A Randomized Controlled Trial on Efficacy of Surgical Excision of Nondysplastic Leukoplakia to Prevent Oral Cancer

Paolo G. Arduino[1], Giovanni Lodi[2], Marco Cabras[1], Alessandra Macciotta[3], Alessio Gambino[1], Davide Conrotto[1], Dora Karimi[1], Giorgia El Haddad[1], Mario Carbone[1], and Roberto Broccoletti[1]

ABSTRACT

The aim of this study was to evaluate the effectiveness of surgical excision to prevent cancer in patients with nondysplastic oral leukoplakia (OL). This study was the first randomized controlled clinical trial comparing surgical treatment with standard care in this group of patients. Patients were divided into two groups. The first group underwent standard care, that is smoking counseling, follow-up visits every 6 months, and control biopsy when indicated. The second group underwent surgical excision, together with standard care. Oral cancer onset was the primary outcome; secondary outcomes included healing, recurrence after surgery, onset of new lesions, and worsening of the primary lesions. The differences in distribution of the patients' and lesions' characteristics were investigated through nonparametrical tests (Wilcoxon rank-sum and Fisher exact). Univariate and multivariate logistic regressions have been performed to estimate the odds ratio of the treatment on the recurrence or worsening of the lesions. A total of 260 patients took part in the study of which 132 were women (50.8%); during the follow-up period, two subjects developed oral cancer, one for each arm. Surgical treatment, when compared with standard care, was associated with a lower probability of the treated zone to remain healed during the follow up period (OR = 7.43; 95% confidence interval, 2.96–22.66). In conclusion, it is possible to assumed that regular clinical follow-up could be considered a reliable standard of care among patients with nondysplastic OLs.

Prevention Relevance: Oral white patches can transform into cancer and none has provided clinical guidelines to prevent it. For the first time ever, we have showed that the clinical follow up of non dysplastic lesions was able to provide benefits if compared with surgical excision.

Introduction

In 1978, the WHO Collaborating Centers for Oral Precancerous Conditions described the term oral leukoplakia (OL) as a "white mucosal lesions that have a risk of progressing to squamous carcinoma" (1). Actually, the term OL is used to identify a "predominantly white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer" (2). A biopsy is required for the differential diagnosis (2). Accordingly, OL could be possibly defined as a clinical term made on a single visit after the elimination of suspected etiologic factors (3, 4).

OL has been often associated with tobacco, smoking or chewing, although idiopathic forms are reported (5). Despite the plausible association of OL with smoking and alcohol, there is a lack of well-designed studies to examine the precise causal association (4, 6); furthermore, published data suggest geographic differences. It is also still uncertain the exact role of alcohol in the etiology of OL, with particular reference to moderate chronic intake and different risk associated with several beverages and drinking pattern (4). Moreover, to date, the role of viruses and systemic conditions for the development of OL needs further investigation (6).

OL has been reported as one of the most common oral potentially malignant disorders (OPMD), affecting 2.60% [95% confidence interval (CI), 1.72%–2.74%] of the worldwide population, with a higher frequency in middle aged and elderly males (7). The majorities of OLs are localized lesions and follow a benign course. Little subsets of these, conversely, acquire progressive dysplastic cellular changes (8) and ultimately develop an oral cancer. This subset of OLs should be viewed as dynamic rather than static lesions, especially since they progress overtime (9), even if it is not possible to truly detect these changes.

The primary objective of treatment should be to prevent onset of cancer, but there is a lack of consensus of the most appropriate method; surgical interventions have never been studied by means of randomized control trials (RCTs; ref. 6).

For the first time ever reported in a randomized approach, the aim of this study was to evaluate the surgical outcome of patients diagnosed with nondysplastic OLs, compared with

[1]Department of Surgical Sciences, CIR-Dental School, University of Turin, Turin, Italy. [2]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy. [3]Department of Clinical and Biological Sciences, University of Turin, Turin, Italy.

Corresponding Author: Paolo G. Arduino, University of Turin, Via Nizza 230, Turin 10100, Italy. Phone: 00393356011953; E-mail: paologiacomo.arduino@unito.it

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patients with the same diagnosis who did not undergo surgery but mere followed-up.

Materials and Methods

Study design and population

This study was designed as a surgical versus standard care RCTs, and performed at the Oral Medicine Unit of the Department of Surgical Sciences, CIR-Dental School, University of Turin, Turin, Italy. It was conducted in line with the principles of the Helsinki Declaration of 1975, as revised in 2000, and accepted by the Main Board of the CIR-Dental School, University of Turin (AP-RB2009/1234), Turin, Italy.

The present trial has been registered with ISRCTN (#12617344) and the report prepared according to the CONSORT statement for improving the quality of reports of RCTs (http://www.consort-statement.org/).

Subjects were recruited among consecutive patients, referred for the clinical evaluation of a single oral white patch with a major axis <20 mm. Patients received detailed information about the study and agreed to participate voluntarily by signing an informed written consent form.

Patient selection

Patients were clinically evaluated by two oral medicine experts (PGA, RB), who recorded the clinical aspect of the lesions, size, and sites of oral involvement. The lesions size was recorded using a disposable millimeter ruler, measuring the major axis; lesions were than divided in two groups: those with a major axis ≤10 mm and those >10 mm. Localization of the lesion was classified according to five zones: gingiva, tongue, buccal mucosa, palate, and inner lip; for the analysis, however, we detailed three groups: tongue, gingiva and palate, and buccal mucosa and inner lip together.

The following demographic and medical details were recorded: age, gender, pregnancy, breastfeeding, smoking and drinking habits, associated systemic disease, history of malignancies, and drug treatments.

A baseline biopsy was undertaken for every patient. After this, the following inclusion and exclusion criteria were adopted:

Inclusion criteria

(1) Clinical diagnosis of OL.
(2) Age > 18 years.

Exclusion criteria

(1) Presence of histological signs of dysplasia.
(2) Presence of histological signs of oral lichen planus, on the basis of WHO criteria (1).
(3) Presence of clinical and histologic signs of proliferative verrucous leukoplakia, on the basis of the 2010 and 2013 classifications (10, 11).
(4) Presence of white lesions on the lip vermillion.
(5) Incapacity to understand verbal and written instructions.
(6) Pregnant or breast-feeding women.
(7) Previous or current diagnosis of oral squamous cell carcinoma.

Randomization

After histologic assessment (every sample was blindly seen by two different medical pathologists, and the final evaluation performed jointly), patients were enrolled and divided into two groups. They were randomly assigned in a 1:1 ratio to surgical or standard treatment with the use of computer-generated sequence (RANCODE version 3.6). The patients were given enrolment number–matched sealed envelopes, including group assignments, which were opened after enrolment. Researchers were blinded to assignment before opening the envelope.

Methods

The first group of patients (GROUPS SC) underwent standard care, consisting of regular follow-up every 6 months and counselling on smoking cessation and moderation of daily alcohol intake (no more than two glasses of wine daily) through delivery of an informative brochure. Such document contained some simple, patient-friendly explanatory information on the risks of OPMD and oral cancer caused by tobacco and alcohol, together with the main contact details of the nearest smoking-cessation centers, as offered by the Italian Observatory on smoke, alcohol, and drugs (12), provided before enrolling and discussed repeatedly during each control visit. Moreover, a control biopsy was performed in case of significant clinical modifications of the observed lesion (changes of color, thickness, size), onset of a new lesion, or whenever the clinician considered appropriate, especially if a malignant change was suspected.

The second group of patients (GROUP TS) underwent surgical excision of the lesion with a traditional scalpel, together with standard care.

Surgical procedure

An experienced oral surgeon (R.B.) made the surgical treatments. Local anesthesia was achieved by infiltration around the lesions using 4% articaine hydrochloride and epinephrine 1:100,000; a number 15 blade, mounted in a number 3 handle, was used for the excision. An elliptic incision was made to fully enucleate the lesion along with the overlying mucosa. When necessary, the wound was sutured with interrupted sutures using silk 4.0 (Perma-Hand). All patients were informed about the procedure and potential complications, and surgical informed consent was acquired.

Clinical assessment and study outcome

To evaluate the clinical response, patients were followed for at least 12 months up to 60. Every 6 months, during each visit, lesions were assessed as follows:

GROUP TS

- Healing (H): if the patient was lesion-free.
- Recurrence (R): if a new leukoplakia arose in the same place of the primary disease.
- New lesion (NL): if a new lesion arose in a different site.
- Oncological Event (OE): if a tumor was diagnosed in the same place of the primary disease.

GROUP SC

- Healing (H): if the patient was lesion free.
- Stable (S): if the primary lesion remained unchanged.
- Worsening (W): if any modification of the primary lesion was observed (changes of color, thickness size) making a control biopsy indicated, regardless of the histologic outcome (except malignant transformation).
- New lesion (NL): if a new lesion arose in a different site.
- Oncological Event (OE): if a tumor developed from the OL.

Outcomes

The primary outcome was the incidence of oral cancer in the same place of the primary disease. Secondary outcomes included: (i) severe adverse events; (ii) clinical fading (in GROUP TS: incidence of recurrences or new lesion; in GROUP SC: clinical worsening of the primary lesions or recurrence of new lesions).

Statistical analysis

Sample size was challenging to estimate based on the lack of any previously reported changes in patients treated with this protocol, thus a *post hoc* estimation of the achieved power was computed: the considered sample size, based on the proportions of recurrence (or worsening) of the lesion observed in the two treatment groups, allowed to determine the two-sample equivalence (considering a noninferiority margin at least of 0.15) with a statistical power of 90% and an α probability error of 5%.

All the efficacy analyses were performed on the intent-to-treat (ITT) population, with primary efficacy end points determined for all patients by follow-up clinical examination at 5 years. For those subjects whose endpoint measurements were not available, the ITT analysis utilized the most recent measurements to determine the clinical response outcome.

A descriptive analysis was performed on age, gender, risk factors (smoking and drinking habits), clinic-pathological characteristics (lesions' type, localization, and size), and duration of follow-up. Continuous variables were expressed as median and interquartile range, categorical variables as frequencies and percentages. Nonparametrical tests (Wilcoxon rank-sum and Fisher exact tests for continuous and categorical variables, respectively) were used to analyze differences in distribution of the variables listed above by the treatment (surgery or not surgery). Univariate and multivariate (adjusted by potential confounders) logistic regressions were performed to estimate the OR of the treatment on the recurrence or worsening (clinical or histologic) of the lesions. Statistical analyses were performed using R software (version 3.6.2). Statistical significance was defined at P value of ≤ 0.05.

Results

A total of 300 patients were screened from September 2009 to June 2014; of these, 25 were excluded (23 had dysplastic lesion, 1 presented a neoplastic lesion, and 1 reported to be pregnant after first biopsy) and 15 refused to be part of this study. Finally, 260 subjects met the eligibility criteria; **Figure 1** shows the flow diagram for patients' enrolment and selection. No deviation from the operative protocol occurred. Of the 260 patients participating the study, all were Caucasian and 132 were women (50.8%).

The demographic and clinical characteristics of the enrolled subjects are reported in **Table 1**. At baseline, the demographic, risk profile, and clinical characteristics were evenly distributed in the two groups regarding age, smoking, and alcohol habits, but not for gender; in particular, male subjects were allocated more frequently in the surgical group than female ($P = 0.03478$). More than 84% of the initial lesions were described as homogenous. The gingiva was the site most commonly affected (38.1%), followed by the buccal mucosae (28.1%), the tongue (23.5%), palate and inner lips (9.2% and 1.1% respectively). Almost 60% of the total case were bigger than 10 mm in diameter; the mean diameter was 11.8 mm (SD $\pm$ 4.18; **Fig. 2**).

One hundred and thirty patients were enrolled in each group. From those allocated to intervention, 12 were lost because they did not show up on the day of surgery and 3 withdrew in the first 12 months of follow-up. In the SC group, 5 subjects abandoned in the first 12 months of follow-up. Finally, 110 patients were evaluated in GROUP TS and 125 in GROUP SC. Regarding demographic and risk profile also in the finally analyzed group of patients, male subjects underwent more surgical sessions than female ($P = 0.037$).

Regarding the site of involvement, a difference was noticed between the two groups: more tongue lesions were treated with surgery, but less on buccal mucosae, gingiva, and palate ($P = 0.008$). However, no differences in size were noticed ($P = 0.5078$).

During follow-up, 2 subjects (0.9%), both males, 1 in each arm, developed oral cancer in the same site of the primary OL, with a mean time of 49.5 months after the initial diagnosis (SD $\pm$ 12.02). Clinical features of the tumors and habits of the two subjects are reported in **Table 2**; tumor grade according to the WHO classification was also detailed, moderately or poorly differentiated (G1, G2, or G3 respectively). Because of the limited number of cancers reported, the evaluation of the oncologic event was nonstatistically significant ($P > 0.999$ with Fisher exact test).

Regarding the secondary outcomes, patients treated with surgery showed a poorer outcome. Five cases of the untreated lesions (4%) got worse, whereas 50 cases (40%) improved (in terms of a smaller detailed evaluation), and 70 cases (56%) remained stable. In the surgery group, a new white change was diagnosed again in 10 patients (9.1%), bigger than baseline (with similar histopathological pattern), whereas 16 patients (14.5%) showed a recurrence similar in size from the baseline, with one displaying mild dysplasia. **Table 3** showed that there was a possible association between the standard care group and a better clinical outcome evolution ($P < 0.0001$).

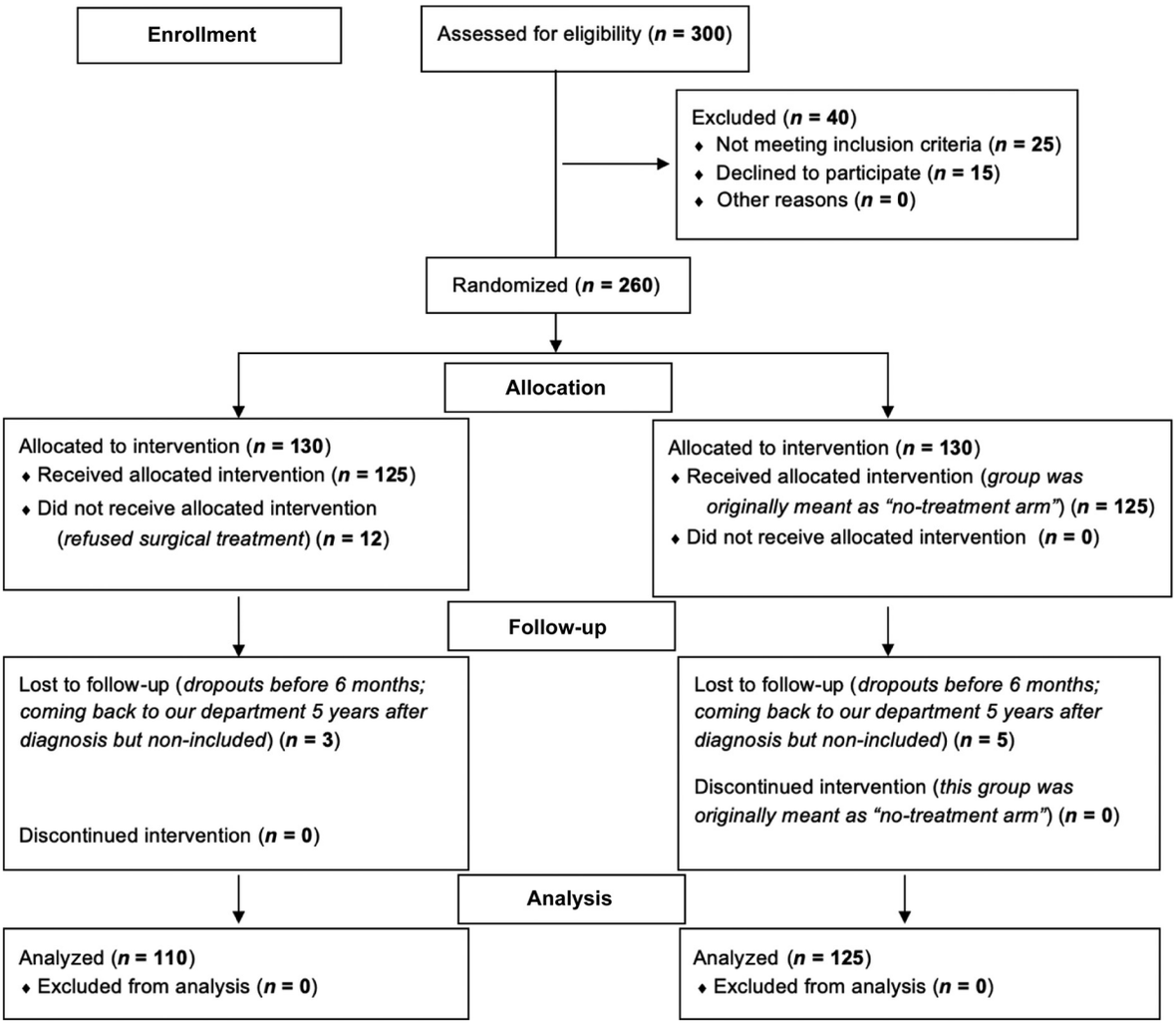

Figure 1.
CONSORT flowchart of the study.

Logistic regression models showed that surgical treatment was associated with a lower probability of the treated area to remain healthy with no recurrences (OR = 7.43; 95% CI, 2.96–22.66), when compared with nonsurgical treated areas, in which it was possible to see few cases of worsening and more lesions remained stable. Even adjusting for probable confounders, the OR estimate did not lose its significance: the association between treatment and clinical outcome did not seem to depend on the other characteristics of the subjects under study, potential confounders of the association (**Table 4**).

No new lesions arose in different sites of the oral cavity and no severe adverse events were detailed.

Discussion

No surgical RCTs are actually available in literature regarding the most appropriate method of management for OPMDs; however, for nondysplastic lesions, it has been said that standard care might be enough as regards to their long-term management, but with no comparison provided with surgical excision (6). Thus, the need to test this hypothesis, by comparing these two approaches in a prospective, randomized manner.

To the best of our knowledge, this is the first report comparing the effectiveness of standard care versus surgical treatment in the management of patients with nondysplastic OLs. This study failed to identify any significant differences between the two treatments in terms of cancer onset, suggesting that surgical excision of the lesion may not significantly affect this outcome in patients with nondysplastic OL; surgery moreover seemed to be associated with a poorer outcome.

According to recent Cochrane review (6), a range of topical and systemic approaches have been tested in various

Table 1. Demographic and clinical characteristics of the study population (at randomization and at the final evaluation; **Fig. 1**).

Variables at randomization		Group TS ($n = 130$) *n* (%)	Group SC ($n = 130$) *n* (%)	Total ($n = 260$) *n* (%)	Test for homogeneity (*P* value)
Age and gender	Age (median [IQR])	60.00 [53.00, 70.00]	59.00 [52.00, 70.00]	59.00 [53.00, 70.00]	0.979[a]
	Gender				0.034[b]
	Male	72 (55.4%)	56 (43.1%)	128 (49.2%)	
	Female	58 (44.6%)	74 (56.9%)	132 (50.8%)	
Risk factors	Smoking status				0.917[b]
	Current smoker	58 (44.6%)	57 (43.9%)	115 (44.2%)	
	Never smoker	47 (36.2%)	51 (39.2%)	98 (37.7%)	
	Ex smoker	25 (19.2%)	22 (16.9%)	47 (18.1%)	
	Alcohol status				0.356[b]
	Drinker	39 (30%)	47 (36.2%)	86 (33.1%)	
	Non-drinker	91 (70%)	83 (63.8%)	174 (67.7%)	
Clinico-pathologic characteristics	Clinical type				1[b]
	Homogeneous	110 (84.6%)	109 (83.8%)	219 (84.2%)	
	Non-homogeneous	20 (15.4%)	21 (16.2%)	41 (15.8%)	
	Histopathology				—
	No dysplasia	130 (100%)	130 (100%)	260 (100%)	
	Local site				0.049[b]
	Tongue	40 (30.8%)	23 (17.7%)	63 (24.3%)	
	Gum/palate	56 (43.1%)	65 (50.0%)	121 (46.5%)	
	Buccal/inner lip	34 (26.1%)	42 (32.3%)	76 (29.2%)	
	Size				0.615[b]
	<10 mm	52 (40%)	57 (43.8%)	109 (41.9)%)	
	>10 mm	78 (60%)	73 (56.2%)	151 (58.1%)	

Variables at evaluation		Group TS ($n = 110$) *n* (%)	Group SC ($n = 125$) *n* (%)	Total ($n = 235$) *n* (%)	Test for homogeneity (*P* value)
Age and gender	Age (median [IQR])	60.00 [53.00, 70.00]	59.00 [52.00, 70.00]	59.00 [53.00, 70.00]	0.979[a]
	Gender				0.037[b]
	Male	63 (57.3%)	54 (43.2%)	117 (49.8%)	
	Female	47 (42.7%)	71 (56.8%)	118 (50.2%)	
Risk factors	Smoking status				0.601[b]
	Current smoker	47 (42.7%)	58 (46.4%)	105 (44.7%)	
	Never smoker	44 (40%)	48 (38.4%)	92 (39.1%)	
	Ex-smoker	19 (17.3%)	19 (15.2%)	38 (16.2%)	
	Alcohol status				0.212[b]
	Drinker	31 (28.2%)	45 (36.0%)	76 (32.3%)	
	Nondrinker	79 (71.8%)	80 (64%)	159 (67.7%)	
Clinico-pathologic characteristics	Clinical type				0.568[b]
	Homogeneous	97 (88.2%)	106 (84.8%)	203 (86.4%)	
	Nonhomogeneous	13 (11.8%)	19 (15.2%)	32 (13.6%)	
	Histopathology				
	Hyperplasia				
	Yes	96 (87.3%)	105 (84%)	201 (85.5%)	0.578[b]
	No	14 (12.7%)	20 (16%)	34 (14.5%)	
	Ortho-keratosis				0.529[b]
	Yes	88 (80%)	95 (76%)	183 (77.9%)	
	no	22 (20%)	30 (24%)	52 (22.1%)	
	Para-keratosis				0.691[b]
	yes	98 (89.1%)	109 (87.2%)	207 (88.1%)	
	No	12 (10.9%)	16 (12.8%)	52 (22.1%)	
	Acanthosis				
	yes	64 (58.2%)	70 (56%)	134 (57%)	0.792[b]
	No	46 (41.8%)	55 (44%)	101 (43%)	
	Hypergranulosis				
	yes	67 (60.7%)	74 (59.2%)	141 (60%)	0.89[b]
	No	43 (39.3%)	51 (40.8%)	94 (40%)	

(Continued on the following page)

Table 1. Demographic and clinical characteristics of the study population (at randomization and at the final evaluation; **Fig. 1**). (Cont'd)

Variables at evaluation		Group TS ($n = 110$) *n* (%)	Group SC ($n = 125$) *n* (%)	Total ($n = 235$) *n* (%)	Test for homogeneity (*P* value)
	Chorium mild inflammation				
	Yes	58 (52.8%)	70 (56%)	128 (54.5%)	0.69[b]
	No	52 (47.2%)	55 (44%)	107 (45.5%)	
	Local site				0.008[b]
	Tongue	39 (35.5%)	22 (17.6%)	61 (26.0%)	
	Gum/palate	44 (40.0%)	63 (50.4%)	107 (45.5%)	
	Buccal/inner lip	27 (24.5%)	40 (32.0%)	67 (28.5%)	
	Size				0.508[b]
	<10 mm	43 (39.1%)	55 (44%)	98 (41.7)%)	
	>10 mm	67 (60.1%)	70 (56%)	137 (58.3%)	

[a]Wilcoxon Rank-Sum test.
[b]Fisher exact test.

RCTs, varying from vitamin A, retinoids, carotene, carotenoids, NSAIDs, herbal extracts, bleomycin. Despite some encouraging, short-term effects in reduction of OL size coming from vitamin A and β-carotene, many of the studies included were affected by a high risk of bias, providing a body of evidence of very low quality. In addition, only five studies included oral cancer onset among the outcomes, none of which showed any benefit in terms of cancer incidence. More notably, this review highlighted the absence of RCTs regarding the effectiveness of surgery, the most common approach chosen in the treatment of patients with OL. In line with what suggested by Lodi and colleagues (6), as well as in other papers (13) regarding the urgency for RCTs on this specific matter, we carried out this RCT to provide some preliminary evidence concerning role of surgery on patients with nondysplastic OL.

As previously said, we failed to show a benefit of surgical excision, in terms of reduction of cancer onset in subjects affected by nondysplastic OL. Oral cancer developed in 0.9% of the subjects undergoing surgery plus standard care, compared with 0.8% among those treated with standard care only. Such percentages are not so surprising, with one of the most recent systematic reviews (14), reporting a wide range of malignant transformation for OL from 0.13% to 34%, and an overall malignant rate of 3.5%. Moreover, development of a T3 lesion from a nondysplastic OL could be considered as somehow unexpected, if no proper context is given. It is worth noticing that a timespan of 6 months, as that chosen in the present study, can be occasionally sufficient for a persistent OPMD to evolve into an invasive OSCC, especially if located in a high-risk site, such as ventral surface of the tongue, of a patient smoking 20 cigarettes per day, unresponsive to any attempt of smoking cessation (**Table 2**). Once again, this unpredictable, although isolated, outcome confirms lack of data about which exact amount of time can be reliable for follow-up recall visit amid patients with OPMDs.

Furthermore, a 9.1% recurrence as novel onset of OL with higher diameter than baseline was detected in surgery group, being two-fold higher than the 4% worsening rate of OL undergoing mere clinical follow-up.

This work bears strengths and limitations. The main strength of this study relied in its novelty, being the first prospective RCT

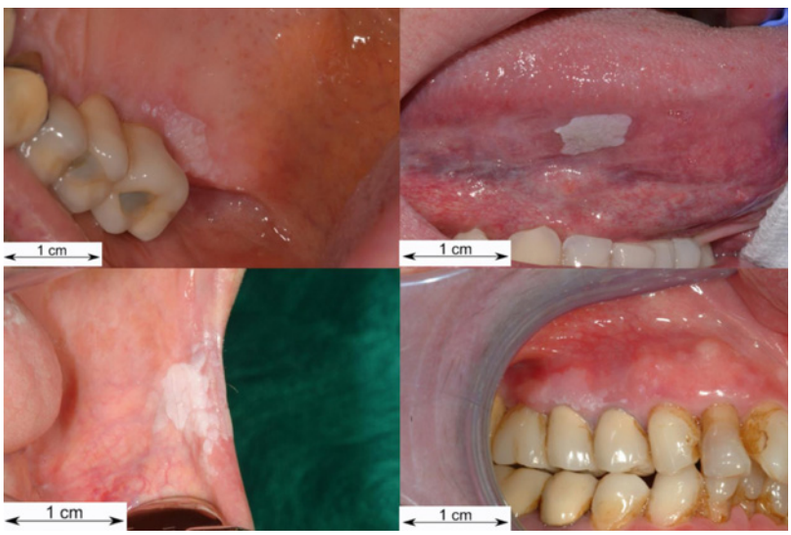

Figure 2.
Different clinical pictures of homogeneous OLs (clockwise): top right palatal gingiva; right lateral border of the tongue; left anterior buccal mucosa; top right vestibular gingiva.

Table 2. Characteristics of OL patients with malignant development.

Pt	Sex	Age[a]	Medical history	Baseline site of OL diagnosis	Main characteristic of OL	Clinical characteristics	Group	Site of cancer	TNM[b]	Grading	Tobacco usage	Alcohol usage	Latency[c]
1	M	92	Hypertension	Left ventral surface of tongue	Homogenous, >1 cm in diameter	– Relapsed 1 year after excision, as homogeneous plaque – Unchanged for 2 years – Sudden change in the last 6 months as wider, hardened nonhomogeneous plaque with speckled pattern	TS	Left ventral surface of tongue	T1N0M0	G1	None	None	41
2	M	55	Unremarkable	Right ventral surface of tongue	Homogenous, >1 cm in diameter	– Since biopsy, stable appearance as homogeneous plaque – Persistent and stable for 4 years – Sudden change of appearance in the last 6 months as nonhomogenous plaque with focal ulceration	SC	Right ventral surface of tongue	T3N0M0	G2	20 cig/daily	None	58

[a]At malignant development.
[b]T classification and neck nodes involvement at the time of diagnosis (16).
[c]Follow-up in months before the cancer diagnosis.

to ever explore the role of surgery in preventing malignancy and recurrence of nondysplastic OL. Furthermore, although single-center, this trial could rely on a low dropout rate, with less than 20% of patients allocated in both groups lost throughout the years, and an adequate follow-up, extended from a minimum of 12 months to a maximum of 5 years.

Evidently, this trial has certain limitations. First, the relatively small number of patients enrolled, with no more than 235 patients distributed between the two groups. Second, no differential treatment was conducted among patients enrolled in the TS group, choosing scalpel alone, rather than scalpel versus laser-mediated surgery. This choice must be considered, since it might have provided some influence on the recurrence rate. Data on this specific aspect, however, are contrasting, with scalpel surgery still remaining the gold standard: a recent retrospective study (15) on dysplastic and nondysplastic OLs was able to detect significantly lower recurrence rates amid those treated with Er:YAG when compared with scalpel. On the other hand, our experience suggested no significant differences between these two approaches, as reported in a 5-year prospective study on nondysplastic OLs (16), with Er:YAG laser showing some advantages in term of milder pain and better acceptance by the patients in the immediate postoperative period (17). Third, gingival onset of OL was the most common event within this sample, with more than a third (38%) of OLs detected in this site. These data are only partially in agreement with what shown by previous study, where frequency of gingival OL ranged from 18% to 38% (18, 19). However, in our clinical experience gingival localization is not so rare for premalignant condition, with up to 86.4% of all gingival OPMD being nondysplastic OLs, as previously reported by our group (20); moreover, very few data in literature is available, as to whether the present cohort could be considered a reliable representation of the spectrum of appearance of nondysplastic OLs. To our knowledge, no study has been published providing such a detailed, site-by-site distribution of nondysplastic OLs alone, on a sample of adult Caucasian patients of a similar scale to that of 245 individuals enrolled in the present trial (4). Furthermore, it is well known that gingiva might be affected by white patches or plaques in cases of frictional keratosis, as well. Regarding this matter, we aimed to minimize the overlapping between these two entities, which might otherwise lead to an overestimation of frequency of gingival OL by giving a timeline of at least 4 weeks after removal of possible mechanical causes (i.e., vigorous brushing) to any white lesion of the attached gingiva of suspected frictional etiology. Whenever such approach offered no signs of remission in this timespan, and histopathology lead to a pattern of oral leukoplakia, such diagnosis was considered valid. Third, we selected a group of patients at relatively low risk. We have reported a percentage of dysplastic events in our group of 7.6%, mainly because the clinical type of lesions selected; data from literature analysis confirmed that homogeneous and small OL usually showed dysplasia in less than 10% of total cases, in line with our data (21). As reported, our patients were all affected by

Table 3. Analysis to examine the significance of the association between treatment (surgery or no surgery) and the clinical outcome (healing or worsening/recurrence of the lesion).

	Group TS ($n = 110$) *n* (%)	Group SC ($n = 125$) *n* (%)	Total ($n = 235$) *n* (%)	Test for homogeneity (*P* value)
Months of follow up				0.718[a]
Time (median [IQR])	72.00 [36.00, 72.00]	72.00 [36.00, 72.00]	72.00 [36.00, 72.00]	
Surgery vs. standard care				<0.0001[b]
Healing	84 (76.4%)	120 (96.0%)	204 (86.8%)	
Worsening/recurrence	26 (23.6%)	5 (4.0%)	31 (13.2%)	

[a]Wilcoxon Rank-Sum test.
[b]Fisher exact test.

nondysplastic OL, and the great majority (84%) had lesions with homogenous pattern and major axis smaller than 20 mm. These characteristics might have also influenced the low rate of events (oral cancer) in both groups after 5 years of follow-up (21). In a previous work conducted on a sample of 254 leukoplakias (22), nonhomogeneity (OR = 7.0) and more than 200 mm^2 of diameter (OR = 5.4) seemed to exert a significantly higher impact on the onset of cancer, rather than histologic findings, with dysplasia being irrelevant on later onset of cancer.

Conversely, histologic grading was a significant factor for malignant transformation in a more recent analysis of 85 leukoplakias from Northern Spain (23).

The low percentage of nonhomogeneous lesions (less than 16%) in the present trial might also have affected the relatively low recurrence rate (9%) of surgically excided OLs. As confirmed by a recent multicenter study (24) conducted on 226 patients, nonhomogeneity was more significantly associated with recurrence of OL ($P = 0.021$) than dysplasia or smoking. Similarly, in a 20-year hospital-based retrospective study (25), despite lack of information on the potential role played by dysplasia, nonhomogeneous OLs were once again the subset of OLs significantly more associated to malignancy (OR = 6.26; 95% CI, 3.16–12.38).

In our evaluation, the placebo-controlled approach was not pursued, due to the all-or-none nature of surgery as treatment, and the absence of measurement of subjective, patient-related measurements, for example pain, oral health profile scale measurements—that could have been influenced by the differential exposure to surgery. For the same reasons, in this study no blinded evaluation of the outcome measures was provided, with the aim to have the same experienced clinicians (PGA and RB) carrying out the most precise evaluations, especially in terms of actual recurrence In TS group and tangible worsening in the SC group. Moreover, we speculated that if the same few clinicians were to carry out the follow-up visits and measurements throughout the years, this first-hand methodology would have provided a higher adherence to the trial, due to the trustworthiness coming from continuity of care.

In this sense, it is our intention to carry out such evaluations even further in time, while at the same time enrolling new patients willing to undergo surgery and/or clinical follow-up for nondysplastic OLs in our Department. In addition, as a group (University of Milan and University of Turin), we have just started a new RCT similar to this first one but also considering both dysplastic and nondysplastic OPMDs.

In conclusion, it emerged that regular clinical follow-up after initial biopsy can be considered a reliable standard of care, with surgical excision unable to provide significant benefits. However, with a relatively small cohort of patients enrolled, and less than 1% of patients developing cancer in each group, it is not possible to draw a clear conclusion regarding the differential

Table 4. Univariate and multivariate (adjusted by potential confounders) logistic regression models of the treatment on the clinical outcome.

	Univariate logistic regression			
	OR	95% CI		*P* value
Surgery (yes vs. no)	7.43	2.96	22.66	<0.0001
	Multivariate logistic regression			
	OR	95% CI		*P* value
Surgery (yes vs. no)	9.98	3.78	31.97	<0.0001
Age	1.01	0.97	1.05	0.43
Gender (M vs. F)	1.66	0.69	4.08	0.26
Smoking habits (yes vs. no)	1.40	0.51	3.81	0.50
Drinking habits (yes vs. no)	1.86	0.78	4.40	0.15
Local site (gum/palate vs. tongue)	1.39	0.48	4.27	0.55
Local site (buccal/inner lip vs. tongue)	1.88	0.59	6.37	0.29

efficacy of surgery against observation alone, with further studies on larger samples, ideally from different ethnicities, being required to evaluate these preliminary findings. These results are more of a step forward for enhanced management of the treatment of nondysplastic oral lesions; however, it would be interesting to know if this statement would be the same with a greater number of patients or in a different clinical setting.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

P.G. Arduino: Conceptualization, data curation, supervision, validation, investigation, methodology, writing-original draft, project administration, writing-review and editing. **G. Lodi:** Methodology, writing-original draft, writing-review and editing. **M. Cabras:** Conceptualization, data curation, formal analysis, validation, writing-review and editing. **A. Macciotta:** Data curation, formal analysis, validation, methodology. **A. Gambino:** Data curation, investigation, writing-review and editing. **D. Conrotto:** Supervision, validation, investigation. **D. Karimi:** Validation, visualization, project administration. **G. El Haddad:** Formal analysis, writing-review and editing. **M. Carbone:** Conceptualization, resources, data curation. **R. Broccoletti:** Investigation, visualization, methodology, writing-original draft.

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