigilance of primary care providers and a well-conducted referral system.[17] A meta-analysis study indicated that more oral carcinomas can be detected at an early stage if the diagnostic delay in primary care is shortened.[18] Thanks to the high coverage rate of national health insurance in Taiwan, this study cohort could be readily referred to specialists for prompt diagnosis and treatment. Although the annual follow-up adherence rate was only 42.2% in this study, 73% of interval carcinomas were found at an early stage, a significantly higher rate than for carcinomas detected at screening (45.2%).

The betel quid chewing dose is strongly associated with the incidence of both OPMDs and OSCC.[19,20] An epidemiological study indicated that aboriginal students or those at schools located in mountainous regions had a higher percentage of chewing behavior.[21] A nationwide survey on betel quid chewing in adolescent students indicated an increasing prevalence of this habit among adolescent students in less urbanized areas.[22] Most of the patients in this study lived in rural areas of southern Taiwan. Compared with the nationwide screening outcomes, the different OPMD distributions and higher rate of screening-detected OSCCs in this study could be attributed to a high prevalence of tobacco smoking and betel quid chewing.[14] This indicates that education for high-risk people in rural areas should emphasize ceasing smoking and betel quid chewing and raise awareness of the symptoms and signs of OPMDs.

Because the presence of OPMDs can indicate a relatively higher risk of malignant development, proper management should aim to reduce incidence of oral carcinomas as well as their mortality. The rate of malignant development reported in various studies ranges from 0.13% to 50% depending on the subtype distribution, the number of cohorts, and the corresponding treatment types.[23] The three most common OPMDs in our cohort, namely leukoplakia, OSF, and OVH, were consistent with the results of nationwide screening in Taiwan.[14] Oral leukoplakia, as the most common OPMD, is defined as a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable type. The global prevalence of leukoplakia is estimated at 2.6%, and its pooled prevalence in Asian studies is 7.8%.[17] The malignant transformation rate is between 4.5% and 17.5%.[24,25] A follow-up study of 218 patients who did not receive surgical intervention indicated that the leukoplakia localized on the tongue, had a higher degree of dysplasia, or were nonhomogeneous in appearance, with a significant risk of progression to cancer.[26] In another study of 183 patients with leukoplakia who underwent surgical intervention, the results indicated that surgery significantly reduced the risk of cancer development and that a close surgical margin and gingival leukoplakia were indicators of a significant risk of disease recurrence.[27] However, another similar study indicated that surgery does not play a significant role in preventing malignant development of leukoplakia.[28] Etiology could explain the difference in inclusion criteria between these studies. In the study by Kuribayashi et al, 17.2% of patients in the surveillance group exhibited moderate to severe epithelial dysplasia (high risk), whereas only 6% of the patients in the nonsurgical group of Holmstrup's study were at a high risk. The study by Saito et al equally distributed the percentage of high-risk (epithelial dysplasia) cases and found no significant difference in malignant development between patients who received surgical treatment (5.5%, 5/91) and those who did not (7.8%, 4/51).[29] One follow-up study

conducted in Sweden reported that 43% of screening-detected leukoplakias disappeared without surgical intervention.[30] Although our study showed surveillance did not increase the risk of carcinoma development in patients with homogeneous leukoplakia, however, the patients have high accumulation dose of betel quid chewing with alcohol drinking habit having a significant higher incidence of carcinoma development; therefore, they should be advised to undertake excision and to be followed closely.

OSF is characterized by vesicles, ulcerations, petechiae, melanoses, and mucosal rigidity due to fibro-elastic changes in the juxtaepithelial layer, resulting in a progressive limitation of mouth opening. OSF was the second most common OPMD type in this cohort, consistent with the screening results in betel quid–prevalent regions.[10,14,31] The 23.8% prevalence and 9.2% malignant transformation rates for OSF in this study were higher than in previous OSF studies, which reported 4.96% prevalence and 2%-7.6% malignant transformation.[12,32] A study using the Taiwan National Health Insurance database indicated that the malignant development rate of OSF accompanied by leukoplakia (15.7%) was higher than that of OSF alone (7.0%).[33] Of the 27 OSF cases with accompanying leukoplakia in this study, 48% underwent surgery. As a result, the carcinoma development rate in OSF cases with accompanying leukoplakia was 18.5%, which was significantly higher than the 4.6% found in patients with OSF alone. For patients with OSF with accompanying leukoplakia, clinicians should consider removing the lesion for checking any malignant development.

OVH, a whitish or pink elevated oral mucosal plaque or mass with an either verrucous or papillary surface, is a specific OPMD type in areas with a prevalence of betel quid chewing.[34] In a hospital-based follow-up study from southern Taiwan, the malignant transformation rate in a cohort of 869 male patients with OVH was estimated at 6.8%, with a mean duration of 33.5 months during follow-up of at least 1 year.[31] In this study, all patients with OVH were followed up for at least 5 years and 20% of them developed interval carcinomas, with a mean duration of 48.8 months, which is close to the 30% 5-year cancer development rate found in our earlier study.[35] Based on these OVH studies, the annual interval carcinoma rate sustainably increased over time, and patients with OVH should thus receive long-term follow-up.

Candida is a normal commensalism of microorganisms in the oral cavity that assumes various forms. The association of Candida with oral carcinogenesis had been reported for decades.[36] The role of Candida hyperplasia in OPMDs has been debated, and the risk of malignant development remains doubtful. Oral cancer has been found to supervene in 9% to 40% of Candida hyperplasia cases, compared with the 4.5% to 17.5% risk of malignant transformation for leukoplakias in general.[37] Because this study found a relatively high incidence of interval carcinoma in patients with Candida hyperplasia, the potential for malignancy cannot be ignored.

Refusal of surgery in many cancers has been studied extensively and may partially explain some disparities observed among certain demographic groups of patients with cancer. A number of risk factors have been identified, including concerns about adverse effects, underlying illness, poor support systems, financial situation, transportation problems, and alternative medicine use. A literature review indicates that few studies have explored the outcomes and risk factors for patients with OSCCs who refuse surgery.[38,39] Old age, lower socioeconomic status, poor family support, and advanced stages are common contributing factors of treatment refusal. However, some studies have indicated that older people have difficulty in understanding their disease, leading to depression and thereby contributing to refusal of surgery.[40] To the best of our knowledge, no studies have discussed the impact of surgery refusal on malignant development in patients with OPMDs. Our study indicated that patients with high-risk OPMDs, including both those who underwent and those who refused surgery, had poorer cancer-free survival than low-risk patients for whom surveillance was recommended. In general, treatment according to risk assessment using clinicopathological factors is appropriate for patients with OPMDs in betel quid–prevalent areas. Patients with high-risk OPMDs undergoing surgery had similar cancer-free survival to low-risk patients over 3 years, after which malignant development gradually increased. Therefore, clinician should increase their vigilance for patients with high-risk OPMDs, even when excision to remove the primary lesion has been performed.

Patients with OPMDs can be cured and enjoy a higher quality of life if diagnosed early, thus highlighting the importance of predicting malignant OPMD development before the onset of clinical symptoms. According to 12.4% rate of interval carcinoma in high-risk OPMDs, the judgment based on clinical and pathological features is practicable for categorization. Thus, the patients with high accumulation dose of betel quid–chewing, nonhomogeneous leukoplakia, OVH, or OSF with accompanying leukoplakia should not only undergo excision to detect occult carcinoma but also receive periodic follow-up for early detection of malignant development.

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