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ORIGINAL ARTICLE

Oral leukoplakia diagnosis and treatment in Europe and Australia: Oral Medicine Practitioners' attitudes and practice

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Abstract

The management of oral potentially malignant disorders (OPMD) including oral leukoplakia (OL) is not currently structured according to agreed guidelines. The current report presents survey data gathered from Oral Medicine Practitioners (OMPs) in Europe and Australia and is aimed to investigate attitudes and practice in the diagnosis, risk stratification and treatment of OL. In the presence of a clinical provisional diagnosis of OL, respondents reported always undertaking biopsy in 83% of cases, with most OMPs also relying on diagnostic adjuncts. The potential for malignant transformation is almost invariably assessed through epithelial dysplasia status, with other biomarkers described in the literature used less often. Active treatment of OL was considered mandatory by 20% of OMPs, while others reserve treatment for selected cases only. OMPs are mostly driven to active treatment by lesion-related features which are frequently jointly considered including lesion site, clinical appearance and dysplasia status. Inconsistent assessment was observed regarding mild dysplasia, lesion size, presence of unavoidable trauma, exposure to tobacco and patient age. Frequently observed geographical variations were seldom statistically significant. In agreement with previous surveys, a lack of consensus around the management of OL was observed, supporting claims from learned academies and societies for treatment guidelines aiming to reduce inter-practitioner variability.

KEYWORDS
cancer and pre-cancer, diagnostics, oncology

1 | BACKGROUND

To date, widely accepted criteria for the diagnosis and management of oral potentially malignant disorders (OPMDs) including oral leukoplakia (OL) are still lacking. Inconsistency in the management of patients is therefore expected, but data describing attitudes and practice of expert Oral Medicine Practitioners (OMPs) in the management of OL are uncommon. Some surveys have described the management of OPMD in the UK by consultant oral medicine practitioners and oral and maxillofacial surgeons, and in the USA by oral medicine practitioners (Epstein et al., 2007; Kanatas et al., 2011; Marley et al., 1996; Marley et al., 1998; Thomson et al., 2015). These studies mainly focused on features driving the diagnostic workup and the frequency of follow-up, lacking information on lesion or

patient-related features driving the management of OL. Such nationally based studies were unable to provide evidence on potential geographical variations and were not able to report any data from Europe or Australia.

The present study aimed to provide information about the current management of OL and early Oral Squamous Cell Carcinoma (OSCC) amongst OMPs across European countries and Australia. Potential geographical variations and differences in clinical practices related to OMP characteristics were assessed.

2 | METHODS

Data used for the current report were derived from a 93-item survey designed by the European Association of Oral Medicine (EAOM) Position Paper on Diagnosis and Management of Oral Leukoplakia Expert Panel aiming to analyse clinical practice variability in the diagnosis and management of OPMD focusing on OL and early OSCC. By means of consensus, a questionnaire including previously validated items as well as items specifically designed for the survey was developed in the English language and pre-tested on a group of potential respondents to ensure practicability, validity and interpretation of answers. The whole survey took approximately 10–25 min to complete. The wide range of questions and potential answers relied on the use of skip logic branching creating a custom path through the survey based on a respondent's answers. All responses were completely anonymous. The sections of the survey which were used for the present study can be accessed in the Appendix S1.

To obtain a representative sample of OMPs from Europe and Australia, members of the EAOM and the Oral Medicine Academy of Australasia (OMAA) were invited to participate in the survey. An email was sent to members of both organisations in June 2018 with a cover letter describing the study's aim and a link to participate. The survey was administered through SurveyMonkey® (San Mateo), an online survey development cloud-based software. Mailing was repeated 15 and 45 days after the first post.

The first section (17 questions) collected respondents' sociodemographic characteristics, academic training and clinical practice information already reported and discussed elsewhere (Pentenero, Sutera, et al., 2021). From those data the following OMPs' characteristics were extracted and considered in the present study as detailed below: age, gender, geographical practice setting (EAOM Regions/OMAA), attainment of postgraduate training in OM, clinical practice mainly dealing with OM (exceeding 40% of total clinical practice), OM practice significantly dealing with the management of OL/OSCC (exceeding 20% of total OM practice), OMPs' practice including surgery (exceeding 20% of total clinical practice), OMPs' significant involvement in research (exceeding 20% of total working time).

The following sections of the survey, representing the main topic of the current study, investigated OMPs' clinical habits and attitudes in the diagnostic pathway of OPMD/OSCC and specifically in the management of OL.

The survey investigated practitioner practices in the diagnostic workup of OPMD/OSCC including routine biopsy sampling; the use of diagnostic aids including toluidine blue (TB), autofluorescence (AF), cytology (CYT), Narrow Band Imaging (NBI); and the use of biomarkers suggestive of increased risk of malignant transformation including epithelial dysplasia status, ploidy status, loss of heterozygosity (LOH) and HPV infection.

Oral medicine practitioners' attitude towards OL treatment was investigated in order to determine which type of treatment was preferred and which patient-related features (if any) drive active treatment.

Investigated patient-related features included age, gender, tobacco/alcohol exposure, presence of potential chronic and unavoidable trauma, OL size, anatomical subsite, clinical appearance, dysplasia status and presence of suspected *Candida* infection.

Potential associations between OMP characteristics and the above-reported clinical practices were assessed. Potential associations within the above-reported clinical practices were also assessed.

2.1 | Data evaluation and statistical analysis

Responses were collated electronically and held securely at the Oral Medicine and Oral Oncology Section of the Department of Oncology, University of Torino, Italy. Data were entered into an SPSS database and analyses were performed using SPSS release 27.0 (SPSS Inc.). The "EAOM Regions" as reported in Table 1 and the OMAA membership (henceforth jointly referred as Regions) served to assess geographical variations associated with clinical practice. Due to strong heterogeneity, Region 6 was not included in the present study, and

TABLE 1 EAOM regions

EAOM region	Country
Region 1	Ireland, **UK**
Region 2	Denmark, Estonia, Finland, Iceland, Latvia, Lithuania, Norway, **Sweden**
Region 3	Austria, Belgium, Czech Republic, Germany, Hungary, Luxemburg, **Netherlands**, Poland, Slovakia, Switzerland
Region 4	France, **Italy**, **Portugal**, **Spain**, Malta
Region 5	Albania, Bosnia Herzegovina, Bulgaria, Croatia, Cyprus, **Greece**, **Israel**, Romania, Russia, Serbia, Slovenia, Ukraine, Turkey
Region 6	Rest of the world

Note: Countries in bold are represented by at least 5 respondents.

EAOM members from Australia were grouped with OMAA members. Analyses were carried out in two stages. Firstly, descriptive statistics (frequency/per cent distribution) were generated to describe the sample and each response from the survey. The chi-square test was employed to detect possible associations in the presence of qualitative data, including different clinical practices. Based on normal or non-normal distribution of quantitative data, one-way analysis of variance (ANOVA) or non-parametric tests (Independent-Samples Kruskal–Wallis or Mann–Whitney U Test) was used to determine the presence of any statistically significant differences between groups identified by nominal variables among which included OMP characteristics reported above. Spearman's rho correlation coefficient was used to assess the relationship between quantitative data (OMP age and number of patient-related features considered in planning active treatment or scheduling of follow-up visits).

Binomial logistic regression analyses were performed to test the importance of the effect of OMPs' characteristics on clinical practice. OMP characteristics were used as predictors (independent variables) in the regression analyses. A full model, when all the variables were entered simultaneously into the model, was used to evaluate the relative contributions of these variables to clinical practice preferences.

3 | RESULTS

3.1 | Respondents

Excluding EAOM Region six members as described above, invitations were sent to 276 subjects: 242 EAOM members and 34 OMAA members. One hundred and forty subjects participated corresponding to a response rate of 50.7%. No significant differences between EAOM and OMAA members were observed in the response rate, and the EAOM respondents were representative of the 5 EAOM Regions. The respondents have been fully described in our previous report (Pentenero, Sutera, et al., 2021).

3.2 | Diagnosis

3.2.1 | Biopsy

When faced with a mucosal lesion clinically consistent with OL, 83% of respondents always performed tissue sampling to obtain a histopathological diagnosis without any geographical variation. Almost half (46%) of OMPs practising in Region 1 (UK) refer patients to other colleagues to perform biopsies, while in the rest of Europe and Australia, 97% of OMPs perform biopsies themselves ($p < 0.001$). No data from the present survey were able to characterize OMPs who did not always require a biopsy to complete their diagnostic workup. The regression model showed no predictors significantly related to the practice of not always requiring a biopsy to complete the workup. Fourteen percent of OMPs reported interpreting biopsy slides of OPMDs themselves; this proportion ranging from 0 in Regions 1 and 3 to 17%–22% in Regions 2, 4 and 5, and only 7% in Australia, although such variations were not statistically significant ($p = 0.097$). As expected, OMPs who attained additional postgraduate training in oral pathology were more likely to interpret tissue slides themselves ($p < 0.001$; OR = 11.6, 95% CI:3.37–40–17).

3.2.2 | Diagnostic adjuncts

Most OMPs (75%) reported employing diagnostic adjuncts even if only in selected cases, with just under half (38%) relying on more than a single technique in their practice. Diagnostic adjuncts were more frequently used by OMPs who performed biopsy themselves ($p = 0.023$). TB was used by 43% of OMPs, with a similar proportion using CYT (42%) and AF (36%), while NBI was only used by 21% of respondents. The practise of never using diagnostic adjuncts had significant differences across Regions ($p = 0.007$). In Region 1, 56% of respondents reported never using adjuncts; this proportion decreased to 23%–29% for Regions 3 and 5, and to 13%–17% for Regions 2, 4 and Australia. The regression model for the overall use of diagnostic adjuncts was significant, $p = 0.026$, $R^2 = 0.280$, confirming geographic variations ($p = 0.041$) and showing a positive relationship with age ($p = 0.047$; OR = 1.06, 95% CI:1.00–1.11) and surgical practice ($p = 0.052$; OR = 3.66, 95% CI:0.97–13.62).

The employment of TB and AF showed significant geographical variations ($p < 0.001$ and $p = 0.003$, respectively). TB is used in selected cases by most respondents from Region 4 (64%), 30%–40% of respondents in Regions 3 and 5 and by 17%–20% of respondents in Regions 1, 2 and Australia. The use of AF is characterized by outlier data from Australia where most OMPs use AF either in selected or in all patients (46% and 26% of respondents, respectively). In Regions 1 and 2 almost all OMPs (83–96%) never use AF, while in Regions 3, 4 and 5 29%–36% of OMPs use AF in selected cases. AF is less frequently used by OMPs who consider that surgery is the only treatment modality for OL ($p = 0.046$). The regression model for the use of TB was significant, $p = 0.001$, $R^2 = 0.344$, but only confirmed geographic variations ($p = 0.004$). Similarly, the regression model for AF use ($p = 0.001$, $R^2 = 0.363$) confirmed geographic variations ($p = 0.009$), but it also revealed that AF is more often used by OMPs involved in research ($p = 0.010$).

Cytology is more commonly used by OMPs who practice oral surgery ($p = 0.002$; OR = 5.34, 95% CI:1.85–15.41), with no other significant association revealed by the regression model ($p = 0.026$, $R^2 = 0.256$).

The employment of NBI showed significant geographical variations ($p = 0.028$). NBI is used in selected cases by almost one-third of respondents from Region 4 and Australia (36% and 33% of respondents, respectively), by 14% of respondents in Regions 3 and 5, by 8% of respondents in Region 1, while no respondent from Region 2 reported taking advantage of this tool. Nevertheless, in the regression model, no predictor was significantly related to the use of Narrow Band Imaging (NBI).

The habit of using diagnostic adjuncts was not driven by any of the following attitudes or practises: always performing biopsy ($p = 0.580$), always actively treating OL ($p = 0.444$), always performing surgery rather than undertaking medical or surgical treatment depending on the specific case ($p = 0.970$).

3.2.3 | Markers of progression

Almost all respondents (94%) rely on epithelial dysplasia status in order to better assess the potential for malignant transformation, without any variations associated with OMP features or other clinical practices assessed.

DNA-ploidy status assessed either by Image or Flow Cytometry (ICM or FCM) is accessed by 11% of respondents, with significant geographical variations ($p = 0.030$). The highest proportion was observed in Region 1 (29%), followed by those in Regions 3 and 5 (14%–17%) and by a negligible number in Regions 2, 4 and Australia (0%–7%). The regression model showed no predictors significantly related to this clinical practice.

The use of LOH was reported by 8% of all respondents. Assessing geographical variation ($p = 0.059$), a peculiar interest among OMPs from Australia (27%) was observed. The regression model showed no predictors significantly related to this clinical practice.

Almost half of respondents (52%) assess HPV status. This being quite common in Region 1 (67%), less frequent in Regions 3, 4, 5 and Australia (50–53%) and quite uncommon in Region 2 (33%). Such geographical variations were not statistically significant ($p = 0.570$). The regression model once again was unable to highlight any predictor for this practice.

3.3 | Active treatment

Active treatment of OL (irrespective of which type of treatment) was considered mandatory for all patients by 20% of respondents; the remaining 80% reserving treatment for selected cases. OMPs who always planned active treatment were more frequently observed in Australia (40%), with intermediate values (14%–29%) noted in Regions 3, 4 and 5, and the lowest proportion (8%) found in Regions 1 and 2, but such variations were not statistically significant ($p = 0.160$). Of note, none of the respondents considered that OL should never be treated. Management of OL always included surgery for 68% of respondents; the remaining 32% relying on surgery or medical treatment depending on the specific case, while no respondent opted for medical therapy alone for all OL cases. Geographical variations were observed, but they were not statistically significant ($p = 0.351$). The proportion of OMPs who considered that surgery was an active treatment in all cases ranged from 70% to 86% in all Regions but in Region 5 where this decreased to 48%.

Oral medicine practitioners who considered that OL should always be treated, more often considered that surgery was the only treatment modality ($p = 0.028$; OR = 3.9, 95% CI:1.08–14.24).

The regression model showed that OMPs with a clinical practice mainly dealing with oral medicine were more used to choosing between medical or surgical treatment depending on the case ($p = 0.032$; OR = 0.77, 95% CI:0.04–0.87), whereas OMPs whose practice significantly dealt with the management of OL/OSCC more often considered that intervention was mandatory for all patients ($p = 0.046$; OR = 1.15, 95% CI:1.02–9.81), and more often considered that OL should always be treated by surgery ($p = 0.011$; OR = 1.49, 95% CI:1.41–13.91).

Analysis of features driving the subset of OMPs who reserved active treatment to selected cases was performed. The following patient-related features were considered by different OMPs including epithelial dysplasia status (99%), clinical appearance (91%), lesion site (76%), suspected *Candida* infection (68%), tobacco habit (57%), lesion size (55%), alcohol habit (42%), presence of potential and unavoidable trauma (41%), age (18%), and gender (8%). Most OMPs (59%) selected 5–7 of the reported 10 features (range 1–9) as useful in order to define the need for active treatment. The joint assessment of these features is shown in Table 2. Among OMPs, female practitioners usually jointly considered a larger number of patient-related features compared to their male counterparts ($p = 0.009$).

Of note, some features were not consistently considered by OMPs. All OMPs who considered the patient's gender as a determining factor for treatment were more likely to actively treat female patients; conversely age under 40 most often (75%) was considered a factor for active treatment, but some OMPs also considered it worthwhile to actively treat patients over 60 (25%). The regression model showed that OMPs less involved in research more often based their decisions on age ($p = 0.039$; OR = 7.72, 95% CI:1.11–53.88).

Geographical differences in considering tobacco habit ranged from 45–47% in Regions 2 and 5 to 75% in Australia but were not significant ($p = 0.690$). Tobacco habit was not consistently considered; OMPs were almost equally distributed in two groups driven to active treatment by the absence (46%) or the presence of tobacco use by patients (54%). A low proportion of OMPs only treated heavy smokers (6%). The regression model revealed that OMPs particularly involved in the management of OL/OSCC were less likely to treat patients who were not tobacco users ($p = 0.017$; OR = 0.16, 95% CI:0.03–0.72), while OMPs less involved in research were more likely to ($p = 0.042$; OR = 5.18, 95% CI:1.06–25.25).

Oral medicine practitioners driven to active treatment in the absence of tobacco exposure were also driven to active treatment in patients aged under 40 ($p = 0.017$; OR = 4.78, 95% CI:1.34–16.98) and in female patients ($p = 0.001$; OR = 21.0, 95% CI:2.37–185.93).

An alcohol habit was considered by 42% of OMPs; with geographical differences ranging from 27% in Regions 5 to 75% in Australia,

TABLE 2 Patient-related features jointly considered in planning active treatment of oral leukoplakia

	Age	Gender	Tobacco exposure	Alcohol exposure	Unavoidable trauma	Lesion size	Lesion site	Clinical appearance	Mild dysplasia	*Candida* infection
Age	-									
Gender	0.020* 7.56 (1.50–38.10)	-								
Tobacco exposure	0.005* 7.2 (1.52–34.02)	0.018* NA	-							
Alcohol exposure	0.261 2.09 (0.70–6.28)	0.448 1.94 (0.41–9.24)	<0.001* 8.70 (3.07–24.68)	-						
Unavoidable trauma	0.262 1.93 (0.63–5.95)	0.696 0.56 (0.10–3.05)	0.825 0.83 (0.35–1.98)	>0.999 1.07 (0.45–2.56)	-					
Lesion Size	0.025* 4.59 (1.20–17.52)	0.124 5.43 (0.62–47.17)	0.384 1.58 (0.67–3.73)	0.830 1.12 (0.47–2.63)	>0.999 0.97 (0.41–2.31)	-				
Lesion Site	0.336 2.61 (0.54–12.57)	0.673 0.78 (0.14–4.34)	0.321 1.69 (0.63–4.55)	0.801 1.27 (0.47–3.48)	0.796 0.81 (0.30–2.24)	0.453 1.55 (0.58–4.16)	-			
Clinical appearance	>0.999 1.64 (0.19–14.36)	0.500 0.57 (0.06–5.41)	0.072 4.50 (0.85–23.71)	0.459 2.33 (0.44–12.27)	>0.999 0.91 (0.19–4.33)	0.458 2.21 (0.49–9.88)	0.008* 10.00 (1.77–58.34)	-		
Mild dysplasia	0.788 1.19 (0.40–3.52)	>0.999 0.87 (0.18–4.15)	0.277 0.57 (0.24–1.34)	0.088 0.46 (0.19–1-11)	0.004* 4.18 (1.66–10.54)	0.518 1.37 (0.58–3.24)	0.803 1.22 (0.45–3.28)	0.698 0.61 (0.13–2.92)	-	
Candidal infection	0.371 2.21 (0.57–8.52)	0.202 0.32 (0.07–1.52)	0.818 1.21 (0.49–2.99)	0.818 1.18 (0.47–2.95)	0.001* 6.37 (1.96–20.68)	0.244 1.87 (0.75–4.70)	0.286 1.85 (0.67–5.12)	0.706 1.32 (0.29–5.96)	0.250 1.86 (0.74–4.70)	-

Note: The joint evaluation of patient-related features was assessed by chi-square or Fisher's exact test: p-values ≤0.05.

*Indicates a joint evaluation by OMPs. Each cell shows p-value and Odds Ratio with 95% Confidence Intervals.

but were not significant ($p = 0.310$). In the regression model, OMPs who mainly practice oral medicine were less likely to consider alcohol consumption when selecting patients requiring active treatment for OL ($p = 0.016$; OR = 0.18, 95% CI:0.05–0.73). When the habit was considered, OMPs were mainly driven to active treatment by its presence (78%) rather than by its absence (22%). Among alcohol consumers, 28% of OMPs scheduled active treatment only in the case of heavy consumption.

Oral medicine practitioners who treated non-exposed patients had the same attitude for both tobacco and alcohol consumption ($p < 0.001$).

The presence of unavoidable trauma encouraged treatment for OL by 41% of OMPs without significant geographical variations ($p = 0.073$).

Lesion size was considered by 55% of OMPs; among them most (67%) considered that a maximum diameter or spread exceeding 20 mm was reason enough to treat OL actively. No geographical variations were observed ($p = 0.906$).

Lesion site was one of the most considered features by 76% of OMPs without differences across Regions ($p = 0.885$; range 62%–81%). The oral sites most often considered to imply the need for active treatment were floor of mouth (98%), lateral/ventral surface of the tongue (92%), soft palate (41%), vermilion (29%), buccal mucosa/alveolar mucosa/trigone (21%), gingiva (14%), dorsal surface of the tongue (11%) and hard palate mucosa (9%).

Male OMPs ($p = 0.004$; OR = 0.11, 95% CI:0.03–0.50) were less likely to consider OL site when selecting patients requiring active treatment. OMPs who practiced oral surgery were more likely to consider lesion site ($p = 0.033$; OR = 5.38, 95% CI:1.14–25.27) and *Candida* infection ($p = 0.036$; OR = 4.28, 95% CI:1.10–16.66) when selecting patients requiring active treatment for OL.

A very high proportion of OMPs (91%) considered clinical appearance in order to plan active treatment, and almost all of them (95%) were likely to actively treat non-homogeneous lesions. Neither geographical variations ($p = 0.513$) nor OMP-related characteristics were associated with this practice. OMPs driven to active treatment by non-homogeneous clinical appearance were additionally more often driven to that practice by the presence of tobacco exposure ($p = 0.026$; OR = 4.86, 95% CI:1.22–19.45).

All OMPs (99%) reported basing their indication for active treatment on epithelial dysplasia status. The presence of any grade of dysplasia was enough to mandate active treatment of OL for 45% of OMPs, while 49% considered that at least moderate dysplasia was required before active treatment was instigated. A more aggressive surgical approach including lesions with mild dysplasia displayed geographical variation ($p = 0.058$). In Region 1, 20% of OMPs actively treated mild dysplasia; this proportion rose to 33% in Region 3, 44% in Region 4 and 62%–67% in Regions 2, 5 and Australia. Nevertheless, the regression model did not show any feature which could identify OMPs who performed active intervention in the presence of mild dysplasia.

A suspected *Candida* infection drove 68% of respondents to active treatment, without geographical variations ($p = 0.781$).

3.4 | Surgical treatment

Half of respondents (50.5%) always referred patients when surgery was required, with significant geographical variations ($p = 0.001$); the highest proportion was observed in Region 1 (91%), followed by 57% in Australia, 43% in Regions 3 and 5, and 33% in Regions 2 and 4. OMPs who considered that OL should be treated only in selected cases and OMPs who considered that OL could be treated through medical or surgical approaches depending on the specific case were more likely not to perform surgery themselves ($p < 0.001$; OR = 6.92, 95% CI:2.17–22.10 and $p = 0.007$; OR = 3.41, 95% CI:1.43–8.12, respectively). OMPs who never used diagnostic adjuncts in their diagnostic workup were more likely to always refer patients for surgery ($p = 0.007$; OR = 3.75, 95%CI:1.43–9.87).

The regression model for patient referral for surgery was significant, $p < 0.001$, $R^2 = 0.523$, confirming geographic variations ($p = 0.035$) and showed negative relations with the attainment of postgraduate training in oral medicine ($p = 0.017$; OR = 0.12, 95% CI:0.02–0.68), oral medicine practice significantly dealing with OL/OSCC ($p = 0.004$; OR = 0.18, 95% CI:0.05–0.58) and surgical practice ($p = 0.032$; OR = 0.29, 95% CI:0.09–0.90).

Oral medicine practitioners who performed surgery (81%) mostly never referred patients presenting with OL; conversely, in the presence of early OSCC (T1 tumour according to 8th Edition of AJCC [Amin et al., 2018]) not requiring nodal dissection, 23% of OMPs performed surgery only in selected cases and most usually referred patients to other professionals including maxillofacial (63%), head and neck (21%), otolaryngology (12%) or oral (4%) surgeons.

When performing surgery, optical adjuncts to help determine margins were used by 43% of OMPs; TB was used by 70% of OMPs, AF by 52% and NBI by 30%. The regression model revealed that optical adjuncts were more often used by OMPs involved in research ($p = 0.032$).

The most frequently used clinical margin of clearance for excision of OL was 1–2 mm in the absence of dysplasia (used by 92% of OMPs), 2–5 mm in the presence of dysplasia (used by 86% of OMPs), and 5–10 mm in the presence of OSCC (used by 85% of OMPs).

4 | DISCUSSION

Most evidence on the treatment of OPMDs is based on observational and retrospective data, and as yet no good quality RCTs are available. As a result, we have no universally agreed guidelines on the management of OPMD, including OL, which remains controversial. OMPs' attitudes and practice in the management of OL have never been investigated comparing practitioners from different geographic areas. Two past studies from the UK and USA have reported approaches for diagnosis and management of OPMD in their specific jurisdictions (Epstein et al., 2007; Marley et al., 1998). Data from European and Australian OMPs however have never been reported.

The definitive diagnosis of OL depends on a histological assessment. Notwithstanding this, a not negligible group of OMPs (17%)

rely on clinical skill alone rather than diagnostic tests. The data presented in this study are consistent with previous reports from the USA showing that 11% of OMPs do not always perform a biopsy in the presence of a mucosal lesion clinically consistent with OL (Epstein et al., 2007). Conversely, we observed an increased proportion of practitioners from the UK always performing/requiring biopsy (87%) compared to more historic data investigating this attitude amongst British OMPs (70%) (Marley et al., 1996). Even with the lack of widely accepted guidelines, the need for a histological definitive diagnosis is clearly reported, so that the proportion of OMPs not routinely performing biopsy seems striking. The present survey is not able to elicit an explanation for this; we could only assume that this could occur in the presence of homogeneous white patches.

The habit of relying on diagnostic adjuncts, most often TB staining, was previously reported in about 40% of OMPs from the USA when performing a biopsy (Epstein et al., 2007). More than 10 years have passed since that report and with potential limitations due to different geographical settings, we could argue that the overall higher proportion observed in the present survey could be related to an increasing number of clinicians using more recent technologies such as AF or NBI. Nevertheless, more traditional adjuncts such as TB or CYT are still more commonly used compared to AF. Of note, the uncommon use of diagnostic adjuncts in Region 1 could be related to the low proportion of OMPs performing biopsy themselves. Nevertheless, a previous survey from the UK involving both OMPs and surgeons (oral and maxillofacial, otolaryngology, and plastic surgeons) reported an even higher rate of practitioners (71%) never using diagnostic adjuncts (Thomson et al., 2015).

Notwithstanding the vast amount of literature investigating biomarkers for progression of OL towards malignancy, OMPs still rely on epithelial dysplasia status for determining their treatment approaches. No other method has entered routine clinical practice yet. Of note, HPV infection seems to be very often considered despite lack of evidence supporting its role in oral cavity carcinogenesis (Sundberg et al., 2021; Wu et al., 2019). The present survey did not investigate which methods were used to assess HPV infection or its surrogate state, and respondents did not include any such information in their replies. Other biomarkers (namely DNA-ploidy status or LOH) supported by more consistent evidence (Farah, 2021; Nikitakis et al., 2018; Odell, 2021) were less frequently utilised, and only one respondent mentioned p53 status as a potentially useful biomarker.

The present study offers novel data on OMPs' attitudes in performing active treatment of OL, with a significant lack of such data in the literature. In fact, previously cited surveys describe attitudes mainly relating to biopsy sampling and follow-up (Epstein et al., 2007; Kanatas et al., 2011; Marley et al., 1998); with only one study investigating whether OMPs considered the presence of dysplasia in active treatment of OPMDs (Marley et al., 1998). Twenty percent of OMPs consider any OL worthy of active treatment while the remainder consider that at least a subset of OL should be subjected to active treatment. This is despite at least one systematic review showing a decreased likelihood of malignant transformation in those who undergo treatment compared to those who do not (Mehanna et al., 2009). Finally, even in the absence of significant differences, the wide geographic variability is notable and related to the role of OMPs in the surgical management of patients. Region 1 had the lowest proportion of OMPs who consider active treatment mandatory for any OL (8%) and the highest proportion of OMPs who always refer patients for surgical treatment (91%). It is notable that in Region 1 (UK), the proportion of OMPs who consider active treatment mandatory even in the absence of dysplasia seem to have decreased in the last 20 years. In fact, in 1998 Marley et al. observed that 23% of UK OMPs considered excision for non-dysplastic lesions (Marley et al., 1998).

For OMPs who only select a subset of patients for active treatment, their decision is usually based on several features, with the lesion-related ones being the most frequently considered. Only lesion-related features such as dysplasia status, clinical appearance and lesion site were considered by more than 75% of OMPs. Moreover, such features were jointly and consistently considered. In agreement with current evidence on the risk of progression associated with histological and clinical features (Speight et al., 2018), the presence of dysplasia, non-homogeneous appearance and the location on ventral tongue/floor of mouth consistently drove most OMPs to active treatment. The presence of mild dysplasia remains a contentious area, as it directed active treatment in almost half of OMPs resulting in a highly inconsistent treatment approach among practitioners. Similar results were reported in a British national survey mainly involving maxillofacial surgeons, where mild dysplasia was always-sometimes treated by 8%–39% of respondents, respectively (Thomson et al., 2015). An earlier survey showed that in the presence of mild/moderate dysplasia, 11% of OMPs from the UK rejected active treatment while 55% favoured excision (Marley et al., 1998).

Among OMPs from Europe and Australia, the assessment of epithelial dysplasia is currently the predictive factor most widely used to stratify risk for cancer development and guide management. The presence of at least moderate dysplasia was a driver to active treatment for 49% of OMPs. The present study has shown which features were more frequently considered, even if we are not able to know their weighting in the decision process. It is nonetheless notable that lesion-related features were mostly and jointly considered.

Patient-related features such as age or gender are infrequently considered even if invariably reported in the literature (Speight et al., 2018). Irrespective of how often these were considered, lack of consensus was observed in the assessment of lesion size, presence of unavoidable trauma, exposure to tobacco and age. When dealing with lesion size, despite the positive relationship between size and risk of malignant transformation, a not negligible proportion of OMPs (33%) who consider this feature, prefer to actively treat lesions not exceeding 20 mm, thus paying more attention to surgical feasibility and morbidity rather than to the risk of progression. When choosing between surgery or other treatment modalities, similar results were observed, such that 55% of OMPs considered OL size and 68% of them were driven to treat

large lesions. Unfortunately, the present study is not able to determine which alternative treatment modalities OMPs considered when surgery was not the preferred method of choice. Even in the absence of evidence supporting a role for chronic mechanical irritation in oral carcinogenesis (Pentenero, Azzi, et al., 2021), almost half OMPs are driven to active treatment in the presence of unavoidable trauma. OMPs mainly jointly considered the classical exogenous patient-related risk factors (tobacco and alcohol) in order to determine active treatment. Alcohol consumption consistently drove OMPs to treatment. Conversely, even though non-smoker status is considered an important determinant of malignant transformation, tobacco smoking had a highly inconsistent role in driving OMPs to active treatment (Kerr & Lodi, 2021; Speight et al., 2018).

Completely novel results describe the direct involvement of OMPs in the surgical management of OL. Even though oral medicine is frequently defined as aiming to provide diagnosis and mostly non-surgical care for patients, approximately 40% of OMPs undertake surgical treatment (Pentenero, Sutera, et al., 2021) and almost 50% are directly involved in the surgical treatment of OL. The observed strong geographical variation is mainly related to the fact that in Region 1 91% of OMPs always refer patients for surgery and this is consistent with the high proportion of OMPs who do not perform biopsy themselves. Notably, direct involvement of OMPs in surgical treatment is significantly related to different attitudes toward the management of OL. OMPs able to surgically treat OL more often rely on such an approach. Patient referral to perform surgery is less frequently observed not only as expected among OMPs who practice surgery, but also among OMPs with postgraduate training in oral medicine. Overall, OMPs seem to be interested in undertaking surgical treatment of OL themselves. A converse scenario is observed in the presence of early OSCC requiring local excision. In the presence of OSCC, thorough staging assessments are required to allow multidisciplinary oncologic committees to determine recommended treatment. In such cases, few OMPs perform surgery themselves with most respondents preferring to refer patients to maxillofacial or head and neck surgeons who are routinely involved in oncological committees compared to oral surgeons who typically are not.

5 | CONCLUSION

Despite the vast amount of research on OPMDs, clinical lesion-related features, epithelial dysplasia status and traditional diagnostic adjuncts remain the cornerstones of clinical practice for most OMPs in the diagnosis and management of OL. In agreement with previous surveys, a lack of consensus still exists around the management of OPMDs. Taking into account the variety of features considered, risk assessment is still highly dependent on OMPs' opinions, with potential inconsistency in the management of patients. Despite the lack of evidence to support stringent treatment guidelines, such lack of consistency amongst practitioners highlights the need for broad recommendations at minimum to reduce inter-practitioner variability.

AUTHOR CONTRIBUTIONS

Monica Pentenero: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; supervision; validation; writing – original draft. **Samuele Sutera:** Data curation; writing – review and editing. **Giovanni Lodi:** Conceptualization; methodology; writing – review and editing. **Jose V. Bagan:** Conceptualization; methodology; writing – review and editing. **Camile S. Farah:** Conceptualization; methodology; project administration; writing – review and editing.

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CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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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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