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ORIGINAL ARTICLE

Oral cavity carcinoma in patients with and without a history of lichen planus: A comparative analysis

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Abstract

Background: Oral potentially malignant disorders (OPMD) are associated with the risk of malignant transformation (MT) into oral cavity carcinoma (OCC). Oral lichen planus (OLP) is one of the most common OPMDs in western countries. Although there is a substantial amount of research on progression to cancer, a specific analysis of the clinical characteristics and prognosis of cancer developed in patients with a history of OLP versus patients without a history of OLP has not been investigated so far.

Methods: Retrospective evaluation of 82 patients treated for OCC with a known history of OLP compared to a representative sample of 82 patients treated for OCC without a known history of LP. Comparative analyses were performed on age at presentation, sex, TNM staging, clinical characteristics, pathology characteristics, 2- and 5-year overall survival (OS), and disease-free survival (DFS).

Results: It was shown that patients with a history of LP were significantly younger at first presentation than patients without a history of LP (mean age difference 6.7 years, 95% CI 3.1–10.3, $p < 0.05$). Also, patients with a history of OLP were in higher proportion females. The main pathological stage at presentation was significantly lower in the OLP group ($p < 0.05$). The 2-year survival analysis showed that DFS and OS were significantly lower in patients without a known history of OLP, with a hazard ratio (HR) of 3.1 (95% CI 1.4–6.8) and HR of 2.6 (95% CI 1.3–5.3), respectively. The 5-year survival analysis showed that DFS and OS were significantly lower in patients without a known history of OLP, with a hazard ratio of 3.1 (95% CI 1.6–6.2) and of 2.9 (95% CI 1.5–5.6), respectively.

Conclusions: Cancer arising from OLP has peculiar characteristics compared to cancer in naïve patients. It most commonly affects younger patients, women, and nonsmokers. It is usually diagnosed at earlier stages and appears

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to have less aggressive behavior at presentation. Moreover, when 2- and 5-year survival is analyzed, it appears that patients in OLP group have an overall and a disease-free survival advantage. These results suggest that cancer from OLP is less aggressive and thus has a potential biological difference with cancer arising in non-OLP patients. Further clinical and basic investigations are needed to confirm the results of this study.

KEYWORDS

malignant transformation, OPMD, oral cancer, oral cavity carcinoma, oral lichen planus, potentially malignant disorder

1 | INTRODUCTION

Oral potentially malignant disorders (OPMD) are associated with the risk of malignant transformation (MT) into squamous cell carcinoma (SCC). Oral lichen planus (OLP) is one of the most common OPMDs, with an estimated global prevalence of 0.89% (95% confidence interval [CI] 0.38–2.05) among the general population and 0.98% (95% CI 0.67–1.43) among clinical patients.[1] OLP is a chronic inflammatory disease characterized by a variety of clinical and histopathological features, the most common ones being the presence of white or red, symmetrical, lace-like lesions on the oral mucosa that can be ulcerated, plaque like, or atrophic, with evidence of band-like lymphocytic infiltrate below the basal membrane at the histopathological examination.[2] Differential diagnosis must be made with oral lichenoid lesions (OLL), atypical forms of lichen-like mucosal lesions without the usual clinical–pathological characteristics of OLP.[3] Compared to other OPMDs,[4–8] OLP has a lower MT rate potential, but it has been estimated that OLP has a cumulative MT rate of 1.4% (99% CI 0.9–1.9), with a yearly MT rate of 0.28%.[9] Arduino et al. in a recently published study[10] conducted on 3173 OLP patients with a long-term follow-up confirmed this conclusion. Although there is a substantial amount of research on progression to cancer,[11–13] a specific analysis regarding SCC developed on OLP lesions and its differences with SCC in patients without a history of OLP has not been investigated so far. The objective of the present research is to analyze the clinical characteristics and prognosis of SCC in patients with and without history of OLP, or any other OPMD, treated and followed up at a single academic hospital.

2 | MATERIALS AND METHODS

This is a retrospective observational study on 164 patients affected by SCC diagnosed and treated at the Operative Units of Maxillo-Facial Surgery and Oral Medicine of the University of Turin, Italy. Eighty-two patients had a SCC developed on OLP between 1988 and 2020, the remaining 82 patients had no history of OLP or any other oral premalignant disorder. The non-OLP cases were included retrospectively from 2014, when the electronic health records became available in our institution and so it was sure, even retrospectively, that a detailed history was recorded and the absence of past OPMDs confirmed with certainty. To avoid any selection bias patients were selected consecutively. Patient data was collected anonymously in a standardized digital database containing information regarding age, primary subsite of cancer occurrence, T, N, grading, smoking history, treatment, primary subsite of OLP, type of lichen lesion (red or white), previous corticosteroid therapy, history of hepatitis C infection, and time interval between last check-up for OLP and diagnosis of SCC. Diagnosis of OLP was confirmed by strict clinical features (characteristic bilateral papular and/or reticular lesions, alone or in association with atrophic or erosive lesions) and histopathological features (hyperkeratosis, "band-like" zone of lymphocytic infiltration in the lamina propria, evidence of "liquefaction degeneration" of the lower layer of the epithelium and absence of dysplasia). Oral lichenoid lesions were excluded from the analysis. Histopathological diagnoses were checked independently by two pathologists with a specific expertise in head and neck pathology. Comparative analyses were performed on data considered clinically meaningful. The assumption of normality for continuous data was confirmed through Shapiro–Wilk test. Chi-square tests were used for categorical variables and analysis of adjusted residuals was performed to better interpret statistically significant results. Given the small sample size, for all statistical tests bootstrap procedure was performed based on 5000 samples, the chosen output was corrected accelerated 95% confidence interval (BCa 95% CI).

Overall survival (OS) and disease-free survival (DFS) at 2 and 5 years of follow-up were calculated through Kaplan–Meier curves and a log-rank test was used to test any difference in survival between the two groups. A Cox proportional hazards model was constructed to provide hazard ratios with their 95% CI. Statistical significance was set as $p < 0.05$. Analyses were performed with SPSS 21.0 (SPSS Inc.). It was noted that the buccal cancer subsite was slightly more represented in the OLP group, given that this could create an improbable but still possible bias between the groups, a post hoc sensitivity analysis was planned for analyzing the difference between the two groups with all the buccal cancer cases removed from the analysis.

TABLE 1 Demographical and pathological characteristics of the included patients

	Cancer on lichen planus (%)	Cancer without history of lichen planus (%)	*p*-value
Age (mean, 95% CI)	60.7 (58.5–63.4)	67.4 (64.5–70.3)	<0.05
Gender			
Male	32 (39%)	47 (58%)	<0.05
Female	50 (61%)	35 (42%)	
Primary subsite			
Tongue	32 (39%)	31 (37%)	<0.05
Buccal mucosa	24 (29%)	10 (8%)	
Gingiva	18 (22%)	19 (23%)	
Floor of mouth	1 (<1%)	9 (11%)	
Palate	2 (2.4%)	9 (11%)	
Lip	5 (6%)	4 (4%)	
T			
T1	55 (67%)	24 (29%)	<0.05
T2	20 (24%)	26 (32%)	
T3	2 (3%)	13 (16%)	
T4	5 (6%)	19 (23%)	
N			
N0	65 (79%)	32 (39%)	<0.05
N1	9 (12%)	10 (8%)	
N2	8 (10%)	34 (41%)	
N3	0	1 (<1%)	
Nx	0	5 (6%)	
Smoking history			
Yes	7 (9%)	43 (52%)	<0.05
No	75 (91%)	39 (48%)	
Grading			
G1	44 (53%)	11 (13%)	<0.05
G2	32 (39%)	59 (71%)	
G3	6 (8%)	12 (15%)	
Staging			
Stage I-II	62 (75%)	26 (32%)	<0.05
Stage III-IV	20 (25%)	56 (68%)	
Treatment approach			
Surgical +/− adjuvant treatment	79 (96%)	71 (87%)	<0.05
Inoperable	3 (4%)	11 (13%)	

3 | RESULTS

The characteristics of the patients enrolled in the study are shown in Table 1. Median follow-up was 36.1 months. Seventy-nine patients were males and 85 were females, with a mean age of 64 years old (95% CI 62.2–66.1). A significant difference in age was observed between the two groups: the 82 patients that developed SCC from OLP had a mean age at presentation of 60.7 years (95% CI 58.5–63.4) while for the non-OLP group the mean age was 67.4 (95% CI 64.5–70.3). There was a significant difference based on gender between the two groups, with females in the OLP group constituting 50/82 (61%) but only 35/82 (42%) in the non-OLP group ($p < 0.05$). The statistical analysis also showed a significant difference when evaluating cancer subsites: the buccal mucosa was more likely associated with cancer arising from lichen planus while the floor of mouth and the palate were more frequently involved in cancer without OLP ($p < 0.05$). The tongue and the gingiva were equally interested in the two groups. In most cases, the SCC on OLP lesions was diagnosed at an early stage (T1-T2 and N0 disease) while T3, T4, and N2/N3 disease was more likely associated with cancer not arising from lichen planus ($p < 0.05$). Of the cancers on OLP, 53% were G1 graded while 86.6% of SCCs in patients without OLP were G2-G3 lesions ($p < 0.05$). Among patients with a history of lichen planus, 3 out of 82 were considered inoperable at diagnosis, compared to 11 out of 82 patients in the non-OLP group ($p < 0.05$). A statistically significant difference was also found when evaluating the smoking

habits. The 52% ($n = 43$) of non-OLP patients were positive for a smoking history versus the 9% ($n = 7$) in the OLP group ($p < 0.05$).

Table 2 summarizes the characteristics of oral lichen planus lesions. Most cases were characterized by a multisite involvement with a different combination of lesions originating from the buccal mucosa, the tongue, and the gingiva. Half of the patients had a white lesion, while the other half had a red lesion. The mean time from last OLP clinical check-up before the diagnosis of cancer was 17 months (95% CI 10.4–24.2). Out of 82 patients, 10 (8%) had a documented history of hepatitis C infection. Twenty-six patients in the OLP group were under treatment with corticosteroids at the moment of cancer diagnosis.

All the above results were tested with the bootstrap method showing almost identical results and 95% BCa CI. This shows that the results are reliable and that the sample size is likely to be adequate.

The 2-year survival analysis (Figure 1) showed that DFS and OS were significantly lower in patients without a known history of OLP, with a hazard ratio of HR 3.1 (95% CI 1.4–6.8), when analyzing DFS, and of HR 2.6 (95% CI 1.3–5.3) for OS. The difference in prognosis remained evident for DFS when the two groups were sub stratified for T and N (figure 2). In particular, the analysis of T1-T2 SCCs showed a significant improvement of 2 year DFS for OLP patients and similar results were observed for N0 lesions ($p < 0.05$). The 2 year OS difference was instead not significant when groups were stratified for T and N.

The 5-year survival analysis (Figure 1) showed that DFS and OS were significantly lower in patients without a known history of OLP, with a hazard ratio of 3.1 (95% CI 1.6–6.2), when analyzing DFS, and of 2.9 (95% CI 1.5–5.6) for OS. The difference in prognosis at 5 years remained evident when the two groups were sub stratified for T and N (Figure S1). In particular, the analysis of T1-T2 SCCs showed a significant improvement of 5 year DFS for OLP patients and similar results were observed for N0 lesions ($p < 0.05$). The OS confirmed these findings even if with a statistical significance only for N0 patients (Figure S1). Such differences in prognosis were not statistically significant when considering the T3-T4 and N+ lesions.

Results of the post hoc analysis show the same results of the full analysis. In detail, the 5-year survival analysis conducted eliminating all the buccal mucosa cancer cases (Figure S2) showed that DFS and OS were significantly lower in patients without a known history of OLP, with a hazard ratio of 3.4 (95% CI 1.4–7.8), when analyzing DFS, and of 3.1 (95% CI 1.5–6.3) for OS. This post hoc analysis confirms that the slight imbalance in the number of buccal mucosa cancer cases in the OLP group does not seem to be a determining bias in the results of the statistical analysis.

TABLE 2 Specific characteristics of the lichen planus cases

	***n* (%)**
Primary subsite	
Buccal mucosa, tongue	24 (29%)
Buccal mucosa	21 (25.6%)
Buccal mucosa, tongue, gingiva	11 (13%)
Tongue	7 (8%)
Buccal mucosa, gingiva	6 (7%)
Buccal mucosa, gingiva, palate	3 (4%)
Other multiple sites in the oral cavity combined	10 (8%)
Type of lichen	
White	41 (50%)
Red	41 (50%)
History of corticosteroid therapy	
Yes	26 (32%)
No	56 (68%)
History of Hepatitis C infection	
Yes	10 (8%)
No	72 (92%)
Last check-up before cancer diagnosis in months (median, IQR)	6.0 (7.25)

4 | DISCUSSION

To the best of our knowledge, this was the first direct comparison of the characteristics of oral squamous cell carcinoma arising from OLP versus cancer not arising from OLP treated at the same institution. The results of the study confirm that patients with carcinoma arising from OLP have a different way of presentation at initial diagnosis compared to patients with carcinoma arising from traditional risk factors. As expected, the cancer subsite in the OLP cases reflects the distribution of lichen planus lesions commonly encountered in clinical practice,[14] namely the buccal mucosa and tongue. Also, compared to traditional oral SCC, cases associated with OLP occur more often in female and young patients, which is not surprising given that OLP characteristically affects these subgroups of patients.[15] It could be assumed that a good proportion of OLP patients undergo regular follow-up visits and, consequently, cancer in these patients is theoretically detected at earlier stages, at least

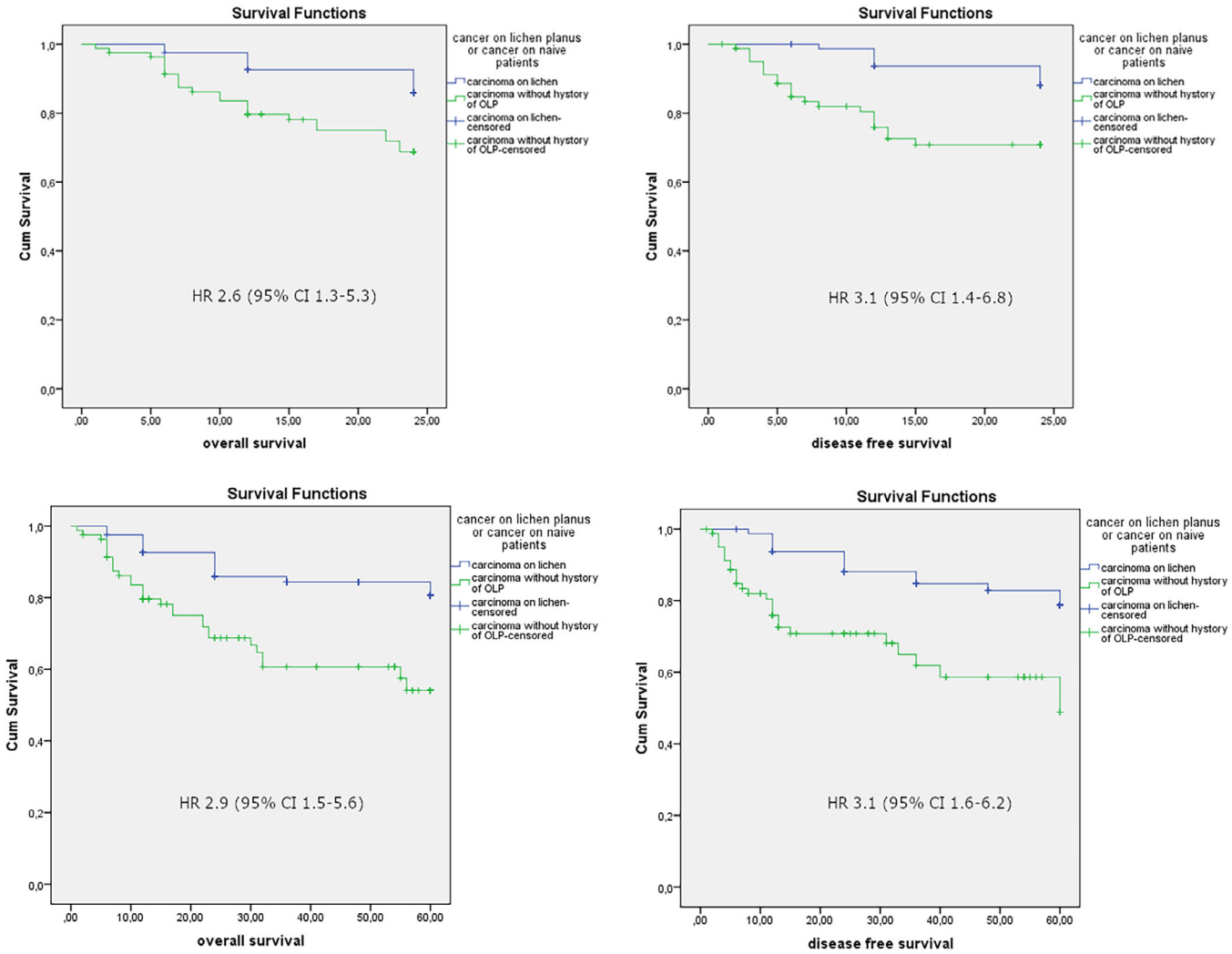

FIGURE 1 Overall and disease-free survival curves at 2 and 5 years. HR, hazard ratio; OLP, oral lichen planus [Color figure can be viewed at wileyonlinelibrary.com]

in patients compliant to frequent check-ups. This was confirmed in the present analysis, in which T1 and N0 disease was the most common diagnosis at presentation in the OLP group, while non-OLP oral carcinoma presented at more advanced stage at initial diagnosis. The relationship between tobacco smoking and malignant transformation of OLP has not been defined so far.[16] It is still unclear if smoking acts as a main triggering factor responsible for cancer development, or if OLP has an intrinsic malignant potential independent from the exposure to tobacco or other cancerogenic toxins. The results of the present analysis seem to confirm that smoking exposure is not essential for the malignant transformation of OLP. In fact, just 7 out 82 cases were confirmed smokers, in contrast with the much higher proportion in the non-OLP group. This corroborates the hypothesis that OLP has an intrinsic potential to transform into cancer. It must be pointed out that, given the retrospective nature of the analysis, it was not possible to break down the smoking history into pack-years, ex-smoker, and other detailed smoke related variables. Unfortunately, not enough data on alcohol consumption was available in the two groups and so a comparison on this aspect was not possible. We analyzed if HCV positivity was higher in the OLP group, and we were able to confirm this assumption. It has been reported that OLP is causally linked to HCV, with the hypothesis that the virus could replicate in the oral mucosa and be linked to OLP pathogenesis.[10] Although the incidence of HCV is decreasing in Western countries, the number of HCV positive patients was significantly higher in the OLP group with 10 out of 82 patients affected (8%) compared to 2 out of 82 (2%) patients in the non-OLP group with a positive anamnesis of HCV positivity ($p < 0.05$).

This strengthens past results in which it was shown that HCV is linked to OLP. On the other hand, it was not

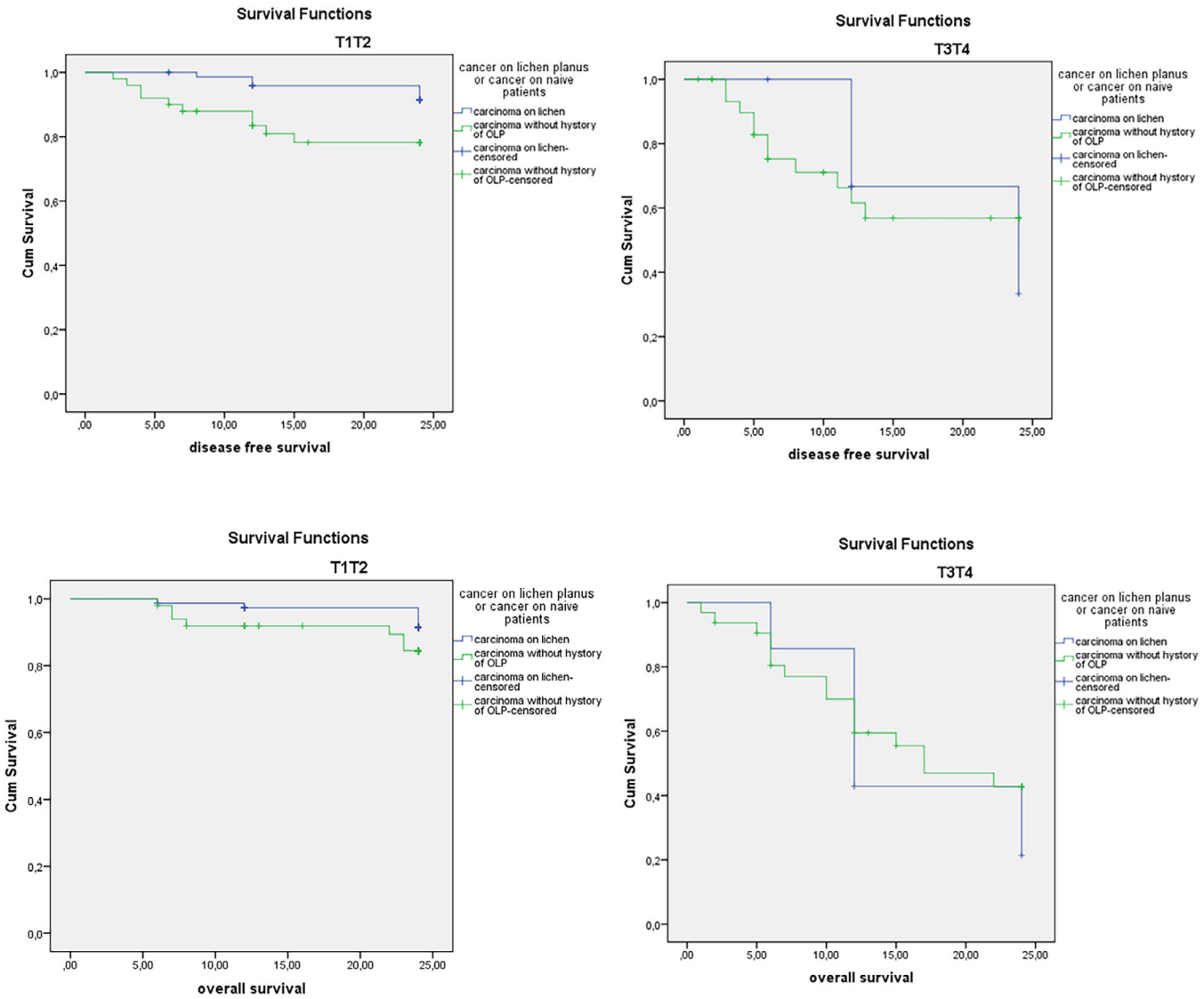

FIGURE 2 Overall and disease-free survival curves at 2 years stratified by T and N status. HR, hazard ratio; OLP, oral lichen planus [Color figure can be viewed at wileyonlinelibrary.com]

possible to establish if HCV status increases the chances of malignant transformation.

Over the last two decades, it has been investigated whether OLP and oral lichenoid lesions have different malignant transformation potential, it appears that the rate of transformation into cancer is different among the two lesions such that the OLL have a greater tendency to progress to cancer compared to OLP,[9,17] it follows that these are two distinct pathologic entities with their own biological characteristics. In the present study, strict diagnostic criteria were adopted in the diagnosis of OLP so that similar potentially confounding lesions, such as OLL, were excluded. Also, cases of OLP in which dysplasia was present at diagnosis were also excluded.

Based on the results of the present study, it can be speculated that cancer originating from OLP harbors a less aggressive potential than traditional oral cavity carcinoma. For example, the fact that G1 grading, reflecting a more differentiated tissue, had a statistically significant association with OLP cancer cases, while G2-G3 disease was significantly associated with non-OLP cases, might be a signal of some form of biological diversity between the two groups. The peculiar biological characteristics of OLP and OLL have gained attention recently[18,19] and will definitely deserve more research efforts in the future. Also, when survival analysis was performed, it was shown that OLP cases had a significantly higher disease-free and overall survival rate. This may correlate with the fact that patients with OLP have regular check-ups and so cancer is detected at an earlier stage. On the other hand, when stratified for T and N, the difference in DFS and OS is still evident among the two groups. In detail,

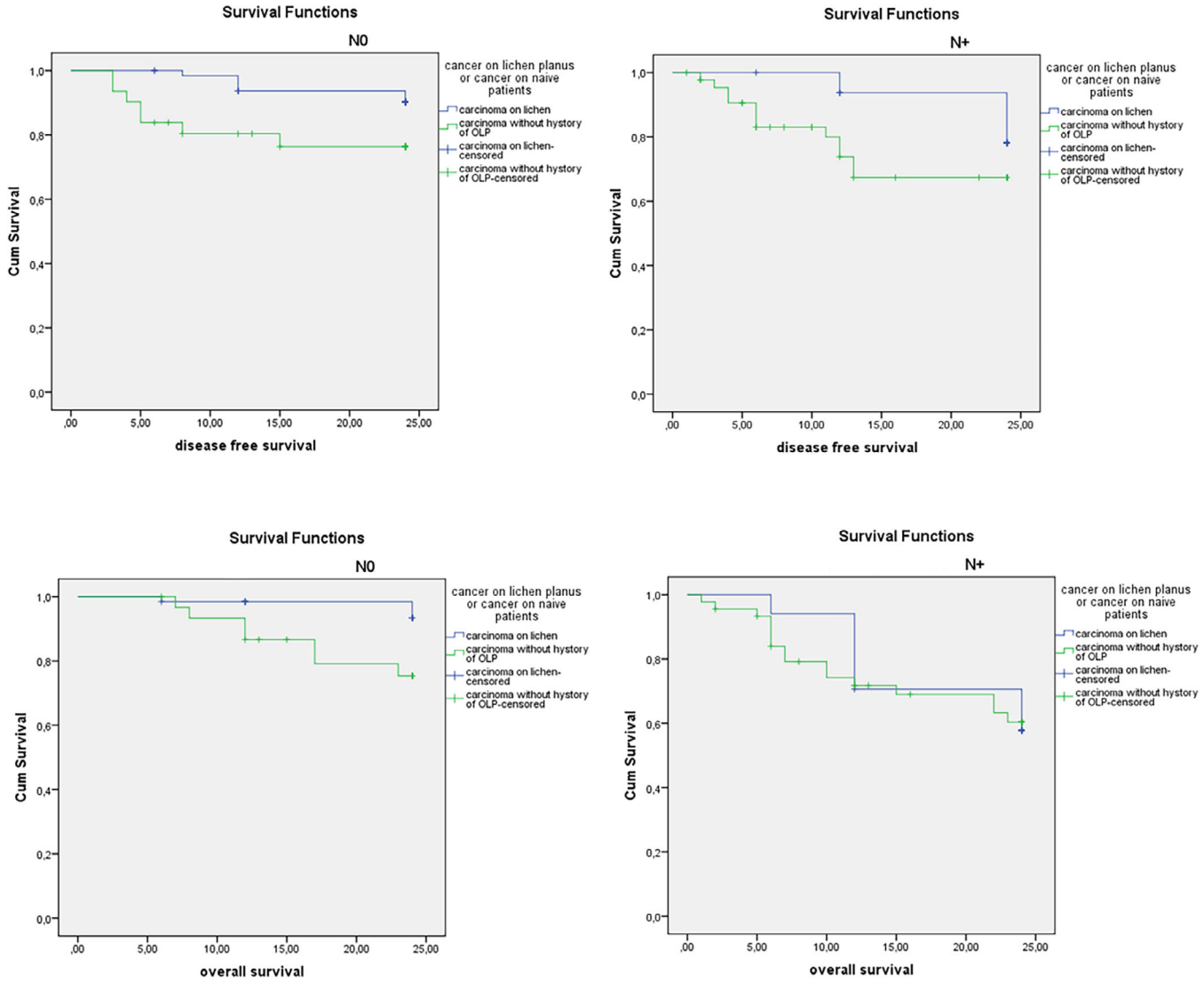

FIGURE 2 (Continued)

the DFS of OLP group remained higher in the T1-T2 group and the same was observed in the N0 group. The same survival patterns were seen when OS was considered. An overall survival advantage trend was seen in the T1-T2 OLP group compared to the non-OLP T1-T2 groups, although this was not statistically significant. A significant survival advantage was instead seen in the N0 OLP group. In the T3-T4 and N+ groups, no difference in overall or disease-free survival was observed. This can be explained by two factors: one is that advanced disease is characterized by a reduced survival, likely independent by other factors, and the second is that much fewer cases in the OLP group were T3-T4 or N+ so it is possible that not enough events were available to show a statistical significance. These results clearly point toward a survival advantage in the OLP group. The survival analysis results should anyway be taken with caution because the sample size of the various subgroups is relatively small, and the proportion of censored cases is higher in the non-OLP group. Nonetheless, our results are consistent with another indirect comparison reported in the literature.[20] The authors evaluated a group of OLP cancer cases and compared them to a similar group of naïve oral cancer cases extracted from the Surveillance, Epidemiology, and End Results (SEER) database. The study found that OLP patients have increased OS and DFS compared to the SEER group.

Regarding treatment approaches, it is interesting to outline that 11/82 (13%) of non-OLP SCC cases were considered inoperable at first presentation, this was a significantly higher number than the OLP group, of which only 3/82 (4%) were not deemed candidates for surgery. This is consistent with the fact that OLP patients are likely to undergo regular follow-ups and so when cancer occurs it

is likely detected at early stages. It is now established that malignant transformation of OLP does happen in a small fraction of patients, that is, around 1.4% of the cases (99% CI 0.9–1.9), it follows that regular follow-up strategies must be implemented.[9] In the present study, the mean time from the last OLP clinical visit before the diagnosis of cancer was 17 months (95% CI 10.4–24.2). This further confirms the importance of proper follow-up strategies for all patients affected by oral lichen planus and that any clinical change suspicious for malignant transformation should be promptly biopsied. Early detection of OCC is fundamental to prolong survival[21] and to avoid complicated treatment options to the affected patients.[22–24]

The strengths of the present study are numerous. This is the only available direct comparison of OLP versus non-OLP cancer cases based on a pool of patients treated at the same institution. Moreover, the OLP cases diagnoses were all confirmed histologically by an experienced pathologist. Also, in our institution, over the last 10 years an electronic health care record has been implemented such that any prior history of mucosal disorders is carefully recorded, for this it is safe to assume that all the patients in control group had no prior history of OLP or any other OPMD, which further strengthens the validity of the comparison. Finally, sound statistical analyses were adopted to explore any difference between the two groups.

The limitations of the study are related to its retrospective design. Not enough data was available to explore any difference in alcohol consumption between the two groups or the exact detail of smoking history. Also, some pathology data such as lymphovascular invasion and perineural invasion were not available in the OLP group and so these variables were not evaluated. Furthermore, due to the relatively small sample size, it was not possible to stratify patients according to primary subsite, on the other hand a post hoc sensitivity analysis, conducted after elimination of the buccal mucosa cancer cases, confirmed the results of the main analysis, it follows that it is unlikely that the results would change considerably if single oral cavity anatomic locations were considered individually. It would have been ideal to select the non-OLP group based on a propensity score matched-mode, but this was deemed unfeasible because this would reduce the sample size excessively and the whole analysis would not be feasible. Finally, it must be clear that the results based on T and N stratification are based on a relatively small sample size, for this reason, although the results are statistically significant, they should be taken with caution.

In conclusion, cancer arising from OLP has peculiar characteristics compared to cancer in naïve patients. It most commonly affects younger patients, women, and nonsmokers. It occurs most frequently on the tongue, buccal mucosa, and gingiva. It is usually diagnosed at earlier stages and appears to have less aggressive behavior at presentation. Moreover, when 2- and 5-year survival is analyzed, it appears that patients in OLP group have an overall and a disease-free survival advantage, which is confirmed also in some subgroups when patients are stratified for T and N, especially for disease free survival. These results suggest that cancer from OLP is less aggressive and so has a potential biological difference with cancer arising in non-OLP patients. Further clinical and basic investigations are needed to confirm the results of this study.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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