Second primary cancer after index head and neck squamous cell carcinoma in Northern China

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Objective. To evaluate the clinicopathologic features, prognostic factors, and management of patients in the North Chinese population with head and neck squamous cell carcinoma (HNSCC) who developed a second primary malignancy (SPM).

Methods. This was a retrospective study including 1818 eligible patients between June 1999 and April 2011.

Results. A total of 188 HNSCC patients developed SPM. Multiple oral dysplastic lesions (MODLs) ($P < .001$) were among the risk factors for occurrence of SPM. However, MODLs were closely associated with many mild pathologic features, such as early T stage ($P < .001$), early N stage ($P = .036$), good pathologic differentiation ($P < .001$), and mild growth pattern ($P < .001$). Interestingly, multivariate survival analysis showed that SPM patients had a better prognosis if they had the characteristics of MODLs ($P = .020$).

Conclusions. MODLs were a crucial risk factor leading to the occurrence of oral SPM after an index HNSCC in patients in Northern China. However, SPM patients with the characteristics of MODLs had a better prognosis. (Oral Surg Oral Med Oral Pathol Oral Radiol 2017;123:95-102)

Worldwide, approximately 635,000 new cases of head and neck cancer are diagnosed annually; more than 12% of these cases occur in China. Unfortunately, more than 76,000 patients with head and neck cancer die each year, and the majority of these patients have head and neck squamous cell carcinoma (HNSCC).[1] Today, second primary malignancy (SPM) is the leading cause of death for patients who experience long-term survival after an index HNSCC.[2] Therefore, clarification of the incidence rate, risk factors, and specific mortality for SPM is crucial to further improve the prognosis of patients with HNSCC in China.

Recent data from Europe and the United States show that most SPMs after an index HNSCC tumor are located in the head and neck, lung, or esophagus.[3] These epidemiologic data supported the concept of "field cancerization" as a reasonable interpretation of SPMs after HNSCC.[4] Recently, multiple oral dysplastic lesions (MODLs), especially the proliferative verrucous leukoplakia subtype, were also believed to be crucial factors for occurrence of SPM.[5] However, it is well known that HNSCC is an obviously heterogeneous disease that varies across many characteristics, including age, sex, ethnicity, region, diet, alcohol and tobacco use, tumor-node-metastasis (TNM) classification, histologic grade, treatment modality, prognosis, and so on.[2,6-8] Currently there is little high-level information about epidemiologic data, risk factors, or prognosis for patients with HNSCC in Northern China, which has a population of more than 600 million people, or approximately half the Chinese population.[9]

The aims of this retrospective study were to investigate the clinicopathologic features, prognostic factors, and management of SPM in the North Chinese population and describe our experience with this rare disease.

METHODS AND MATERIALS

Study population

This study was approved by the Institutional Review Board of the Beijing Stomatological Hospital and was conducted in accordance with the World Medical Association's Declaration of Helsinki (2002 version). We retrospectively reviewed the clinicopathological data of patients with HNSCC who were treated in the Department of Oral and Maxillofacial Head and Neck Oncology, Beijing Stomatological Hospital of Capital Medical University, from June 1999 through April 2011. Patients who met the following criteria were

Statement of Clinical Relevance

This study highlights evaluation of prognostic factors and management of second primary malignancy associated with head and neck squamous cell carcinoma.

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included in the study: (1) they had all been affected by a previously untreated HNSCC; (2) they had all undergone curative surgical therapy; and (3) the sites of the primary index HNSCC included the tongue, lower gingiva, buccal mucosa, floor of the mouth, oropharynx, upper gingiva, and hard palate. Finally, a total of 1818 eligible patients with HNSCC were included in this study. The cases were restaged according to the 2002 version of the Union for International Cancer Control/American Joint Committee on Cancer classification based on the initial clinical description and computed tomography (CT), magnetic resonance imaging, chest X-ray, flexible esophagogastroduodenoscopy, or positron emission tomography examination.

Definition of SPM, MODLs, and diffuse infiltration

SPM was first defined by Warren and Gates in 1932.[10] The latest criteria for SPM were modified by the National Cancer Institute as follows: SPM is defined as a metachronous, invasive, solid cancer developing $\geq$6 months after an index HNSCC.[11] Specifically, if the second cancer originated from a nonsquamous cell or developed in a different location, or if the SPM developed in the same region more than 5 years after the index cancer diagnosis, it is coded as SPM.

MODLs are defined as multifocal dysplastic lesions that occur on the oral mucosa and are known to be potentially malignant, including multifocal leukoplakia (e.g., proliferative verrucous leukoplakia), erythroplakia, erythroleukoplakia, and submucous fibrosis of the oral mucosa.[12,13]

Diffuse infiltration, a subtype of histologic signs of severity as described in our previous study, is defined as diffusely invasive growth of primary tumor cell observed under a microscope.[1]

Treatment and pathologic analysis

All patients were initially treated with surgery. The protocols for surgery, radiotherapy (RT), and concomitant chemoradiotherapy were consistent with our previous description.[7] For routine histopathologic analysis of primary tumors and neck dissection specimens, all primary tumors and each node section were placed in different groups and subjected to standard hematoxylin and eosin staining.[14]

Follow-up strategy

The patients were regularly followed up as described previously.[15] The patients underwent semiannual chest X-ray and other imaging examinations (ultrasonography, CT, magnetic resonance imaging, positron emission tomography/CT, and/or flexible esophagogastroduodenoscopy). If a recurrent or second primary or newly developed malignant lesion was suspected, other diagnostic modalities were utilized to confirm these lesions.

Statistical analysis

The follow-up study continued until April 1, 2016. Patients who were lost to follow-up within 1 year of surgery were excluded from the statistical analysis. The baseline demographic data between comparable subgroups were compared using the chi-square test for categorical variables and the t test for continuous variables. The primary outcome assessment parameter was 5-year disease-specific survival (DSS). Statistical significance was tested using the log-rank test. Univariate and multivariate analyses were used to identify the independent predictors of SPM and 5-year DSS. Independent prognosticators were identified by multivariate Cox regression analysis using the forward selection method. All tests were two-sided, and $P < .05$ was considered statistically significant. Statistical software (SPSS, version 17.0; Chicago, IL, USA) was used for all statistical analyses.

RESULTS

Patient characteristics

A total of 1818 cases of primary HNSCC between June 1999 and April 2011 were identified by retrospective retrieval from the database. The patient and tumor characteristics are summarized in Table I. The median follow-up time for patients with HNSCC was 66 months, and 277 patients (15.2%) were lost to follow-up. At the end of follow-up, 188 of the 1818 patients (10.3%) developed SPM, 1354 patients (74.5%) did not develop SPM, and the SPM status of 276 patients (15.2%) was unknown because of loss to follow-up. The median time until occurrence of SPM was 49 months after the first operation. Specifically, the cumulative incidence of SPM was 27.7% within 2 years, 31.4% at 2 to 5 years, and 41.0% beyond 5 years after the index tumor surgery. Of the seven primary subsites in the study, the hard palate (ratio of SPM/non-SPM = 6.4%/2.9%; 2.2) and buccal mucosa (ratio of SPM/non-SPM = 21.8%/14.3%; 1.5) had a relatively higher probability of developing postoperative SPM. Furthermore, SPM locations after index HNSCC were the oral cavity (n = 127, 67.6%), head and neck other than oral cavity (n = 7, 3.7%), lung (n = 9, 4.8%), esophagus (n = 17, 9.0%), breast (n = 5, 2.7%), uterus (n = 3, 1.6%), liver (n = 5, 2.7%), colorectum (n = 5, 2.7%), penis (n = 2, 1.1%), stomach (n = 4, 2.1%), and one each (0.5%) in the leg, gallbladder, kidney, and bladder. Notably, 32 of these patients experienced three to six primary cancers after

Table I. Baseline data of patients and second primary malignancies (SPMs) in the study

	Total (n = 1818)	*Non-SPM (n = 1354)*		*SPM (n = 188)*[*]		
Variable	*No. (%)*	*No.*	*%*	*No.*	*%*	P *value*
Age, years	59 (15-89)	58.8 ± 12.2		58.7 ± 11.3		.912
Gender						
Male	1077 (59.2)	809	59.7	98	52.1	.047
Female	741 (40.8)	545	40.3	90	47.9	
Site						
Tongue	675 (37.1)	534	39.4	56	29.8	.002
Lower gingiva	294 (16.2)	216	16.0	33	17.6	
Buccal mucosa	284 (15.6)	194	14.3	41	21.8	
Floor of the mouth	191 (10.5)	136	10.0	22	11.7	
Oropharynx	140 (7.7)	101	7.5	14	7.4	
Upper gingiva	174 (9.6)	134	9.9	10	5.3	
Hard palate	60 (3.3)	39	2.9	12	6.4	
T stage						
T1	439 (24.1)	328	24.2	61	32.4	.080
T2	687 (37.8)	512	37.8	72	38.3	
T3	201 (11.1)	144	10.6	18	9.6	
T4a	466 (25.6)	349	25.8	36	19.1	
T4b	25 (1.4)	21	1.6	1	0.6	
Pathologic Nodal status						
N0	839 (46.1)	623	55.2	93	64.1	.004
N1	305 (16.8)	230	20.4	35	24.1	
N2	371 (20.4)	274	24.3	17	11.8	
N3	2 (0.1)	2	0.1	0	0.0	
Nx (No ND)[*]	301 (6.6)	-	-	-	-	
Pathologic grade						
I	887 (48.8)	674	51.3	101	54.9	.194
II	777 (42.7)	565	43.0	78	42.4	
III	104 (5.7)	76	5.7	5	2.7	
Missing	50 (2.8)	-	-	-	-	
Growth pattern						
Exophytic	583 (32.0)	406	33.9	77	43.8	.033
Ulcerative	560 (30.8)	399	33.3	53	30.1	
Infiltrative	505 (27.8)	392	32.8	46	26.1	
Missing	170 (9.4)	-	-	-	-	
Smoking history						
Smoker	777 (42.7)	588	45.1	70	38.0	.073
Nonsmoker	980 (53.9)	717	54.9	114	62.0	
Missing	61 (3.4)	-	-	-	-	
Alcohol history						
Drinker	578 (31.8)	436	33.4	54	29.3	.272
Nondrinker	1179 (64.9)	869	66.6	130	70.7	
Missing	61 (3.4)	-	-	-	-	
Extracapsular spread						
Absence	301 (73.8)	255	75.0	27	84.4	.236
Presence	107 (26.2)	85	25.0	5	15.6	
Perineural invasion						
Absence	587 (82.3)	458	81.8	71	88.8	.124
Presence	126 (17.7)	102	18.2	9	11.2	
Vascular/lymphatic emboli						
Absence	697 (98.3)	546	98.0	80	100.0	.375
Presence	12 (1.7)	11	2.0	0	0.0	
Diffuse infiltration						
Absence	530 (74.8)	416	74.7	61	76.3	.763
Presence	179 (25.2)	141	25.3	19	23.7	
MODLs						
Absence	1614 (88.8)	1247	92.1	132	70.2	<.001
Presence	182 (10.0)	107	7.9	56	29.8	
Missing	22 (1.2)	-	-	-	-	

SPM, second primary malignancy; *SD,* standard deviation; *MODL,* multiple oral dysplastic lesion.
*The number of known SPM patients was 188.

an unfortunate SPM. Ultimately, of 188 patients who experienced SPM, 124 patients received surgical treatment, 27 patients received surgery plus adjuvant radiotherapy, 23 patients received palliative radiotherapy and/or chemotherapy, and the remaining 14 patients terminated therapy.

Multiple oral dysplastic lesions are a risk factor leading to SPM occurrence

By the chi-square test, close correlations were seen between the cumulative incidence of SPM and the following clinicopathological parameters: sex ($P = .047$), primary site ($P = .002$), pathologic nodal status ($P = .004$), growth pattern ($P = .033$), and MODLs ($P < .001$). However, there were no correlations between SPM and tobacco use ($P = .073$) or alcohol use ($P = .272$) in the study. Based on logistic regression analysis (forward method), the values of the associated factors (i.e., sex, primary site, pathologic nodal status, growth pattern, and MODLs) in predicting the development of SPM were further evaluated. MODLs (positive correlation, odds ratio: 4.563, 95% CI: 2.793-7.453, $P < .001$) and pathologic nodal status (negative correlation, odds ratio: 0.723, 95% CI: 0.563-0.930, $P = .012$) constituted risk factors for the occurrence of SPM.

MODLs are closely associated with more mild clinicopathologic features of HNSCC

Considering that MODLs were the only positive correlation factor resulting in SPM, we further analyzed the associations between MODLs and other clinicopathologic factors in 1796 of the 1818 patients whose MODL data were available. There were significant associations when occurrences of MODL were compared with regard to tumor and patient characteristics, including female sex ($P < .001$), buccal sites ($P = .012$), early T stage ($P < .001$), early N stage ($P = .036$), good pathologic differentiation ($P < .001$), mild growth pattern ($P < .001$), less tobacco use ($P < .001$), less alcohol use ($P < .001$), and less diffuse infiltration ($P = .025$), reflecting the heterogeneity of HNSCC across MODLs (Table II).

A total of 56 patients who developed SPM had previous MODL disease. In this subgroup, 31 patients (55.4%) had exophytic type (papillary architecture); 11 patients (19.6%) had ulcerative type; 13 patients (23.2%) had infiltrative type; and data were missing for 1 patient (1.8%). The SPM locations for patients with MODLs after an index HNSCC were the tongue (n = 12, 21.4%), lower gingiva (n = 12, 21.4%), buccal mucosa (n = 14, 25.0%), floor of the mouth (n = 5, 8.9%), oropharynx (n = 3, 5.4%), upper gingiva (n = 4, 7.1%), and hard palate (n = 6, 10.8%). Twenty-three patients developed multiple primary carcinomas, including third carcinoma (n = 17, 73.9%), fourth carcinoma (n = 4, 17.4%), and fifth carcinoma (n = 2, 8.7%). For treatment after the first recurrence, 19 patients received surgery alone and the remaining 4 patients received surgery plus adjuvant radiotherapy.

Survival analysis

During the follow-up period, 953 (52.4%) of the 1818 patients survived, 589 patients (32.4%) died, and 276 patients (15.2%) were lost to follow-up. Forty-seven patients died due to causes unrelated to cancer, including 22 patients who died of cardiac failure or cerebral stroke, 9 patients who died of multiple organ failure, 10 patients who died of respiratory failure, 2 patients who died of acute gastrointestinal haemorrhage, 1 patient who died of suicide, 2 patients who died of uncertain causes, and 1 patient who died of septicemia.

In the entire cohort, the 5-year DSS rate was 58.9%. Generally, there was no significant difference when comparing SPM patients with non-SPM patients in DSS (53.7% vs 66.4%, $P = .356$, Figure 1). However, Kaplan-Meier analysis showed that patients whose survival time was longer than 5 years experienced a sharp decrease in DSS rate if they developed SPM (from 97.0% to 68.8%, $P < .001$, Figure 1). Furthermore, patients with SPM located in the head and neck region compared to other sites had better DSS (head and neck SPM vs non−head and neck SPM: 63.4% vs 29.6%, $P < .001$, Figure 2).

As mentioned above, MODLs were a predisposing factor for the development of SPM, and HNSCC patients showed obvious heterogeneity of MODLs. The association between MODL status and prognosis was further analyzed. Interestingly, Kaplan-Meier analysis found that HNSCC patients with previous MODLs (74.8%) had better DSS than those without MODLs (63.7%) ($P < .001$, Figure 3).

HNSCC patients with SPM had a better prognosis if they had the characteristics of MODLs

To evaluate high-risk factors for a poor prognosis for SPM patients, the baseline data served as covariates and were analyzed using Cox proportional hazards regression models. A univariate analysis of the 188 SPM patients showed that sex ($P = .001$), T stage ($P < .001$), pathologic nodal status ($P = .001$), pathologic grade ($P = .002$), tobacco use ($P < .001$), alcohol use ($P < .001$), and no history of MODLs ($P = .032$) were high-risk prognostic factors for determining the DSS of SPM patients. A further multivariate survival analysis showed that alcohol use (hazard ratio [HR]: 2.874, 95%

Table II. Associations between multiple oral dysplastic lesions (MODLs) and clinicopathologic factors in the study (MODLs known [n = 1796][*])

	Patients without MODLs (n = 1614)		*Patients with MODLs (n = 182)*		
Variable	*No.*	*%*	*No.*	*%*	P *value*
Sex					
Male	986	61.1	75	41.2	<.001
Female	628	38.9	107	58.8	
Site					
Tongue	592	36.7	75	41.2	.012
Lower gingiva	268	16.6	23	12.6	
Buccal mucosa	138	14.7	41	22.5	
Floor of the mouth	177	10.0	11	6.0	
Oropharynx	130	8.1	8	4.4	
Upper gingiva	157	9.7	16	8.8	
Hard palate	52	3.2	8	4.4	
T stage					
T1	353	21.9	83	45.6	<.001
T2	618	38.3	66	36.3	
T3	182	11.3	14	7.7	
T4a	438	27.1	18	9.9	
T4b	23	1.4	1	0.5	
Pathologic Nodal status					
N0	756	54.3	70	68.6	.036
N1	284	20.4	16	15.7	
N2	351	25.2	16	15.7	
N3	2	0.1	0	0.0	
Pathologic grade					
I	741	47.3	137	76.1	<.001
II	730	46.6	40	22.2	
III	97	6.1	3	1.7	
Growth pattern					
Exophytic	484	33.4	93	52.2	<.001
Ulcerative	505	34.9	46	25.8	
Infiltrative	459	31.7	39	21.9	
Smoking history					
Smoker	722	46.4	41	22.9	<.001
Nonsmoker	834	53.6	138	77.1	
Alcohol history					
Drinker	543	34.9	28	15.6	<.001
Nondrinker	1013	65.1	151	84.4	
Diffuse infiltration					
Absence	480	73.6	48	87.3	.025
Presence	172	26.4	7	12.7	

*Of all 1818 patients, the number of cases with multiple oral dysplastic lesions was 1796.

CI: 1.743-4.737, $P < .001$), high pathologic grade (HR: 1.755, 95% CI: 1.270-2.426, $P = .001$), and no history of MODLs (HR: 0.430, 95% CI: 0.211-0.876, $P = .020$) were independent prognostic factors for worse DSS in SPM patients. That is, HNSCC patients with SPM had a better prognosis if they had the characteristics of MODLs (Table III).

Prognostic scoring of risk factors and screening of high-risk populations

Prognostic scoring of risk factors for DSS included alcohol use, high pathologic grade, and no history of MODLs. In this study, each risk factor for SPM identified as an independent prognosticator in survival analysis (alcohol use, high pathologic grade, and no history of MODLs) was given a score of 1. The DSS rate differed significantly between patients with a score of 0 (61.4%) and a score of 1 (47.7%) or ≥2 (42.9%). Therefore, patients with a score of 1 or ≥2 were identified as the high-risk population for DSS, and those with a score of 0 were identified as the low-risk population.

Surgery-based salvage treatment for resectable SPM patients could result in good outcomes

By further analysis between prognosis and different treatments in the low-risk population (score of 0), we found that patients with SPM who underwent surgery alone had a similar DSS to those who underwent surgery + RT (69.4% vs 77.8%, $P = .678$, Figure 4). In the high-risk population (score of 1 or ≥2), the patients

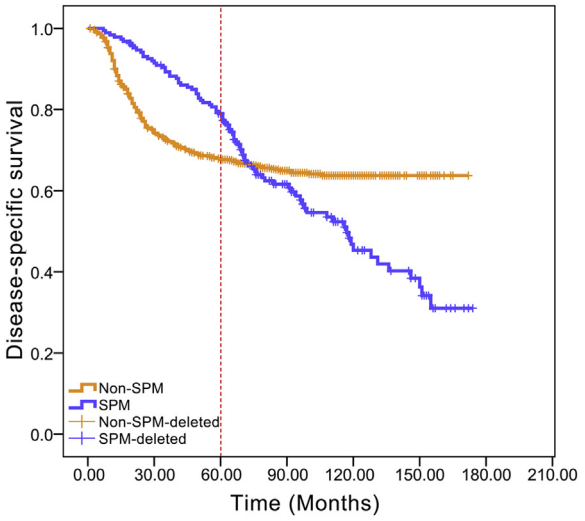

Fig. 1. The survival curve between second primary malignancy (SPM) and non-SPM groups for head and neck squamous cell carcinoma (HNSCC) patients.

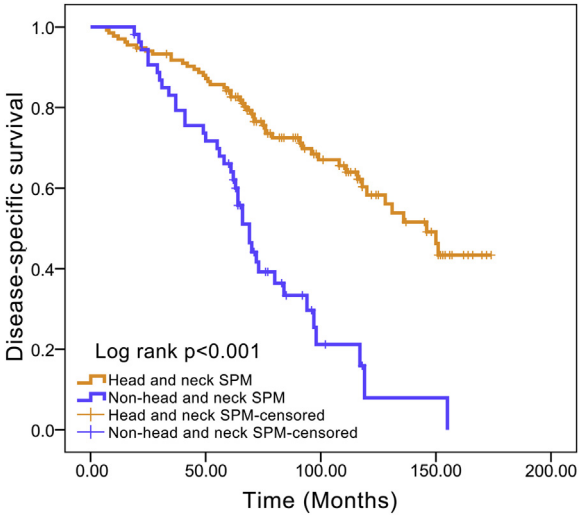

Fig. 2. The survival curve of second primary malignancy (SPM) patients between cases in the head and neck region and those not in the head and neck region.

who underwent surgery alone also had a DSS similar to those who underwent surgery + RT (59.7% vs 55.6%, $P = .647$, Figure 4). In contrast, patients who underwent only palliative radiotherapy/chemotherapy or who stopped therapy had a less favorable DSS regardless of whether they were in the low-risk or high-risk population, but especially if they were in the high-risk population (low-risk vs high-risk: 23.5% vs 0.0%, marginal difference found, $P = .087$, Figure 4). The results showed that surgical salvage treatment for resectable SPM patients could result in a good outcome, regardless of high-risk or low-risk score and whether they accepted adjuvant radiotherapy.

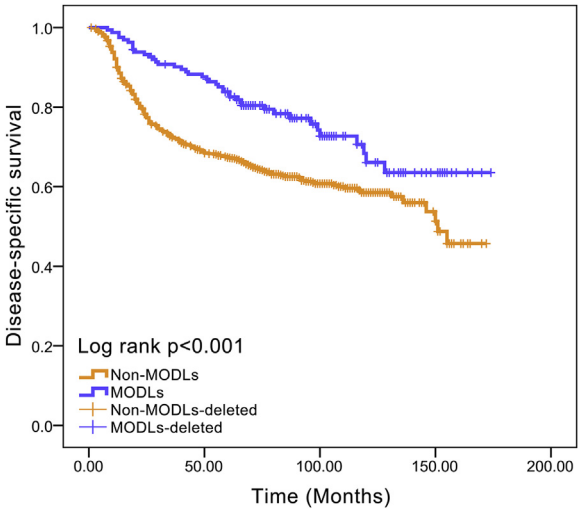

Fig. 3. The survival curve of head and neck squamous cell carcinoma (HNSCC) patients according to presence or absence of previous multiple oral dysplastic lesions (MODLs).

Table III. High-risk factors for disease-specific survival (DSS) among head and neck squamous cell carcinoma (HNSCC) patients who experienced second primary malignancy (SPM)

Variable	*Hazard ratio*	*95% Confidence interval*	P *value*
Univariate analysis			
Sex (male vs female)	0.471	0.303-0.732	.001
T stage (T1, T2, T3, T4a, T4b)	1.453	1.196-1.765	<.001
pN (N0, N1, N2, N3)	1.373	1.131-1.667	.001
Pathologic grade (I, II, III)	1.680	1.218-2.318	.002
Tobacco habit (absence vs presence)	2.296	1.487-3.546	<.001
Alcohol habit (absence vs presence)	2.774	1.789-4.302	<.001
Multiple oral dysplastic lesions (MODLs) (absence vs presence)	0.578	0.350-0.954	.032
Multivariate survival analysis			
Alcohol habit (absence vs presence)	2.874	1.743-4.737	<.001
Pathologic grade (I, II, III)	1.755	1.270-2.426	.001
MODLs (absence vs presence)	0.430	0.211-0.876	.020

DISCUSSION

Although diagnosis and treatment techniques have greatly improved in the past three decades, the prognosis for HNSCC patients remains poor.[1] SPM has become the chief culprit that threatens long-term survival.[16] The objective of this study was to evaluate the clinicopathologic features, prognostic factors, and management of patients in the North Chinese

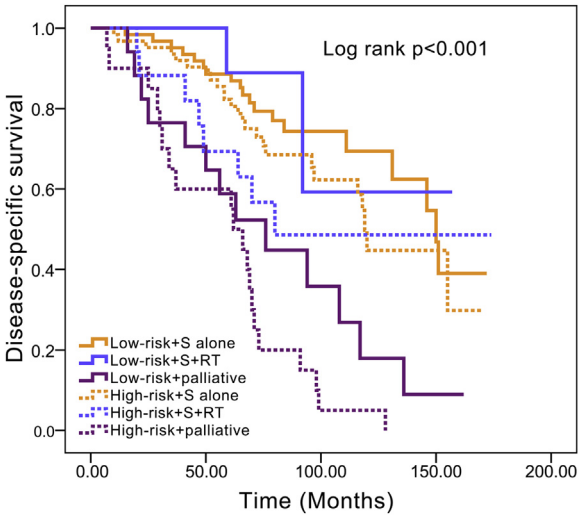

Fig. 4. The survival curves of low-risk and high-risk patients who developed second primary malignancy (SPM) and received different management (surgery alone vs surgery + radiotherapy vs palliative or terminated therapy).

population with HNSCC who developed SPM. The results of our study showed that patients whose survival time was longer than 5 years experienced a sharp decrease in DSS rate if they developed SPM, and the occurrence of SPM was closely associated with MODLs. Interestingly, the presence of MODLs was associated with a better prognosis for SPM patients, and only surgery-based salvage treatment for resectable SPM patients could result in good outcomes.

In this study, the occurrence of SPM was closely associated with MODLs, consistent with the theory of field cancerization. Because betel quid chewing is rare in North China, the pathogenesis, clinicopathologic features, and prognosis of HNSCC are significantly different from those of patients in Southern Asia.[17] Currently, the tobacco/alcohol-related field cancerization theory has been widely accepted as explaining the incidence of SPMs in non−betel quid-chewing areas.[13] A study by Hamadah et al. showed that approximately 3-24% of patients with multiple primary malignancy had a medical history of oral precancerous lesions.[13,18] Tobacco and alcohol habits have been widely identified as major etiologic factors in the populations of Western and Southern Asian countries.[19-21] However, these habits were not closely correlated with SPM in the Northern Chinese population, perhaps because half of the SPM patients in the study were female and had never been exposed to tobacco or alcohol.

Our results showed that alcohol habit, pathologic grade, and MODLs were factors closely correlated with the prognosis of SPM patients. Of these three factors, the presence of MODLs was the sole positive factor predicting better survival, which could be explained by MODLs being closely associated with mild clinicopathologic features in HNSCC patients, such as early T or N stage, good pathologic differentiation, mild growth pattern, less diffuse infiltration, and so on. Additionally, this importance was attributed to the more superficial nature of the lesions in patients with MODLs, stricter follow-up frequency, and stronger cancer-prevention awareness.[12] Therefore, the presence of MODLs was associated with a better prognosis for SPM patients. These results were consistent with Akrish's conclusions, which demonstrated that MODLs presented with significantly better prognostic factors and short-term survival rates and longer duration of disease.[22]

Some recent studies have shown that the burden of SPM is high in patients with HNSCC, with more than 168 second solid tumors developing per 10,000 person-years at risk,[2] and a comparison between the prognosis of SPMs located in the head and neck region and those not in the head and neck region found that the former had better outcomes than the latter.[16] Those results were similar to our results. However, our study found that the head and neck region, especially the oral cavity, was the most common subsite involved in SPM. The results were different from the study of Birkeland et al.,[16] who reported that almost three-quarters of SPMs are located outside the head and neck region. However, survival analysis has demonstrated that patients whose survival time was longer than 5 years experienced a sharp decrease in DSS rate if they developed SPM. The results further indicated that SPM was the leading cause of death for patients with HNSCC who experienced long-term survival.[2]

Based on analysis of different risk populations, surgery-based salvage treatment for resectable SPM patients could also result in a good prognosis. This conclusion was the same as the viewpoint of Strojan et al.: "Whenever feasible, salvage surgery is the method of choice for curative intent; patients at high risk for local recurrence should be advised that post-operative radiotherapy or re-radiotherapy is expected to increase locoregional control at the expense of higher toxicity and without survival advantage compared to salvage surgery alone."[23] Therefore, we recommend that HNSCC patients who experience SPM should adopt an aggressive management strategy.

This study was retrospective and thus had inherent limitations. It could also be criticized for a lack of data about some important baseline factors, including severity of tobacco and alcohol exposure, depth of invasion, and tumor thickness. These limitations will be further considered in future studies. However, because large sample sizes have been analyzed and different variables evaluated, some generalizations are possible.

CONCLUSIONS

MODLs were a crucial risk factor leading to the occurrence of SPM after an index HNSCC in patients in Northern China. However, SPM patients with MODLs had a better prognosis. For HNSCC patients who develop SPM, an aggressive surgery-based strategy of management should be recommended if the SPM is resectable.

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