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

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Abstract

The aim of this study was to evaluate the effectiveness of surgical excision to prevent oral cancer in patients diagnosed with an oral leukoplakia (OL). This study was the first randomized controlled clinical trial comparing surgical treatment with standard care in this group of patients. After histological confirmation, patients were divided into two groups. The first group underwent standard care, i.e. smoking counselling, follow-up visits every six months, and control biopsy when indicated. The second group underwent surgical excision of the lesion with a traditional scalpel, 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 non-parametrical tests (Wilcoxon Rank-Sum and Fisher's Exact). Univariate and multivariate logistic regressions have been performed in order 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 men 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% CI=2.96-22.66). In conclusion, from these results, it emerged that regular clinical follow-up with habit cessation, after initial biopsy, can be considered a reliable standard of care, with surgical excision unable to provide benefits among patients with non-dysplastic OLs.

Key words: oral leukoplakia; standard care; surgery; clinical trial; outcome; malignant transformation.

Introduction

In 1978, the WHO Collaborating Centres 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 definitive histopathological diagnosis and the assessment of epithelial dysplasia, if present, in the specimen (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 frequent (5). Despite the association of OL with smoking and alcohol is plausible and reasonable, there is a lack of well-designed studies to examine the precise causal association (4, 6), and no systematic reviews on this matter. Furthermore, published data suggest geographic differences. It is also still uncertain the exact role of alcohol in the aetiology 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 (OPMDs), affecting 2.60% (95% confidence interval 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.

Most OLs are asymptomatic; therefore, the primary objective of treatment should be to prevent onset of cancer; although a number of options for treatment of OL are available, there is a lack of consensus on the most appropriate method of management and ways to minimize the potential malignant transformation (6). Surgical interventions, also including laser therapy and cryotherapy, have never been studied by means of randomized control trials (RCTs) that included a no treatment or placebo arm. Currently, there is no evidence of a treatment that could be really effective for preventing the development of oral cancer (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 an OL, without baseline signs of dysplasia, compared to 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 *vs* standard care randomized controlled clinical trial, and performed at the Oral Medicine Unit of the Department of Surgical Sciences, CIR-Dental School, University of 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).

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 randomised controlled trials (http://www.consort-statement.org/).

Subjects were recruited among consecutive patients, referred for the clinical evaluation and the histological determination of a single oral white patch with a major axis < 20 mm.

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.

Demographic and medical details were recorded; they included: age, gender, pregnancy, breastfeeding, smoking and drinking habits, associated systemic disease, history of malignancies, and drug treatments.

The lesions size was recorded using a disposable millimetre ruler, measuring the major axis; lesions were than divided in two groups: those with a major axis ≤ than 10 mm and those > 10 mm. The localization of the lesion was classified according to five zones: gingiva, tongue, buccal mucosa, palate and lip; for the analysis, however, we detailed three groups: tongue, gingiva and palate, and buccal mucosa and lip together.

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

Inclusion criteria

a) clinical diagnosis of OL, confirmed by histological examination;

b) age > 18 years;

Exclusion criteria

a) presence of histological signs of dysplasia;

b) incapacity to understand verbal and written instructions;

c) pregnant or breast-feeding women;

d) previous or current diagnosis of oral squamous cell carcinoma.

Randomization

After histological confirmation (for every samples always confirmed by two different pathologists), 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 that included group assignments. The allocation sequence was assured by using sealed envelops, which were open 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 six months and counselling on smoking cessation and moderation of daily alcohol intake (no more than 2 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 (10), provided before enrolling and discussed repeatedly during each control visit. Moreover, a control biopsy has to be

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 every surgical treatment. Local anaesthesia was achieved by infiltration around the lesions using a solution of 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®, Ethicon, NJ, USA).

All patients were informed about the surgical procedure and potential complications, and standard informed consent was obtained before any intervention.

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 tumour 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 histological outcome (except malignant transformation).
- New lesion (NL): if a new lesion arose in a different site.
- Oncological Event (OE): if a tumour 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: 1) severe adverse events, and 2) 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 has been 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 2-sample equivalence (considering a non-inferiority margin at least of 0,15) with a statistical power of 90% and an alpha 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), clinico-pathological characteristics (lesions' type, localization, and size), and follow-up time. Continuous variables have been expressed as median and interquartile range, categorical variables as frequencies and percentages. Non-parametrical tests (Wilcoxon Rank-Sum and Fisher's Exact tests for continuous and categorical variables, respectively) were used in order to analyse differences in distribution of the variables listed above by the treatment (surgery or not surgery). Univariate and multivariate (adjusted by potential confounders) logistic regressions have been performed to estimate the Odds Ratio of the treatment on the recurrence or worsening (clinical or histological) of the lesions. All 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

those, 25 were excluded (23 had dysplastic lesion, one presented a neoplastic lesion and one 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=.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 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 (SD ± 4.18) (Fig. 1).

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 non-intervention group, 5 subjects abandoned in the first 12 months of follow-up. Lastly, 110 patients were evaluated in GROUP TS and 125 in GROUP SC. Regarding demographic and risk profile also in the finally analysed group of patients, male subjects underwent more surgical sessions than female (p =.037). Regarding the site of involvement, a difference has been noticed between the two groups: more tongue lesions were treated with surgery, but

less on buccal mucosae, gingiva and palate (p=.008). However, no differences in size were noticed (p=.5078).

During the follow-up period, two subjects (0.9%), both males, one 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 ± 12.02). The clinical features of the tumours and some lifestyle characteristics of these two subjects are reported in Table 2; tumour grade according to the WHO classification was also detailed as well, moderately or poorly differentiated (G1, G2 or G3 respectively). Due to the limited number of cancers reported, the evaluation of the oncological event was non-statistically significant (P=1 with Fisher Exact's test).

Regarding the secondary outcomes, patients treated with surgery showed a poorer outcome. Five cases of the untreated lesions (4%) got worse, while 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 has been diagnosed again in 10 patients (9.1%), bigger than baseline (with similar histopathological pattern), while 16 patients (14.5%) showed a recurrence similar in size from the baseline, one also displaying a mild dysplasia. Table 3 showed that there was a possible association between the standard care group and a better clinical outcome evolution (p<.0001).

Logistic regression models allowed us to see 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), if compared to non-surgical 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 does not therefore 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 site of the oral cavity and no severe adverse events were detailed.

Discussion

No RCTs are actually available in literature regarding the most appropriate method of management for OPMDs; however, for non-dysplastic lesions, it has been repeatedly 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 OL. The present 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 affect this outcome in patients with OL with no signs of dysplasia. Surgery however seemed to be associated with a poorer outcome if compared to the standard care.

According to the most recent Cochrane review available on this subject (6), a range of topical and systemic approaches have been tested in various 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 beta-carotene, many of the studies included in the systematic review 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 co-workers (6), as well as in other papers (11) 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 non-dysplastic OL.

As previously said, we failed to show a benefit of surgical excision, in terms of reduction of cancer onset in subjects affected by non-dysplastic OL, when compared with standard care. 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 (12) 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 non-dysplastic OL could be considered as somehow unexpected, if no proper context is given. It is worth noticing that a timespan of six 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.

The present work bears strengths and limitations. The main strength of the present study relied in its novelty, being the first prospective randomized clinical trial to ever explore the role of surgery in preventing malignancy and recurrence of non-dysplastic OL. Furthermore, although single-centre, the present 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.

Clearly, this trial has some limitations, as well. Firstly, the relatively small number of patients enrolled, with no more than 235 patients distributed between the two groups. Secondly, 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 taken into account, 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 13-year retrospective study (13) on dysplastic and non-dysplastic OLs was able to detect significantly lower recurrence rates amid those treated with Er:YAG when compared to scalpel. On the other hand, our experience suggested no significant differences between these two approaches, as reported in a 5-years prospective study on non-dysplastic OLs (14), with Er:YAG laser showing some advantages in term of milder pain and better acceptance by the patients in the immediate post-operative period (15). Thirdly, gingival onset of OL was the most common event within this sample,

with more than a third (38%) of OLs detected in this site. This data is only partially in agreement with what shown by previous study, where frequency of gingival OL ranged from 18% to 38 (16,17). However, in our clinical experience gingival localization is not so rare for premalignant condition, with up to 86.4% of all gingival OPMD being non-dysplastic OLs, as previously reported by our group (18). 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. Thirdly, 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, confirming our data (19). As reported, our patients were all affected by non-dysplastic 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 five years of follow-up (19). In a previous work conducted on a sample of 254 leukoplakias (20), non-homogeneity and size seemed to exert a significantly higher impact on the onset of cancer, rather than histological findings. Specifically, 66 non-homogeneous lesions revealed an

OR of 7.0 for cancerization against the 188 homogenous counterparts, and lesions surpassing 200 mm^2 in diameter carried an OR of 5.4 for cancerization against smaller lesions. Conversely, presence of dysplasia in the first biopsy was not significant for further onset of cancer when compared to not-dysplastic lesions.

Concerning this matter, literature showed conflicting results, with histological grading being instead a significant factor for malignant transformation in a more recent analysis of 85 leukoplakias from Northern Spain (21).

The low percentage of non-homogeneous 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 multicentre study (22) conducted on 226 patients, non-homogeneity was significantly associated with recurrence of OL (P = 0.021), more than dysplasia or smoking. Similarly, in a twenty-years hospital based retrospective study from Southern Iran (23), despite lack of information on the potential role played by dysplasia, non-homogeneous OLs were once again the subset of OLs significantly more associated to malignancy (OR: 6.26; 95% CI=3.16-12.38).

OL may derive from one or several clones of cells within a larger oral mucosal area. possibly comprising other defamed cells invisible for routine clinical and histological consideration. These features may explain lacking success of surgical excision, with such a scenario being further complicated by the potential cancer stimulus, which may be provided by surgery itself (11, 24).

In our evaluation, the placebo-controlled approach was not pursued, differently from other RCTs testing either topical or systemic formulations, due to the all-or-none nature of surgery as treatment, and the absence of measurement of

subjective, patient-related measurements - e.g. 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) to carry 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 non-dysplastic OLs in our Department.

Moreover, 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 non-dysplastic OPMDs.

In conclusion, from these results, 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. These results are more of a step forward for enhanced management of the treatment of non-dysplastic 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.

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Conflict of interest

The authors declare that they have no conflict of interest.

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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 & Gender	**Age** (median [IQR])	60.00 [53.00, 70.00]	59.00 [52.00, 70.00]	59.00 [53.00, 70.00]	.979§
	Gender				.03478°
	Male	72 (55.4%)	56 (43.1%)	128 (49.2%)	
	Female	58 (44.6%)	74 (56.9%)	132 (50.8%)	
Risk factors	**Smoking status**				.9176°
	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				.3562°
	Drinker	39 (30%)	47 (36.2%)	86 (33.1%)	
	Non-drinker	91 (70%)	83 (63.8%)	174 (67.7%)	
Clinico-pathological characteristics	**Clinical type**				1°
	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				.049°
	Tongue	40 (30.8%)	23 (17.7%)	63 (24.3%)	
	Gum/palate	56 (43.1%)	65 (50.0%)	121 (46.5%)	
	Buccal/lip	34 (26.1%)	42 (32.3%)	76 (29.2%)	
	Size				.6152°
	< 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 & Gender	**Age** (median [IQR])	60.00 [53.00, 70.00]	59.00 [52.00, 70.00]	59.00 [53.00, 70.00]	.979§
	Gender				.037°
	Male	63 (57.3%)	54 (43.2%)	117 (49.8%)	
	Female	47 (42.7%)	71 (56.8%)	118 (50.2%)	
Risk factors	**Smoking status**				.601°
	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				.212°
	Drinker	31 (28.2%)	45 (36.0%)	76 (32.3%)	
	Non-drinker	79 (71.8%)	80 (64%)	159 (67.7%)	
Clinico-pathological characteristics	**Clinical type**				.5681°
	Homogeneous	97 (88.2%)	106 (84.8%)	203 (86.4%)	
	Non-homogeneous	13 (11.8%)	19 (15.2%)	32 (13.6%)	
	Histopathology				1°
	No dysplasia	110 (100%)	125 (100%)	235 (100%)	
	Local site				.008°
	Tongue	39 (35.5%)	22 (17.6%)	61 (26.0%)	
	Gum/palate	44 (40.0%)	63 (50.4%)	107 (45.5%)	
	Buccal/lip	27 (24.5%)	40 (32.0%)	67 (28.5%)	
	Size				.5078°
	< 10 mm	43 (39.1%)	55 (44%)	98 (41.7)%)	
	> 10 mm	67 (60.1%)	70 (56%)	137 (58.3%)	

§Wilcoxon Rank-Sum's test
°Fisher Exact's test

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 one year after excision, as homogeneous plaque - Unchanged for 2 years - Sudden change in the last 6 months as wider, hardened non-homogeneous 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 non-homogenous 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.

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				.718§
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				<.0001°
healing	84 (76.4%)	120 (96.0%)	204 (86.8%)	
worsening/recurrence	26 (23.6%)	5 (4.0%)	31 (13.2%)	

§Wilcoxon Rank-Sum's test
°Fisher Exact's test

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

Univariate Logistic Regression				
	OR	**Confidence Interval 95%**		**p-value**
Surgery (yes *vs* no)	7.43	2.96	22.66	<0.0001
Multivariate Logistic Regression				
	OR	**Confidence Interval 95%**		**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/lip *vs* tongue)	1.88	0.59	6.37	0.29

Figure 1. CONSORT flowchart of the study.