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Clinicopathological risk factors of oral second primary tumours

Jelena Karan[a,*], **Miriam P. Rosin**[b,c], **Lewei Zhang**[a], **Denise M. Laronde**[a,b]

[a]Faculty of Dentistry, University of British Columbia, 2199 Wesbrook Mall, Vancouver, BC, Canada, V6T1Z3

[b]Cancer Control Research, British Columbia Cancer Agency, 675 W10th Avenue, Vancouver, BC, Canada, V5Z 1L3

[c]Department of Biomedical Physiology and Kinesiology, Simon Fraser University, 8888 University Dr, Burnaby, BC, Canada, V5A 1S6

Abstract

Background: Oral second primary tumours (SPTs) have a poor prognosis due to late-stage diagnosis. This study evaluates the demographic and clinicopathological risk predictors of SPTs.

Methods: Patients with oral squamous cell carcinoma, carcinoma in situ, or severe dysplasia were accrued into the Oral Cancer Prediction Longitudinal study within one year post-curative treatment. Data on demographics, risk habits, and primary tumour characteristics were collected. Clinical follow-up included assessing the presence of second oral premalignant lesions (SOPLs), clinicopathological features, and the results from toluidine blue staining and fluorescence visualization.

Results: Among 296 patients, 23 (8 %) developed SPTs. Older age at primary cancer diagnosis ($P = 0.008$) and a history of chewing tobacco or betel nut ($P = 0.043$) increased the risk of SPTs. Patients with primary tumours located at low-risk sites had an increased risk of SPTs ($P = 0.004$), which often presented at high-risk sites. The presence of SOPLs ($P < 0.001$), and multiple lesions ($P = 0.017$) significantly increased the risk of SPTs. Positive toluidine blue staining indicated a trend toward higher risk of SPTs, whereas fluorescence visualization did not. The median time to SPT diagnosis was 3.25 years post-treatment.

Conclusions: Identifying second or multiple oral premalignant lesions is critical for predicting the risk of SPTs regardless of their clinical or histological characteristics. Routine biopsy of these

*Corresponding author. jelena.karan@dentistry.ubc.ca (J. Karan).

CRediT authorship contribution statement

Jelena Karan: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft. **Miriam P. Rosin:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. **Lewei Zhang:** Data curation, Funding acquisition, Resources. **Denise M. Laronde:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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lesions should be prioritized to ensure timely diagnosis. Incorporating these risk predictors into clinical follow-up can enhance early cancer detection and improve patient outcomes.

Keywords

Oral cancer; Head and neck cancer; Squamous cell carcinoma; Second primary cancer; Risk factors; Tobacco use; Betel nut; Toluidine blue; Biopsy

1. Introduction

The global five-year survival rate for oral squamous cell carcinoma (OSCC) is around 50 %, primarily due to late-stage diagnosis and the high risk of second oral malignancies (SOMs) [1–4]. SOMs include tumour recurrences at the same anatomical site and second primary tumours (SPTs), which develop more than 3 cm from the primary tumour [5]. Recurrence and SPTs are key factors affecting survival in head and neck cancer patients, with recurrence rates of 10–30 % and SPT rates of 2–30 % [2,3,6–9]. Despite advances in treatment and screening using adjunctive tools such as toluidine blue (TB) and fluorescence visualization (FV), incidence rates have seen little improvement, highlighting the need to identify reliable clinical risk factors [2, 10–12].

Previous studies have validated clinicopathological risk factors associated with the progression of primary oral premalignant lesions (OPLs) to oral cancer. These include lifestyle factors such as tobacco and alcohol consumption, clinical characteristics such as lesion site, size, and clinical appearance, and histological features including the degree of dysplasia [2,6,13–17]. Positive TB staining has also been associated with an increased risk of progression [11,18]. In addition, clinical factors associated with recurrence include the presence of a lesion at any follow-up point and TB positivity [19]. While relying on these clinical factors is valuable in follow-up after primary tumour treatment, one reason for the high rate of SPTs may be the lack of evidence on the specific predictors for SPT progression.

This study aimed to determine the clinical risk factors associated with SPT development in patients treated with curative intent for a primary oral malignancy. This is the first study of the clinicopathological indicators of second oral premalignant lesions (SOPLs) and SPTs. Identifying these high-risk features is crucial for early intervention, overall survival, and building a framework for future research to improve patient surveillance protocols.

2. Materials and methods

2.1. Study design

The study included consented participants from the ongoing province-wide prospective British Columbia Oral Cancer Prediction Longitudinal study, with ethics approval from the University of British Columbia and the British Columbia Cancer Agency (H98–61224). This analysis focused on a sub-group enrolled between January 1, 1999 and December 31, 2012. Patient eligibility criteria included: 1) 18 years or older diagnosed with severe dysplasia, carcinoma-in-situ (CIS), or OSCC (referred to as the primary tumour) without a previous oral cancer; 2) curative intent treatment with surgery, radiotherapy or a combination

of both within six months of diagnosis; 3) study accrual, informed consent, and clinical follow-up within the first year post-treatment; and 4) availability of pathology reports, patient charts and images for review. Patients who developed synchronous primary tumours, tumour recurrence, or multiple tumours at the primary site were excluded.

An SPT was defined as a severe dysplasia, CIS or OSCC located 3 cm or more away from the primary tumour site within the oral cavity. Patients with severe dysplasia were included as severe dysplasia and CIS are analogous in pathology and progression [20]. Diagnosis of SPT was confirmed by the British Columbia (BC) Cancer Registry, marking the study endpoint. Patients without an SPT were referred to as no-SPT patients, with the time to endpoint being the duration from the last day of treatment to SPT diagnosis, death, or last follow-up.

Post-treatment follow-up occurred every three months for two years, then every six months until SPT diagnosis or last follow-up. Initial visits were scheduled between 2 and 12 months post-treatment; visits within two months were excluded from analysis due to treatment-related oral mucosal changes. Data collected included: 1) demographics: date of birth, gender, ethnicity, and age at primary tumour diagnosis; 2) risk habits: tobacco and alcohol use, chewing tobacco or betel nut; 3) primary tumour information: diagnosis, site, TNM stage, histological grade, and treatment; 4) clinicopathological examination: lesion presence, characteristics (site, size, margin, colour, appearance and texture), and results of TB staining and FV (VELscope®, Burnaby, BC). Follow-up visits included updates on risk habits, clinical data, and biopsy results. The BC Cancer Registry provided the date and cause of death for patients who died during follow-up.

2.2. Statistical analysis

Statistical analysis determined associations between endpoints (SPT or no-SPT) and independent variables using Pearson's chi-squared, Fisher's exact, Mann-Whitney U, and unpaired t-tests. Survival analysis was conducted with Kaplan-Meier and log-rank tests. Cox regression was used to calculate hazard ratios (HR) with 95 % confidence intervals. All the tests were two-sided, with $P < 0.05$ considered statistically significant. Analyses were performed using the SPSS software (SPSS Inc., Chicago, Illinois).

3. Results

Of the 296 patients who met the eligibility criteria, 23 (8 %) developed an SPT: seven (30 %) were diagnosed with severe dysplasia or CIS, and 16 (70 %) were OSCC. One (4 %) SPT was synchronous (diagnosed within six months of the primary tumour), while the rest were metachronous. Among the 23 SPTs, six (26 %) developed on high-risk sites (tongue or floor of mouth), while 14 (61 %) occurred on low-risk sites (tonsil, lips, mandibular or maxillary gingiva/alveoli, buccal mucosa, soft palate and retromolar trigone). SPTs that formed included those that progressed from SOPLs or de novo occurrences. Fourteen (61 %) were de novo: nine formed without preceding SOPLs recorded, and five developed at a distinct site from the SOPL being followed. Nine out of 23 (39 %) SPTs progressed from SOPLs.

3.1. Demographics and risk habits

The distribution of SPT cases according to demographic variables and risk habits is presented in Table 1. Patients developing SPTs were, on average, seven years older at primary OSCC diagnosis compared to no-SPT patients (P = 0.008). Notably, all patients who developed an SPT were over 40 years old at primary diagnosis. Gender and ethnicity were not associated with the development of an SPT.

There were no correlations found between tobacco and alcohol use and SPT development. Although a greater proportion of continuing smokers developed an SPT, the results did not achieve statistical significance. Approximately two-thirds of all patients reported a history of smoking tobacco, of whom 40 % reported exposure to over 20 pack-years. Also, a large proportion of patients (81 %) had a history of alcohol use. Interestingly, 18 patients (6 %) had a history of chewing tobacco or betel nut, with this subgroup exhibiting nearly a four-fold higher risk of developing SPTs than non-users of smokeless tobacco products (P = 0.043).

3.2. Primary tumour characteristics

Primary tumour site and treatment modality were associated with SPT development (Table 2). Patients with primary tumours located at low-risk sites (18 %) had a four-fold higher risk of developing an SPT than those on high-risk sites such as the tongue and floor of the mouth (5 %) (P = 0.004). Patients who were treated solely with radiation for their primary tumour had a greater proportion of SPTs (20 %) compared to those who received only surgery (6 %), or a combination of radiation and surgery (9 %) (P = 0.017). Further analysis indicated that patients who received only radiation had more than a four-fold risk of SPT development than those who only received surgery (P = 0.009). It is noteworthy that in this study, radiation therapy was mainly administered for more advanced stage and grade oral cancers (P < 0.001 and P = 0.004, respectively – Supplementary Material Table 1). However, primary tumour stage and grade were not associated with SPT development.

3.3. Clinicopathological factors

In the first year of follow-up (Table 3), 50 patients (18 %) developed an SOPL, while 14 patients (5 %) developed multiple lesions. Patients with an SOPL exhibited a four-fold higher risk of SPT development (20 %) compared to those without an SOPL (6 %) (P = 0.003). Similarly, patients with multiple lesions had a 5.5-fold increased risk of SPTs compared to those without lesions (P = 0.017). Figs. 1 and 2 illustrate the cumulative probability of SPT development. At the end of the first year, 40 patients had an SOPL, of whom seven (18 %) developed an SPT (P = 0.003). Additionally, two (22 %) of the nine patients with multiple lesions developed an SPT (P = 0.010). However, no association was found between the clinical characteristics (site, size, margin, colour, appearance, texture, and TB and FV results) of the SOPL and SPT development. Further analysis of clinicopathological data from the second through seventh year of follow-up was conducted. However, due to a small sample size during these years, the investigation lacked statistical power and the results were not included.

The presence of a SOPL at any point during follow-up ("ever"), after primary tumour treatment and preceding SPT diagnosis, significantly correlated with SPT development (Table 3). Of 280 available cases, 67 patients (24 %) had a recorded SOPL with clinical data, among which 28 patients (42 %) retained their lesion for over one year. Significantly, 14 SOPLs (21 %) progressed to an SPT, compared to nine SPTs (4 %) that developed without an apparent lesion present. The presence of a SOPL increased the risk of an SPT by nearly six-fold ($P < 0.001$). Additionally, patients with persisting SOPLs for over one year showed a trend toward a higher proportion of SOPLs progressing to SPTs, versus those with lesions lasting one year or less (22 % versus 7 %, $P = 0.065$). Fig. 3 illustrates the cumulative probability of developing an SPT from the ever-present SOPLs, highlighting their significant role as a risk predictor for SPT development ($P < 0.001$).

Clinical characteristics of ever-present SOPLs did not demonstrate an association with SPT development, likely attributed to the limited statistical power due to the small sample size. However, a considerable trend indicated that changes in the TB status of SOPLs during follow-up were associated with SPT development. More than three-quarters of the SOPLs were always TB-negative (76 %), while 17 % exhibited varied TB results, and only 7 % were always TB-positive. Notably, 50 % of the always positive SOPLs progressed to SPTs, while 40 % of those with varying TB status and 9 % of the always negative TB status progressed ($P = 0.088$). Limited data on temporal change in FV status precluded further analysis. Interestingly, SOPLs that were always FV positive in follow-up progressed to SPTs (12.5 %).

3.4. Histological results

Biopsies of SOPLs during follow-up were limited. In the first year of follow-up, 24 of the 50 SOPLs (48 %) were biopsied. Among these, 10 (42 %) showed no evidence of dysplasia, six (25 %) had mild dysplasia and eight (33 %) had moderate dysplasia. Analyzing SOPLs ever-present, 39 of 67 (58 %) lesions underwent biopsy. Among these, 17 (43.5 %) showed no signs of dysplasia, seven (18 %) had mild dysplasia, and 15 (38.5 %) displayed mild and moderate dysplasia. Nearly twice as many low-grade dysplasias progressed to SPTs compared to those without dysplastic features (32 % versus 18 %). A further examination of patients who underwent biopsy versus those who did not, showed no differences in demographic data, lifestyle factors, primary tumour characteristics or SPT development, suggesting no biases between the groups.

3.5. Endpoint

There were no significant differences in follow-up duration between patients with or without SPTs. The median time from treatment completion to an SPT was 39 months (range 3–158 months), compared to 44 months (range 2–155 months) for those without SPTs ($P = 0.819$).

During follow-up, 57 patients (19 %) died, with causes including oral cancer (9 %), other cancers (4 %), and other systemic diseases or unknown causes (6 %). Among the deceased, 5 % had severe dysplasia or CIS, about 19 % had stage I or II OSCC, and 36 % had stage III or IV OSCC ($P < 0.001$) as their primary cancer. Mortality was 20 % for well/moderately differentiated tumours and 41 % for poorly differentiated tumours ($P < 0.001$). Among the

surviving patients, 19 (8 %) developed an SPT. Of these, 6.5 % had high-grade dysplasia, 8 % had early-stage OSCC, and 4 % had late-stage OSCC as their primary cancer. No patients with poorly differentiated tumours developed an SPT. Notably, those with poorly differentiated primary tumours had the highest mortality rate (18 % from oral cancer and 23 % from other causes), likely succumbing to the disease or comorbidities before an SPT developed. Refer to Supplementary Material Table 2 and Figs. 1–4 for additional details.

4. Discussion

Clinicopathological risk factors of SPTs have not been previously identified. While clinicians rely on the risk factors associated with the progression of primary OPLs to guide early intervention for SOPLs, there is a need to identify the unique risks associated with SPTs. This could help decrease their incidence, reduce patient morbidity, and improve long-term survival rates [3,10]. This is the first study to investigate predictors of SPT risk in a longitudinal setting.

The overall incidence of oral SPTs in this study is 8 % (about 1 % for synchronous, and 7 % for metachronous SPTs), mirroring findings from other reports which range from 2 to 30 % [3,6–9]. The majority (74 %) of SPTs occurred on low-risk sites and tonsils, with almost two-thirds (61 %) being de novo (no preceding SOPL present). These findings suggest that patients with a history of oral cancer are at a high risk of developing additional mucosal changes and that all areas of the head and neck region should be monitored closely. Identifying risk factors unique to the development of SPTs enables the early detection and treatment of secondary premalignant or malignant lesions, potentially improving patient outcomes.

4.1. Patient and primary tumour characteristics

Several demographic and risk habit factors were identified as associated with the development of an SPT. Patients who developed an SPT were diagnosed with primary oral cancer at a mean age of 66 years old, which was seven years older than those who did not develop an SPT. With an average time to SPT of just over three years, patients were typically about 69 years old at SPT diagnosis. This higher incidence of SPTs in older individuals may be attributed to field cancerization, pro-longed exposure to risk habits such as tobacco and alcohol, and declining immune function [3,6,17,21,22]. While alcohol and tobacco use, both independently and in combination, have been associated with the progression of primary OPL to cancer and the development of SOPLs and SOMs [1,13,23–26], this study did not find statistically significant associations between these risk factors and SPT development. However, the use of smokeless tobacco, including chewing tobacco and/or betel nut, was associated with an increased risk of SPT development. Given the potential links between these risk habits and the development of SOPLs or SPTs, promoting immediate cessation of these habits in oral cancer patients is crucial.

Primary tumour site and treatment modality were found to be associated with SPTs. While most primary tumours occurred on high-risk sites, such as the floor of the mouth and ventrolateral tongue, the most common sites for SPT development were low-risk sites. However, if the primary tumour occurred on a low-risk site, patients were at a significantly

greater risk of developing an SPT. Literature suggests that lesions at high-risk sites have a higher rate of malignant transformation [1], and hence the site availability makes it more vulnerable to form an SPT. Additionally, patients who underwent radiation therapy alone or in combination with surgery had a greater risk of developing an SPT compared to those who underwent surgery alone. It is noteworthy that radiation therapy is typically used for managing advanced-stage and high-grade oral cancers [27]. While early-stage disease surgery or radiation alone is effective, the combination of surgery and postoperative radiation is often recommended for late-stage tumours or cases where surgical margins are positive for malignancies [27]. This combined approach helps address the broader field of cancerization and the likelihood of a SOPL and subsequent SPT development by eliminating more genetic alterations within the field [5,6,22].

4.2. Clinicopathological characteristics

Not surprisingly, patients with a history of oral cancer exhibited a higher risk of developing an SOPL compared to the general population's 1–8% risk of a primary OPL [1,21]. The notably higher incidence of SOPLs observed in this study suggests that risk factors contributing to primary oral cancer may also influence SOPL occurrence. These findings align with studies indicating that field cancerization in the oral mucosa increases the risk of developing secondary tumours [5,6,9].

Clinical observations of visible lesions have been fundamental in identifying potential oral cancers, with characteristics like lesion margins, colour, appearance, texture, size and site associated with increased progression risk [1,2,10,15]. However, despite the importance of these clinical observations, risk factors were not predictive of progression in this study. The mere presence of an SOPL increased the risk of an SPT, and multiple lesions further amplified this risk.

TB staining and FV have also proven valuable in visualizing primary OPLs and predicting both primary and secondary malignancy [11,12, 18–20,28,29]. Although TB positivity did not correlate with SPT progression in this study, consistently TB-positive SOPLs should be closely monitored, as the limited TB data available may have affected the results. Given the elevated risk associated with any SOPL, close surveillance and consideration for biopsy remain essential.

It is also important to consider how dysplastic changes in SOPLs might influence outcomes, as research suggests that the risk of malignant transformation increases with the grade of dysplasia in OPL [17, 30]. In this study, lesions with low-grade dysplasia showed about double the progression to SPTs compared to non-dysplastic lesions, although the limited biopsied SOPLs prevented these differences from reaching statistical significance. Despite this limitation, the most noteworthy finding was the need to increase biopsy frequency. New lesions should be biopsied upon appearance to determine a histopathological diagnosis and re-biopsied at two-year intervals to facilitate early detection and monitor progression [15].

Furthermore, the median time to SPT diagnosis was 39 months (approximately three years post-treatment), which aligns with research indicating a median time of 37 months for SPT development in head and neck cancer patients [7]. This further emphasizes the critical

importance of long-term surveillance in OSCC management, as the risk of developing SPTs persists several years after initial treatment.

5. Conclusion

Early detection is key for improving patient survival, emphasizing the need for vigilant post-treatment surveillance for SOMs. This study highlights that any new lesion in patients with a history of oral cancer should be taken seriously due to its high risk for SPT development, regardless of its clinical or histological characteristics. Prompt biopsy and careful monitoring, especially for patients with multiple lesions, are critical due to their increased risk of progression. With the median time to SPT diagnosis being approximately three years post-treatment, sustained long-term follow-up is essential. Further research is needed to better understand the complex interplay between patient habits, tumour characteristics, treatment modalities, and clinical outcomes, with the ultimate goal of enhancing survival rates and patient care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

OSCC	Oral squamous cell carcinoma
SOM	Second oral malignancy
SPT	Second primary tumour
TB	Toluidine blue
FV	Fluorescence visualization
OPL	Oral Premalignant Lesion
SOPL	Second Oral Premalignant Lesion
CIS	Carcinoma-in-situ
BC	British Columbia

HR Hazard Ratio

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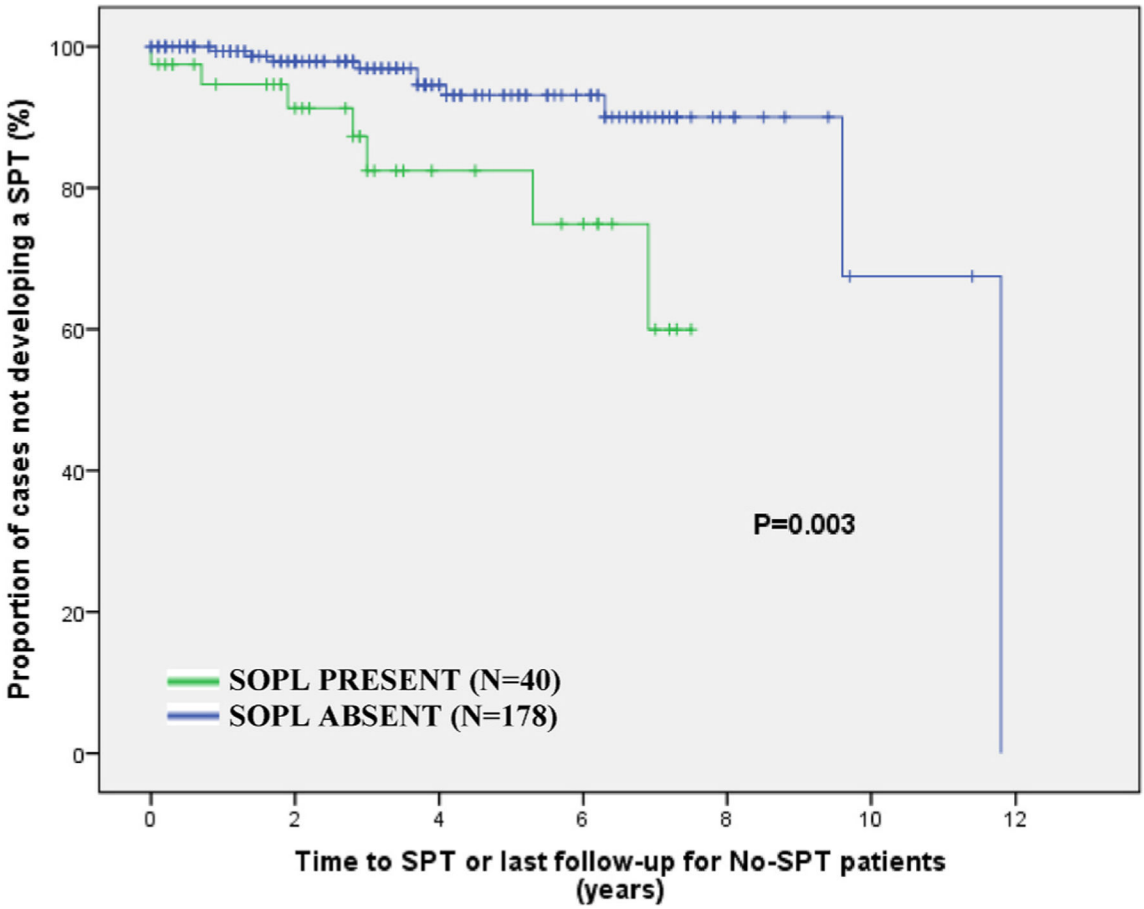

Fig. 1.

Cumulative probability of developing a second primary tumour (SPT) within the first year of follow-up, based on the presence (N = 40) or absence (N = 178) of a second oral premalignant lesion (SOPL) in the total sample (N = 218). At the end of the first year, seven patients (18 %) with an SOPL developed an SPT, compared to 10 patients (6 %) without an SOPL (P = 0.003), indicating a significantly higher risk of SPTs in patients with SOPLs.

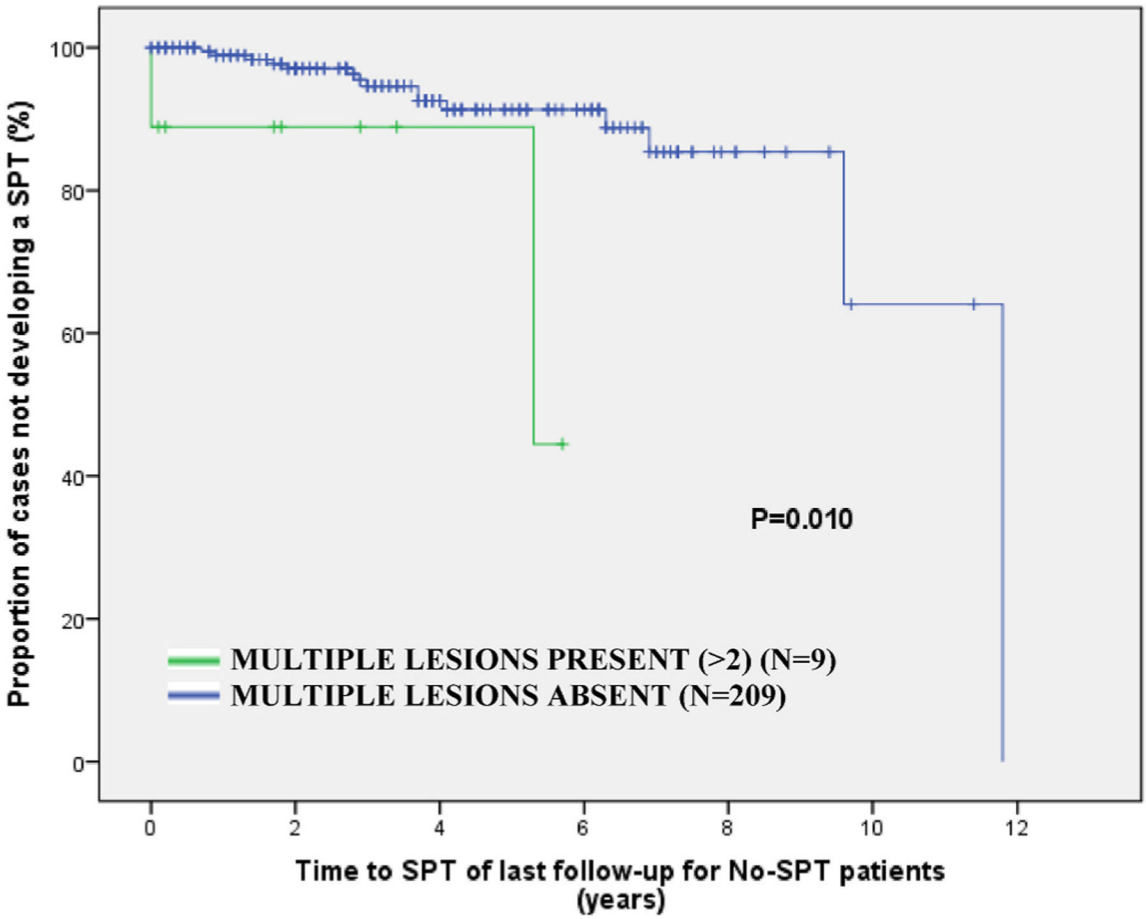

Fig. 2.

Cumulative probability of developing a second primary tumour (SPT) within the first year of follow-up, based on the presence (N = 9) or absence (N = 209) of a second oral premalignant lesion (SOPL) in the total sample (N = 218). At the end of the first year, two patients (22 %) with more than two lesions developed an SPT, compared to 15 patients (7 %) without multiple lesions (P = 0.010), indicating a significantly higher risk of SPT development in patients with multiple lesions.

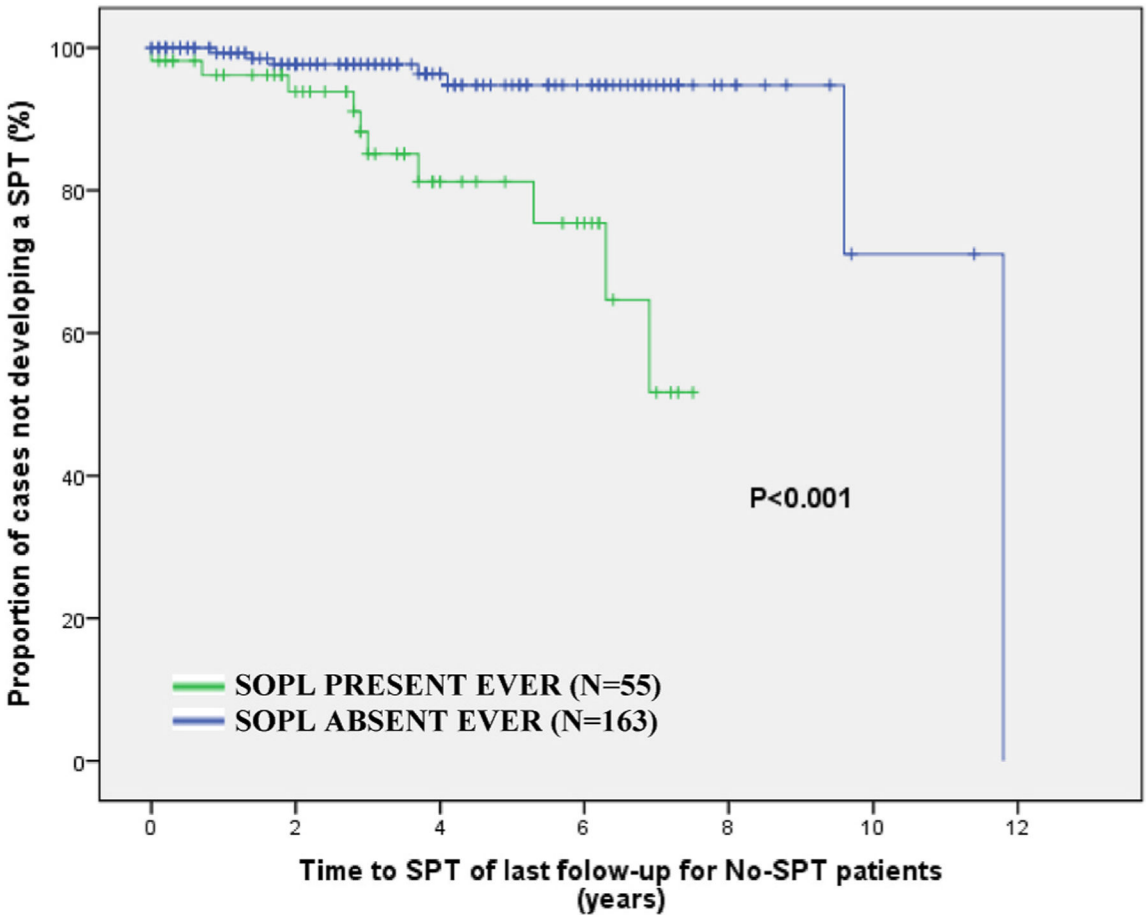

Fig. 3.

Cumulative probability of developing a second primary tumour (SPT) based on the presence or absence of a second oral premalignant lesion (SOPL) “ever” - at any point during follow-up. Among 55 patients with a SOPL ever, 10 (18 %) developed an SPT. In contrast, seven (4 %) of 163 patients without an SOPL ever developed an SPT. This indicates that having a SOPL at any point during follow-up is associated with a significantly higher risk of developing an SPT ($P < 0.001$).

Table 1

Distribution of cases according to demographic variables and risk habits.

Total	All (%)	SPT (%)	NO-SPT (%)	*P* value	HR (95 % CI)
	296 (100)	**23 (8)**	**273 (92)**		
Age at Primary Diagnosis					
Mean [years ± Standard Deviation (SD)]	59 ± 13	66 ± 11	59 ± 13	0.008	1.05 (1.01–1.09)
≤**40**	23 (8)	0 (0)	23 (100)	0.235	1
>**40**	273 (92)	23 (8)	250 (92)		N/A
Gender[a]					
Female	118 (40)	11 (9)	107 (91)	0.377	1
Male	178 (60)	12 (7)	166 (93)		0.70 (0.30–1.65)
Ethnicity[b]					
Caucasian	241 (81)	19 (8)	222 (92)	1.000	1
Other	55 (19)	4 (7)	51 (93)		0.92 (0.30–2.81)
History of Smoking (N = 291)[c]					
Non-smoker	103 (35)	8 (8)	95 (92)	0.636	1
Former smoker – quit before diagnosis	93 (32)	5 (5)	88 (95)		0.67 (0.21–2.14)
Former smoker – quit at diagnosis	31 (11)	2 (6.5)	29 (93.5)		0.82 (0.17–4.07)
Current smoker	64 (22)	7 (11)	57 (89)		1.46 (0.50–4.24)
History of Smoking (pack-years ever) (N = 288)[d]					
0	103 (36)	8 (8)	95 (92)	0.453	1
<**20**	70 (24)	8 (11)	62 (89)		1.53 (0.55–4.30)
20–40	109 (38)	6 (5.5)	103 (94.5)		0.69 (0.23–2.07)
>**40**	6 (2)	0 (0)	6 (100)		N/A
History of Alcohol (N = 295)[e]					
Never-drinker	56 (19)	4 (7)	52 (93)	1.000	1
Ever-drinker	239 (81)	19 (8)	220 (92)		1.12 (0.37–3.44)
History of chewing tobacco/betel nut (N = 291)[f]					
Never	273 (94)	19 (7)	254 (93)	0.043	1
Ever	18 (6)	4 (22)	14 (78)		3.82 (1.15–12.75)

Note: Column percentages depict “all” available patients. Row percentages are reported when displaying SPT vs No-SPT cases. A Fisher’s exact test was used if one or more cells had an expected count of less than 5 (>20 %). The HR ratio could not be calculated (N/A) if one of the cells was zero.

[a]Gender refers to socially constructed roles and identities, spanning a spectrum of expressions that individuals use to define themselves.

[b]Other ethnicity: 51 Asian and Southeast Asian (4 SPT and 47 No-SPT) and 4 First Nations (No-SPT).

[c]History of smoking is divided into non-smoker: smoked less than one cigarette per week for less than one year; former smoker – quit for at least a year before diagnosis; former smoker - quit at diagnosis; current smoker: continued to smoke after diagnosis. 5 cases (4 No-SPT and 1 SPT case) had data that was N/A.

[d]A total of 8 cases (7 No-SPT and 1 SPT case) had data that was N/A.

[e]History of alcohol is further broken down into ever-drinkers: regularly consuming alcoholic beverages more than once per month for one year or more; never-drinkers. 1 case with No-SPT had data that was N/A.

[f]History of chewing tobacco or betel nut is further split into ever-chewers: chewed more than once per week for more than one year; never-chewers. 5 cases with No-SPT had data that was N/A.

Table 2

Distribution of cases according to primary tumour characteristics and treatment.

Total	All (%)	SPT (%)	NO-SPT (%)	*P* value	HR (95 % CI)
	296 (100)	**23 (8)**	**273 (92)**		
Primary Tumour Location					
Tongue and Floor of Mouth	241 (81)	13 (5)	228 (95)	0.004	1
Other	55 (19)	10 (18)	45 (82)		3.90 (1.61–9.44)
Primary Tumour Stage					
Severe Dysplasia/CIS	61 (21)	4 (7)	57 (93)	0.396	1
OSCC I and II (early stage)	180 (61)	17 (9)	163 (91)		1.49 (0.48–4.60)
OSCC III and IV (late stage)	55 (18)	2 (4)	53 (96)		0.54 (0.10–3.06)
Primary Tumour Grade (N = 292)[a]					
Severe Dysplasia/CIS	61 (21)	4 (7)	57 (93)	0.545	1
Well and moderately differentiated	209 (71.5)	17 (8)	192 (92)		1.26 (0.41–3.90)
Poorly differentiated	22 (7.5)	0 (0)	22 (100)		N/A
Primary Tumour Treatment					
Surgery only	226 (76)	13 (6)	213 (94)	0.017	1
Radiation only	35 (12)	7 (20)	28 (80)		4.10 (1.51–11.13)
Both surgery and radiation	35 (12)	3 (9)	32 (91)		1.54 (0.42–5.69)
Primary Tumour Treatment (N = 261)[b]					
Surgery only	226 (86)	13 (6)	213 (94)	0.009	1
Radiation only	35 (14)	7 (20)	28 (80)		4.10 (1.51–11.13)

Note: Column percentages depict “all” available patients. Row percentages are reported when displaying SPT vs No-SPT cases. A Fisher’s exact test was used if one or more cells had an expected count of less than 5 (>20 %). The HR ratio could not be calculated (N/A) if one of the cells was zero.

[a] A total of 4 cases (2 No-SPT and 2 SPT cases) had data that was N/A.

[b] 35 patients who were treated with surgery and radiation were excluded from the comparison.

Table 3

Distribution of cases categorized by the presence of SOPL in the first year of follow-up and at any point during follow-up - “ever”, and results of toluidine blue and fluorescence visualization.

	All (%)	SPT (%)	NO-SPT (%)	*P* value	HR (95 % CI)
SOPL Year 1 (N = 280)[a]					
Absent	230 (82)	13 (6)	217 (94)	0.003	1
Present	50 (18)	10 (20)	40 (80)		4.17 (1.71–10.17)
Multiple Lesions (>2)Year 1					
No	282 (95)	19 (7)	263 (93)	0.017	1
Yes	14 (5)	4 (29)	10 (71)		5.54 (1.59–19.32)
SOPL Ever (N = 280)[a]					
Absent	213 (76)	9 (4)	204 (96)	<0.001	1
Present	67 (24)	14 (21)	53 (79)		5.99 (2.46–14.58)
SOPL Ever >1 year (N = 280)[a]					
Absent	252 (90)	18 (7)	234 (93)	0.065	1
Present	28 (10)	5 (22)	23 (82)		2.83(0.96–8.32)
SOPL Ever Location (N = 67)[b]					
Tongue and Floor of Mouth	27 (40)	5 (18.5)	22 (81.5)	0.694	1
Other	40 (60)	9 (22.5)	31 (77.5)		1.28(0.38–4.34)
SOPL Ever TB (N = 29)[c]					
Always Negative	22 (76)	2 (9)	20 (91)	0.088	1
Variable	5 (17)	2 (40)	3 (60)		10.00 (0.44–228.70)
Always Positive	2 (7)	1 (50)	1 (50)		6.67 (0.67–66.84)
SOPL Ever FV (N = 19)[d]					
Always Negative	7 (37)	0 (0)	7 (100)	1.000	N/A
Variable	4 (21)	0 (0)	4 (100)		N/A
Always Positive	8 (42)	1 (12.5)	7 (87.5)		1

Note: Column percentages depict “all” available patients. Row percentages are reported when displaying SPT vs No-SPT cases. “Ever” is the presence of a SOPL at any point during follow-up. A Fisher’s exact test was used if one or more cells had an expected count of less than 5 (>20 %).

[a] 16 cases with No-SPT had data that was N/A.

[b] A total of 213 cases with no SOPL ever were excluded from the analysis, and 16 cases with No-SPT had data that was N/A.

[c] Excluded 213 cases with no SOPL ever from the analysis, 16 cases with No-SPT that had data that was N/A, and a total of 38 cases (29 No-SPT and 9 SPT cases) had data that was N/A.

[d] Excluded 213 cases with no SOPL ever from the analysis, 16 cases with No-SPT that had data that was N/A, and a total of 48 cases (35 No-SPT and 13 SPT cases) had data that was N/A.