



Malignant transformation of oral leukoplakia treated with carbon dioxide laser: a meta-analysis

Yunmei Dong¹ · Yuxin Chen¹ · Yan Tao¹ · Yilong Hao¹ · Lu Jiang¹ · Hongxia Dan¹ · Xin Zeng¹ · Qianming Chen¹ · Yu Zhou¹

Received: 19 July 2018 / Accepted: 25 October 2018 / Published online: 15 November 2018
© Springer-Verlag London Ltd., part of Springer Nature 2018

Abstract

A series of studies are dedicated to research the clinical outcomes of oral leukoplakia (OLK) treated with carbon dioxide laser (CO₂ laser); however, the results vary from studies especially related to recurrence and malignant transformation. Hence, we performed this meta-analysis to precisely evaluate the malignant transformation of OLK dealt with CO₂ laser and investigate the association between its malignant transformation and kinds of related risk factors, such as gender, clinical classification, long duration of leukoplakia, and degree of epithelial dysplasia and lesion regions. We performed a systematic search of the Cochrane Library, EMBASE, Pubmed, Web of Science, and SCOPUS. Single-arm rate of the overall risk of malignant transformation in OLK treated with CO₂ laser was calculated using the Der-Simonian Liard method. We applied subgroup analysis to compare the risk of malignant transformation according to the degree of epithelial dysplasia, clinical type, and region of OLK. Moreover, a pooled odds ratio (OR) is calculated, along with its 95% confidence interval (CI), to compare the risk of malignant transformation according to patients' gender, tobacco, and alcohol consumption. We used the meta package of R software for quantitative data synthesis and analysis. The rate of malignant transformation of OLK treated with carbon dioxide laser ranged from 0 to 15.38% in included studies. The overall rate of malignant transformation of OLK treated with CO₂ laser is 4.50% under the random effect model [95% CI 0.0305–0.0659]. A systematic review of observational studies of OLK reported that the estimated overall (mean) malignant transformation rate was 3.5%, with a wide range between 0.13 and 34.0%. Interestingly, our result revealed that it was the male, homogeneous type, no tobacco consumption, and without alcohol-use who had a higher tendency of malignancy after laser surgery. However, this result lack statistically significant data. Generally speaking, whether oral leukoplakia patients underwent laser surgical treatment or not, it may have little effect on malignant transformation. In addition, we strongly advise that it had better not to perform CO₂ laser intervention on OLK patients with the following clinical characteristics: homogeneous type, male, no tobacco consumption, and without alcohol-use. Evidence is still lacking in terms of relationship between malignant transformation and risk factors among OLK patients managed with CO₂ laser. Thus, these associations should be further investigated.

Keywords Meta-analysis · Oral leukoplakia · Carbon dioxide laser · Malignant transformation · Oral dysplasia · Oral potentially malignant disorders

Introduction

Oral leukoplakia (OLK) is “a white plaque of questionable risk having excluded other known diseases or disorders that carry no increased risk for cancer”, as defined by the World

Health Organization (WHO) Collaborating Centre for Oral Cancer and Precancer in 2005 [1]. It is one of the most common oral potentially malignant disorders (OPMDs) in the clinical practice of oral medicine, affecting 2.60% (95% confidence interval 1.72–2.74%) of the worldwide population with a higher frequency in middle aged and elderly males [2]. It can occur on any surface of the oral mucosa, and the most commonly described locations are the mandibular alveolus (25.2–40%), buccal mucosa (21.9–46%), palate (27%) or tongue (26%), and floor of mouth (19.3%) [3–6]. Most patients present with multifocal disease [4, 5]. Owing to its potential malignant transformation to oral squamous cell carcinoma (OSCC), OLK has gained great attention from clinicians. A

✉ Yu Zhou
812471898@qq.com

¹ State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, No. 14, Section 3, Renmin South Road, Chengdu 610041, Sichuan, China

systematic review of observational studies of OLK reported the estimated overall (mean) malignant transformation rate was 3.5%, with a wide range between 0.13 and 34.0% [7]. It is confirmed that several factors are closely related to malignant transformation of oral leukoplakia, such as age, gender, tobacco and alcohol habits, clinical classification, degree of epithelial dysplasia, lesion location and size, and HPV infection.

Currently, interventions used to prevent OLK from occurring malignant transformation contain surgical treatment (cryotherapy, laser treatment, and cold knife surgery), chemotherapy (vitamin A and retinoid, beta-carotene or carotenoids, non-steroidal anti-inflammatory drugs, and herbal extracts) and photodynamic therapy. However, there is no treatment shown to prevent the recurrence or significantly reduce malignant development in long-term follow-up studies [8].

Given that laser surgery is associated with low intraoperative and postoperative complication rates, laser surgery is one of the most common surgical treatments of OLK. The main potential advantages of laser surgery are as follows: Firstly, it can excise or evaporate the lesions selectively and cause the minimal damage to the surrounding healthy tissues. Secondly, postoperative wound healing condition is excellent and there is no visible scar. Thirdly, almost all the laser surgery could be done under local anesthesia on an outpatient basis and so on. Besides pain, other reported complications are mental nerve paresthesia, lingual nerve paresthesia, headache, sialadenitis, granuloma formation, and bleeding. Compared to the traditional scalpel, lasers have been increasingly used in oral leukoplakia since the 1970s [9–13]. Among kinds of laser types (CO₂ laser, Nd:YAG laser, diode laser, and KTP laser), CO₂ is the most widely used to manage OLK in clinical practice. The intrinsic property of the CO₂ laser is determined by its wavelength of 10.6 μm. Because of the strong absorption in soft tissues, CO₂ laser light causes a superficial vaporization and excision with minimal thermal damage to the surrounding tissues [14].

A series of studies are dedicated to research the clinical outcomes of OLK treated with CO₂ laser; however, the results vary from studies especially related to recurrence and malignant transformation. Hence, we performed this meta-analysis to precisely evaluate the malignant transformation of OLK dealt with CO₂ laser and investigate the association between its malignant transformation and kinds of related risk factors, such as gender, clinical classification, and degree of epithelial dysplasia and lesion regions.

Materials and methods

We followed the guidelines of the MOOSE statement during the preparation of this meta-analysis [15].

Search strategy

A systematic search of the Cochrane Library, EMBASE, Pubmed, Web of Science and SCOPUS was performed by two investigators to identify all the related studies. No restrictions were placed on the date of publication and language when searching electronic databases. We also scanned the bibliography of included studies to identify any missed studies that are relevant to our subject. The following key words and/or corresponding Medical Subject Heading terms were used: oral leukoplakia or oral potentially malignant disorders or epithelial dysplasia or premalignant lesions or white lesions, and vaporization or CO₂ laser or laser surgery, and malignant transformation or recurrence or risk factors or treatment outcome.

Study inclusion criteria

Studies enrolled in the meta-analysis must meet the following eligibility criteria according to the PICOS principle: (1) Patients: all the patients were definitely diagnosed as OLK through clinical manifestations and histological examination. (2) Intervention: the lesions were evaporated or excised by CO₂ laser. (3) Control: studies are compared to other interventions or no control group. (4) Outcome: after the treatment, recurrence or malignant transformation occurred during a mean follow-up time more than 12 months. (5) Study design: Examples are RCT, retrospective cohorts, case-control studies, and prospective investigations.

Exclusion criteria

The exclusion criteria are as follows: (1) The studies are conference abstracts, articles published as a whole in a non-English language. (2) The studies did not provide clear outcome measures during the defined observation period. (3) Those studies were published for the same study population or unoriginal studies.

Screening and data extraction

All articles identified by our search underwent a preliminary screening of their titles and abstracts to determine whether they met the inclusion criteria or not. Data were extracted from the included studies by two reviewers independently, including authors, published year, country in which the study was performed, number of cases, length of follow-up period, laser parameters, related risk factors, and the incidence of malignant transformation in different subgroups of OLK patients. In the event of disagreement between the two reviewers regarding whether a study met the inclusion criteria, a consensus was reached by the third reviewer.

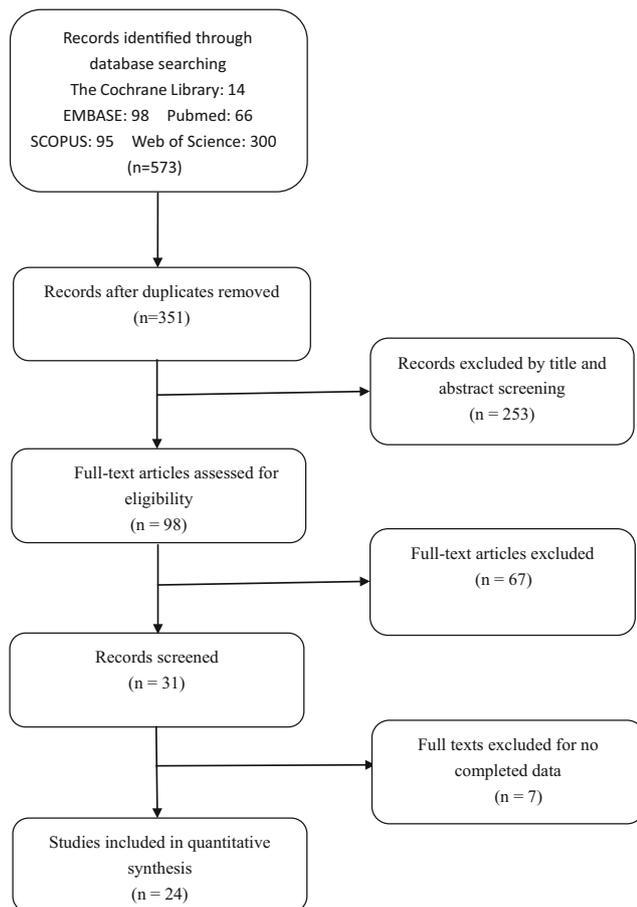


Fig. 1 A flow diagram of literature search and study selection process

Risk of bias assessment

It is well known that randomization is not always possible or feasible in surgical research, and in this meta-analysis, all included articles are non-randomized and lacked of control group. There are few validated instruments to evaluate the quality of observational or non-randomized studies, in terms of the readers' perspective and the purpose of meta-analysis. The Methodological Index for Non-Randomized Studies (MINORS) [16, 17] is applied to each article to further assess the quality of each study. It involves 12 items, the first 8 items specifically designed for non-comparative studies and the remaining 4 items applied to comparative studies. Items are scored as 0 (not reported), 1 (reported but inadequate), and 2 (reported and adequate). The maximum ideal score for non-comparative studies is 16 and for comparative studies 24. Because most of the relevant researches lacked of control group in this meta-analysis, each included study is evaluated based on the following eight terms:

1. A clearly stated aim: the question addressed should be precise and relevant in the light of available literature.

2. Inclusion of consecutive patients: all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion).
3. Prospective collection of data: data were collected according to a protocol established before the beginning of the study.
4. Endpoints appropriate to the aim of the study: unambiguous explanation of the criteria used to evaluate the main outcome which should be in accordance with the question addressed by the study. In addition, the endpoints should be assessed on an intention-to-treat basis.
5. Unbiased assessment of the study endpoint: blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise, the reasons for not blinding should be stated.
6. Follow-up period appropriate to the aim of the study: the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events.
7. Loss to follow-up less than 5%: all patients should be included in the follow up. Otherwise, the proportion lost to follow-up should not exceed the proportion experiencing the major endpoint.
8. Prospective calculation of the study size: information of the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes.

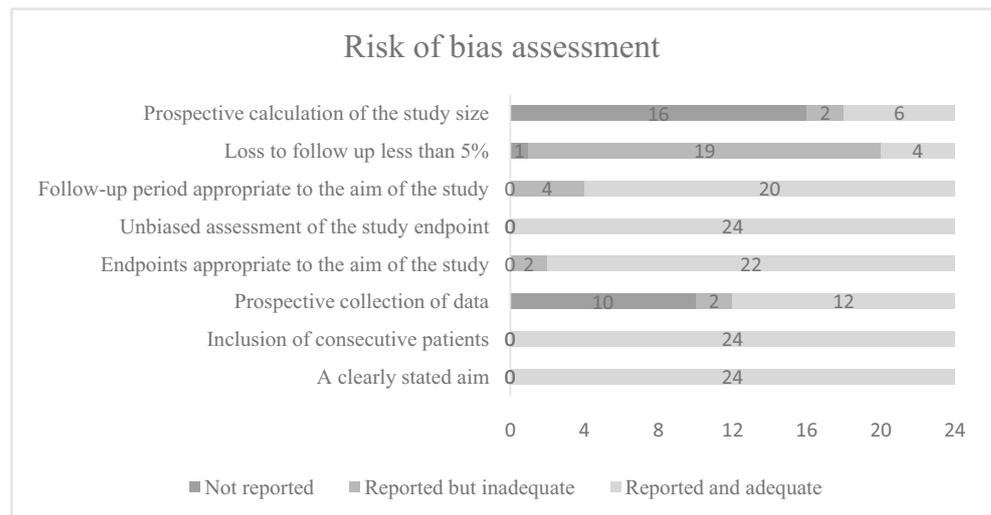
Data synthesis and analysis

Single-arm rate of the overall risk of malignant transformation in OLK treated with CO₂ laser was calculated. I^2 tests were used to evaluate the heterogeneity of included studies: $I^2 < 25\%$ indicating low heterogeneity, 25–50% indicating moderate heterogeneity, and $> 50\%$ indicating a high degree of heterogeneity. If there was statistical significance ($p < 0.05$) with heterogeneity, data analyses were performed using the random effects model; otherwise, the fixed effects model was used. We applied subgroup analysis to compare the risk of malignant transformation according to the degree of epithelial dysplasia, clinical type, and region of OLK. In addition, a pooled odds ratio (OR) is calculated, along with its 95% confidence interval (CI), to compare the risk of malignant transformation according to patients' gender, smoking, and alcohol consumption. We used the Meta package of R software which is a free open software for quantitative data synthesis and analysis.

Table 1 General characteristics of included studies

Study	Country	Patients	Number of OLS	Treatment	Malignant transformation rate (%)	Laser type	Follow up (months)	MINOR
Roodenburg1991 [18]	Netherlands	70	103	Vaporization	0.00	Sharpplan 791\15e20 W	63.6	15
Hamadah2009 [19]	UK	78	78	Excision	3.85	Ultra-pulse CO ₂ laser\10-15w	58	13
Lim2010 [20]	Australia	45	59	Vaporization	5.08	Sharpplan 743\10-15 W	43	14
Jornet2013 [10]	Spain	20	20	Excision	0.00	Lasersat 20 W\5-15 W	27.90 ± 12.05	12
Chu1988 [21]	USA	29	38	Excision	2.63	Coherent 450/451/15-25 W	60	13
Schoelch1999 [22]	USA	55	55	Excision	9.09	Xanar\1-20 W	32	11
Chiesa1993 [23]	Italy	167	167	Excision	2.99	Continuous wave\9e12 W	52	14
Dunsche2000 [24]	UK	91	168	Excision	1.19	3e5 W	35.2	14
Frame1985 [14]	UK	69	75	Excision	0.00	Sharpplan\10w	29	10
Pedrosa2015 [25]	Portugal	59	59	Vaporization	10.17	6e15 W	43.75	12
Thomson2002 [26]	UK	57	62	Excision	6.45	UI	18	11
Galletta2017 [27]	Brazil	40	49	Excision	4.08	UML-30\5-10 W	22	11
Depe2011 [28]	Germany	91	91	Vaporization	1.10	Deka\1-20w	120	11
Jerjes2012 [29]	UK	77	123	Excision\ vaporization	6.50	Sharpplanspcw\2e15 W	76.8	15
Matsumoto2015 [30]	Japan	35	38	Vaporization	0.00	3-10w	120	11
Gooris1999 [31]	Netherlands	23	27	Excision	0.00	Sharpplan 791\10w	50.9	13
Giacomo2015 [32]	Italy	30	30	Vaporization	0.00	Deka Smart office\8-15w	60 ± 32.49	13
Ishii2004 [33]	Japan	38	38	Excision	0.00	15-20w	40	11
Van der2005 [34]	Netherlands	200	282	Excision\ vaporization	2.63	Sharpplan 40C\15e20 W	52	15
Mogedas2015 [35]	Spain	65	65	Vaporization	0.71	Sharpplan 791 CO ₂	15	12
Chandru2005 [36]	Australia	43	73	Vaporization	15.38	laser\15-20w	47.2	11
Yang2011 [37]	Taiwan	114	114	Excision	4.11	Sharpplan 743\10e15 W	40.8	15
Brouns2014 [38]	Netherlands	35	35	Excision	11.40	Lumenisew\12e15 W	61.5	11
Monteiro2017 [39]	Italy	15	15	Vaporization	14.29	4-8w	35	13
				Excision	0.00	CO ₂ 10,600 nm laser\5w		

Fig. 2 Risk of bias assessments



Results

Search results and studies selection

According to the pre-established document retrieval strategy, 573 articles were included through the electronic and manual searches. Figure 1 shows the process of the studies selection. First, 222 articles were excluded because of duplication, and then we excluded 253 articles after the screening of the titles and abstracts. Second, when conducting full-text screening, 67 articles were excluded from the study because of the inconsistencies with our research purpose, and seven studies were excluded for no complete data. Finally, there were 24 studies included in quantitative data synthesis and analysis, and among these 18 studies were from Europe, 2 from the USA, 3 from Asia, and 1 from Brazil. In the included studies, a total of 1546 OLK patients with 1864 lesions underwent CO₂ laser excision or vaporization, and 79 lesions eventually developed into OSCC. The rate of malignant transformation of OLK treated with carbon dioxide laser ranged from 0 to 15.38% in individual studies. The basic characteristics of the enrolled studies are summarized in Table 1.

Risk of bias assessment

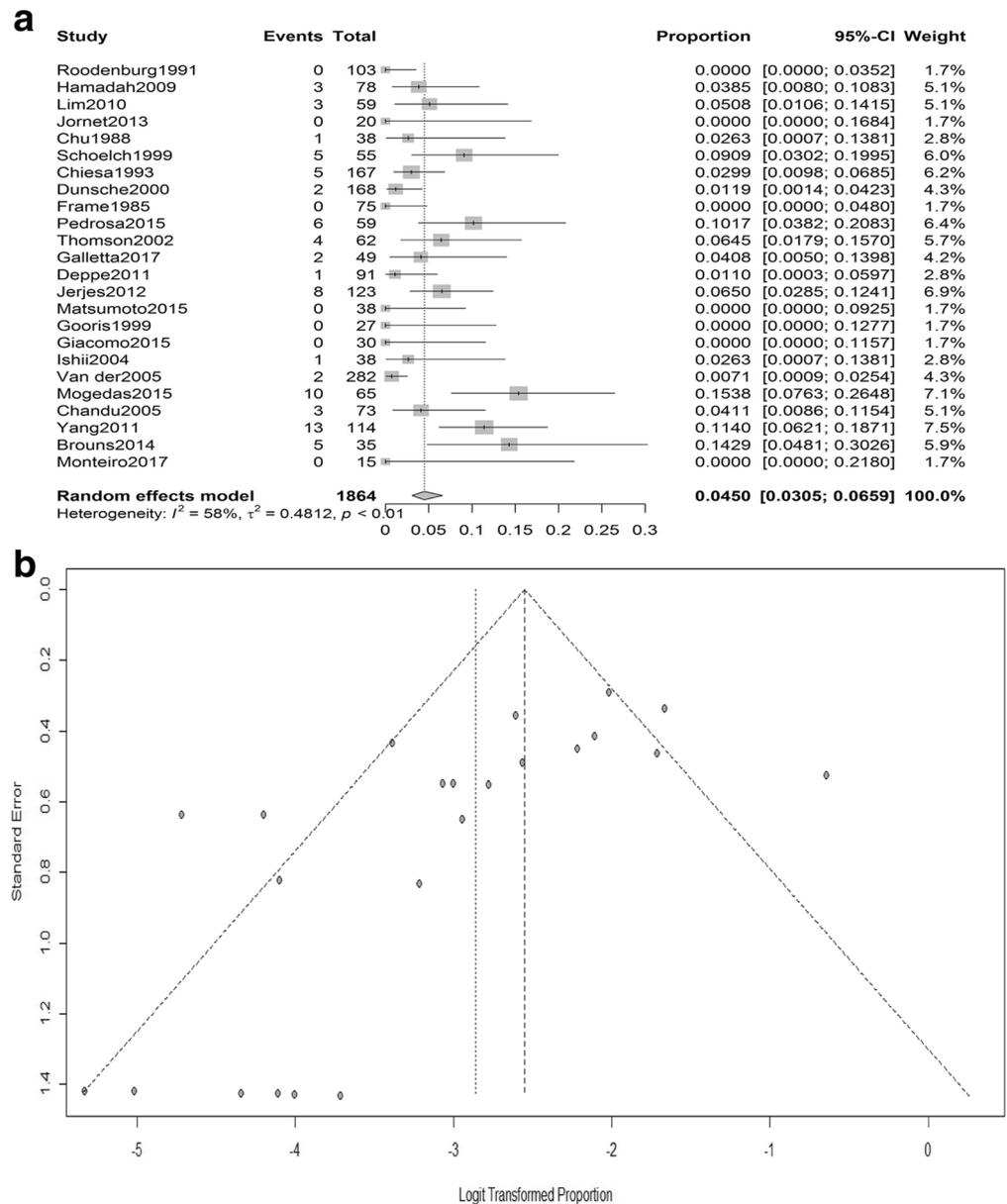
All of the selected articles were assessed for methodological quality. The quality score of each study was presented in Table 1. Each study's MINOR score was more than or equal to 10 points and there were 12 articles were above 12 points. It indicated the number of high-quality studies clearly accounted for significant advantages, as shown in Fig. 2.

Meta-analysis results

Single-arm meta-analysis was used to calculate the pooled proportion (PP) of malignant transformation of OLK treated with CO₂ laser. Owing to the $I^2 = 66\%$ and $p < 0.01$, there was a considerable heterogeneity among the results of individual studies. Hence, we chose the random effects model and used DerSimonian Liard method, which resulted in an overall pooled proportion (PP) of 4.50% [95% CI 0.0322–0.0734] (Fig. 3a). Funnel plot (Fig. 3b) and Egger test were used for the potential publication bias evaluation. Generally, the p value of Egger test was < 0.01 , indicating that there may be existing publication bias in our meta-analysis. So we conducted a trim and fill analysis and the overall PP is 7.18% [95% CI 0.0481–0.1060] (Fig. 4).

We performed subgroup analysis according to the degree of epithelial dysplasia, clinical type, and subsite of OLK (Table 2). The results of subgroup analysis indicated that the rate of malignant transformation was 5.78% [95% CI 0.0162–0.01862] in homogeneous OLK and 5.35% [95% CI 0.0189–0.1419] in non-homogeneous OLK (Fig. 5a). Regarding to the degree of epithelial dysplasia, the rate of malignant transformation was 5.52% [95% CI 0.0198–0.1442] in non-dysplasia, 5.23% [95% CI 0.0248–0.1069] in slight dysplasia, 12.57% [95% CI 0.0646–0.2304] in moderate dysplasia, and 24.98% [95% CI 0.1646–0.3600] in severe dysplasia (Fig. 5b). In terms of subsites of OLK, the rate of malignant transformation was 15.04% [95% CI 0.0641–0.3139] in the buccal mucosa, 14.13% [95% CI 0.0706–0.2627] in the floor of mouth, 10.59% [95% CI 0.0441–0.2329] in the gingiva, 7.46% [95% CI 0.0182–0.2599]

Fig. 3 Forest plots for **a** the pooled proportion of malignant transformation of OLK treated with CO₂ laser under the random effects model, using Der-Simonian Liard method, and **b** funnel plot of the 24 studies included in the meta-analysis



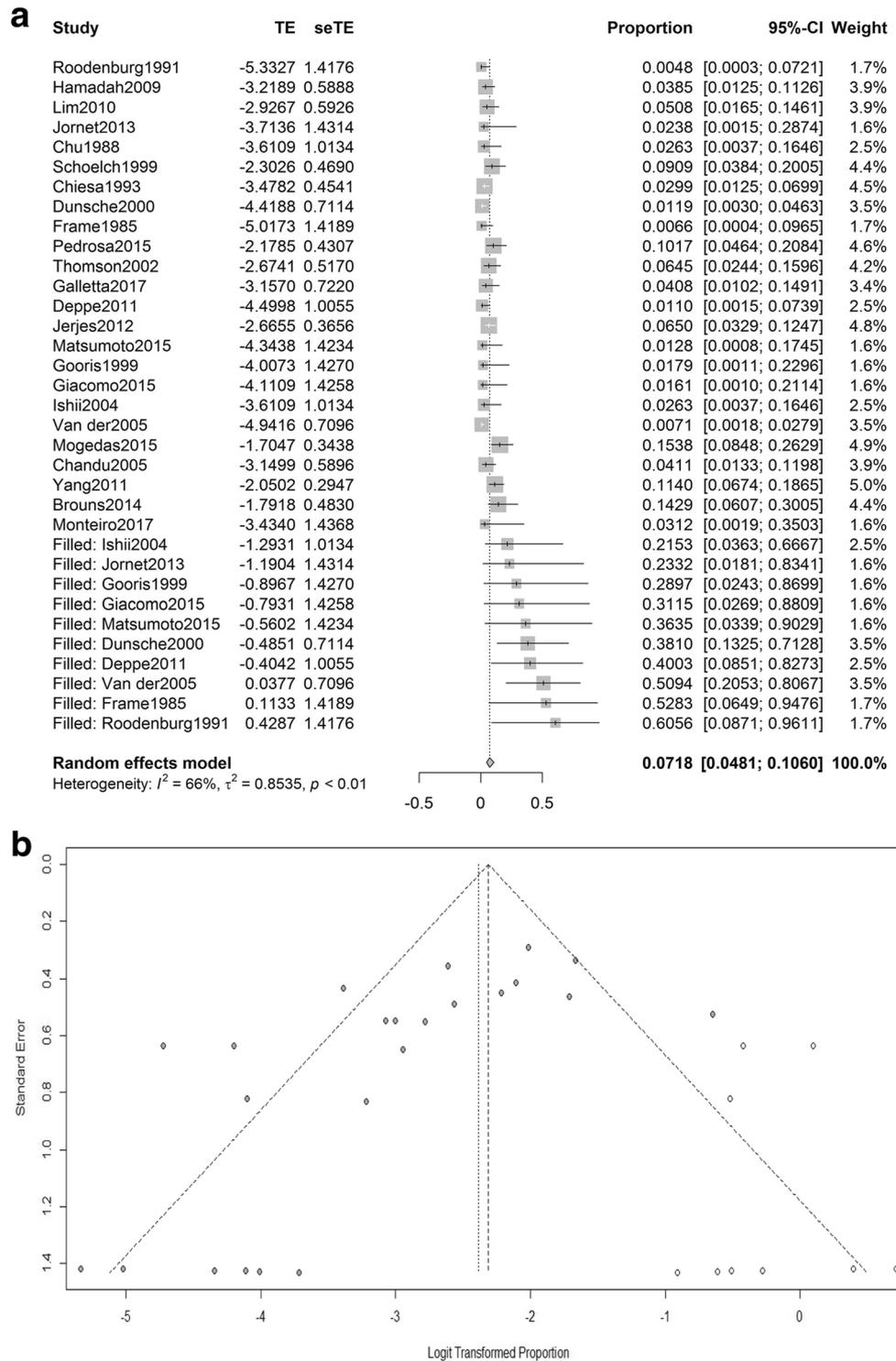
in the lip, 14.71% [95% CI 0.0367–0.4381] in the palate, 8.79% [95% CI 0.0121–0.4301] in retromolar trigone, and 13.3% [95% CI 0.0824–0.2077] in the tongue (Fig. 5c).

Compared to females, males had a significantly higher rate of malignant transformation (OR = 1.7283, 95% CI [0.7380–4.0475]); however, this difference was not statistically significant (Fig. 6a). Interestingly, malignant transformation was more prevalent among non-smokers than smokers (OR = 0.5529 [95% CI 0.2389–1.2798]) (Fig. 6b); and the rate of malignant transformation of alcohol consumers was lower than non-alcohol consumers (OR = 0.9951 [95% CI 0.1498–6.6121]) (Fig. 6c). Regardless of smoking and drinking, there was no statistical difference between them (Table 3).

Discussion

We performed a comprehensive yet careful selection of included studies to provide the most robust evidence about the malignant transformation of OLK under the intervention of CO₂ laser. To the best of our knowledge, the current paper is the first comprehensive meta-analysis dedicated to pool the malignant transformation rate of OLK treated with CO₂ laser. Through rigorous screenings, 24 eligible articles were included with a total of 1546 patients with 1864 lesions in this study. Among included studies, we found that the rate of malignant transformation ranged from 0.00% [10, 14, 18, 30, 31, 33] to 15.38% [39], and the overall rate was 4.50% [95% CI 0.0305–0.0659].

Fig. 4 Forest plots (a) and funnel plot (b) through trim and fill analysis



Every case of leukoplakia must be regarded as at risk of developing to OSCC, not only OLK with dysplasia [40]. It is obviously acknowledged that patients diagnosed with OLK possessing the following characteristics have a greater risk of cancerization: advanced age, female sex, leukoplakia exceeding 200 mm², non-homogeneous type

(e.g., erythroleukoplakia) and the higher grades of dysplasia, etc. [7]. Yet there is still no generally approved standard systematic therapy regimen for treating oral leukoplakia to prevent oral cancer so far [41]. Although there is no evidence showing that treatment prevents from OLK developing into OSCC, some clinicians believe that the

Table 2 The results of subgroup analysis according to the degree of clinical aspect, grade of dysplasia, and lesion location

Factors	Group	Proportion	95% Confidence interval	Effects model
Clinical aspect		0.0565	0.0267–0.1156	Random effects model
	Homogeneous	0.0578	0.0162–0.1862	
	Non-homogeneous	0.0535	0.0189–0.1419	
Grade of dysplasia		0.1104	0.0726–0.1643	Random effects model
	None	0.0552	0.0198–0.1442	
	Slight	0.0523	0.0248–0.1069	
	Moderate	0.1257	0.0646–0.2304	
	Severe	0.2498	0.1646–0.3600	
Lesion location		0.1281	0.0945–0.1714	Fixed effects model
	Buccal	0.1504	0.0641–0.3139	
	Floor of mouth	0.1413	0.0706–0.2627	
	Gingiva	0.1059	0.0441–0.2329	
	Lip	0.0746	0.0182–0.2599	
	Palate	0.1471	0.0367–0.4381	
	Retromolar trigon	0.0879	0.0121–0.4301	
	Tongue	0.133	0.0824–0.2077	

removal of lesions can reduce the malignant tendency to some extent, especially those with a higher tendency to malignant transformation. A 10-year study demonstrated that an 11.6% 10-year risk of malignant transformation in patients without resection, higher than 10.1% with surgical intervention [42]. At the same time, there also exists another point that surgery as an invasive behavior may increase the risk of malignant transformation based on the concept of field canceration, in particular, inappropriate surgical procedures. Oral leukoplakia may be a complex clinically and histologically visible lesion derived from one or several clones of cells within a larger oral mucosal area comprising other clones of cancer-stigmatized cells invisible for routine clinical and histological examination [43]. It is easy to remove the tissue whose appearance has changed, but it is very difficult to eradicate all the genetically altered cells. During the process of postoperative wound healing, the ability of proliferation of the residual altered cells are better than normal mucosal cells [44], and molecular signature generated in microenvironment may stimulate cancer growth [45]. These characteristics may explain the lacking success of surgical excision, and the scenario is further complicated by a possible cancer promotional stimulus by surgery. CO₂ laser as a surgical approach faces the same problem.

Certain factors (gender, age, the grade of dysplasia, affected sites, lesion size, clinical aspect, alcohol consumption, tobacco consumption, multiple-focus OLK, systematic disease history, etc.) are intrinsic elements related to malignant transformation and free from treatment adopted [46]. Several studies were dedicated to find out which clinicopathological features patients with oral leukoplakia had can achieve better

results with carbon dioxide laser. Brouns and Jerjes et al. reported that non-homogeneous leukoplakia ($p < 0.01$), severe dysplasia ($p < 0.01$), lesion size ≥ 4 cm ($p = 0.034$), heavy life-long smokers ($p < 0.01$), and heavy life-long alcohol consumers ($p < 0.01$) may face a higher malignant transformation rate, and the floor of the mouth and ventral tongue remain high-risk sites for precancer; the retromandibular/ mandibular alveolus region appears to be a particularly high-risk site for OSCC development [29, 38]. Mogedas-Vegara et al. pointed that lesion location in the gingiva as opposed to the tongue had a history of OSCC showed a tendency to be risk factors for malignant transformation [35]. In terms of different laser surgical means, Ishii et al. demonstrated that laser excision is suitable for leukoplakia cases on non-keratinized epithelia (such as the tongue and buccal mucosa), while laser vaporization is suitable for the gingival cases [33]. The results of a long-term follow-up of treated patients with oral homogeneous leukoplakias pointed out that the surgical laser protocol respecting the complete excision of leukoplakias, by the removal of a minimum of 1 mm in lesion depth and 3 mm of surrounding healthy-like tissues offers significantly the highest success rate [47]. In overview of all included articles, most malignant transformations occurred in cases with recurrence, but it also could happen without a prior recurrence [37, 38].

Our meta-analysis supported the notion that the overall rate of malignant transformation of OLK treated with CO₂ laser was 4.50% under the random effect model. The results of the meta-analysis suggested the interfered lesions with higher grade of dysplasia and/or located in the oral mucosal danger area faced an increased risk of developing to OSCC, which was consistent with most studies' results. Interestingly,

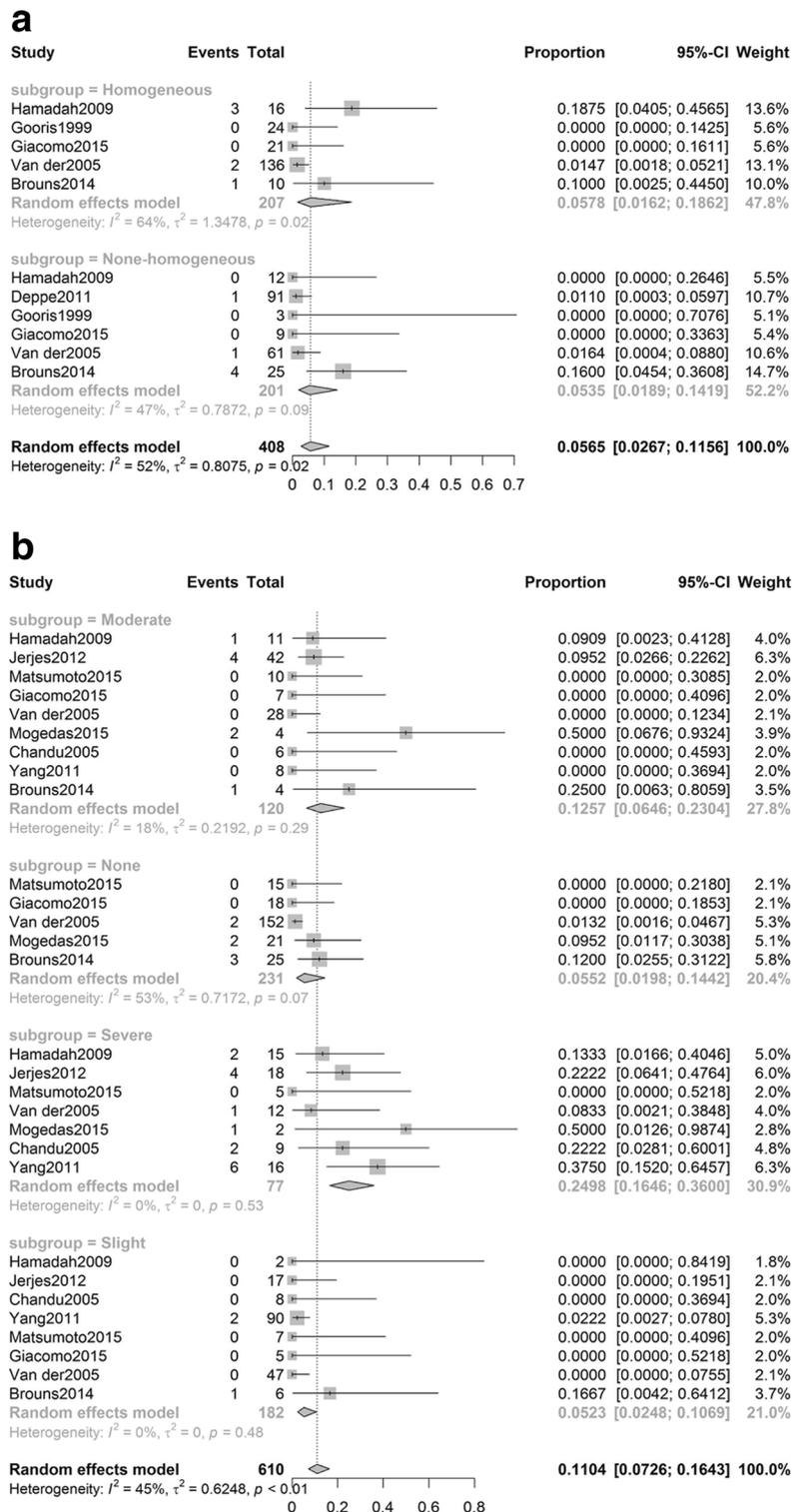


Fig. 5 A forest plot of stratification analysis by the clinical type (a), the degree of epithelial dysplasia (b), and subsite of OLK (c)

our result revealed that it was male, homogeneous type, no tobacco consumption, and without alcohol-use who had a higher tendency to malignancy after laser surgery; however, this result lack statistically significant data.

Above all, it should be prudent to choose which means to manage oral leukoplakia, especially involving surgical methods. Future development of molecular markers may help to determine the risk of malignant leukoplakia transformation

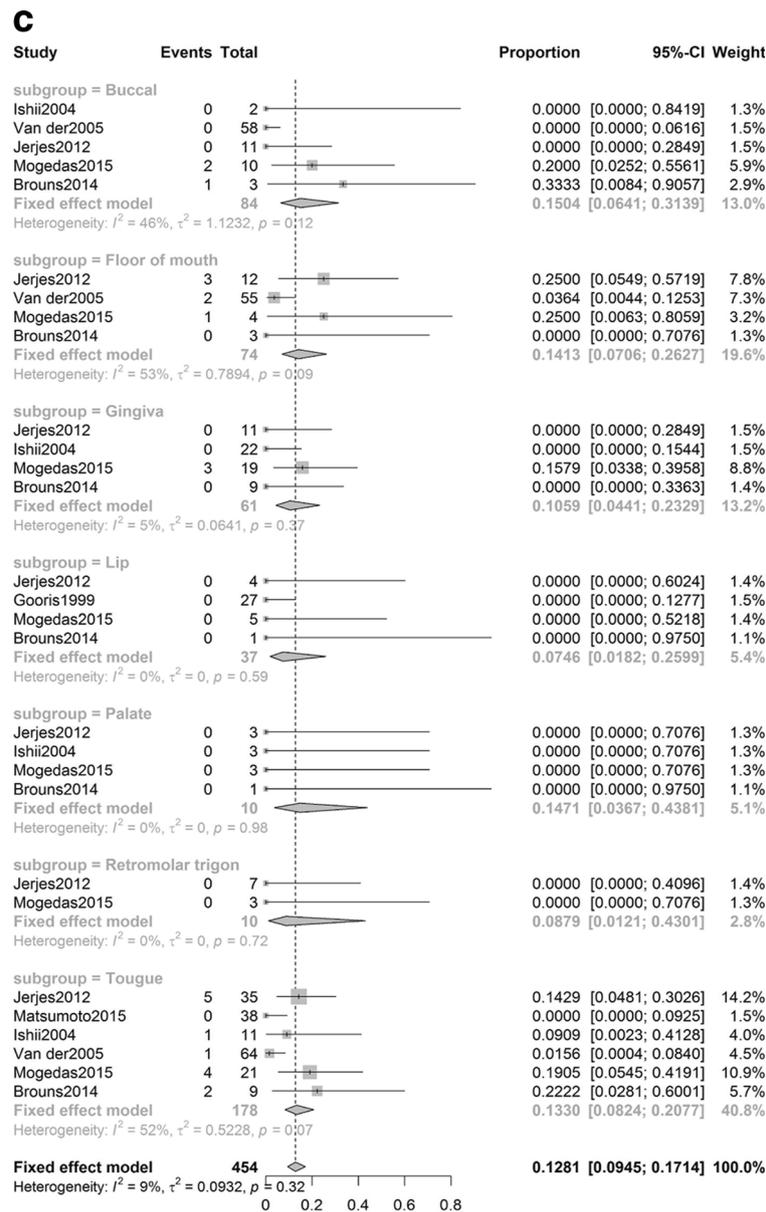


Fig. 5 (continued)

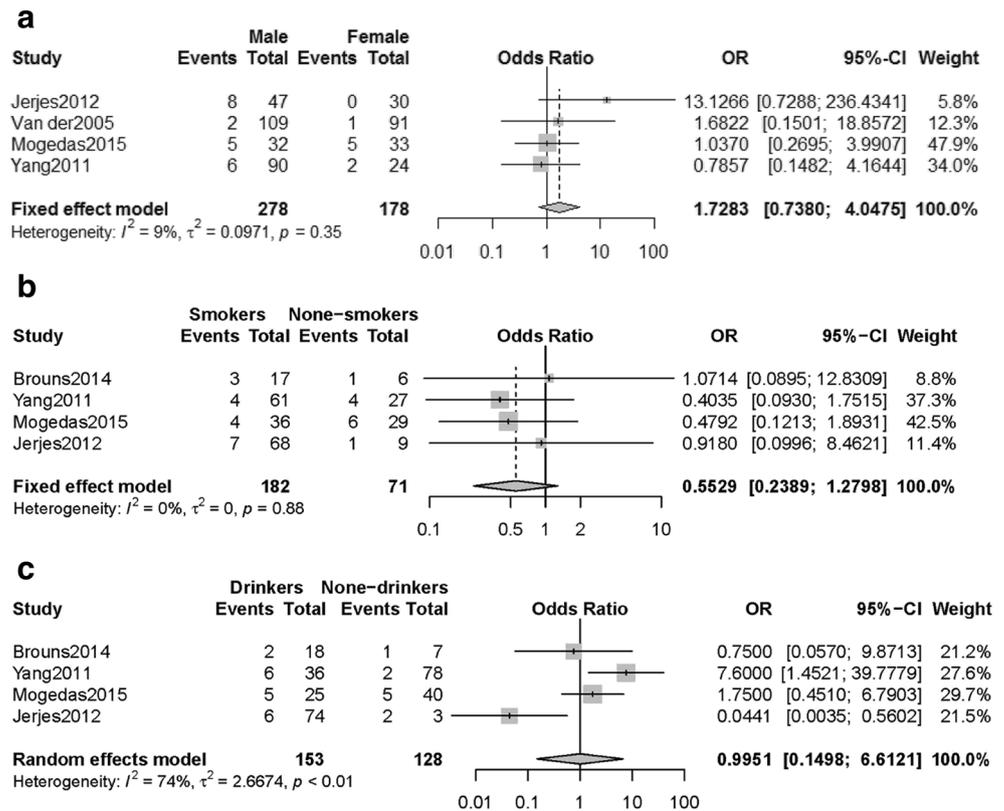
and to choose the best treatment. Our ultimate goal is to achieve the personalized intervention of oral leukoplakia based on the clinical, pathological, and even molecular characteristics.

Conclusions

Based on uncontrolled retrospective studies, this meta-analysis shows that the overall rate of malignant transformation of OLK treated with CO₂ laser is 4.50%. Generally speaking, whether oral leukoplakia patients

underwent with laser surgical treatment or not, it may have little effect on malignant transformation. Moreover, we strongly advise that it is best to take non-invasive treatment means for OLK patients with the following clinical characteristics: homogeneous type, male, no tobacco consumption, and without alcohol-use. Evidence is still lacking in terms of the relationship between malignant transformation and risk factors among OLK patients managed with CO₂ laser. Thus, a few more extensive multi-center RCTs using a large sample to investigate the malignant transformation and recurrence of OLK treated by laser surgery are required in the future.

Fig. 6 Forest plots for odds ratios of the association between malignant transformation and gender (a), smoking (b), alcohol consumption (c)



It is wise to assess the clinical, pathological, and even molecular features to determine whether the surgical intervention for lesions is appropriate or not. In addition, it is urgent to establish widely accepted and suitable laser-supported surgical protocols to meet the requirements of clinical practice.

Limitations

Although this meta-analysis included 24 studies encompassing a larger sample size than individual studies, there were still several limitations that we should consider. Firstly, at present randomized controlled trials of management of oral leukoplakia mostly concentrated on drug intervention, such as vitamin A, retinoids, beta-carotene, carotenoids, herbal extracts, and nonsteroidal anti-inflammatory drugs (NSAIDs). Due to the lack of malignant and relapse-

related randomized controlled trials of OLK treated with CO₂ laser, the included studies of this meta-analysis were almost retrospective studies without a control group. Secondly, the literatures searched were limited to articles published in English or Chinese. This means that the non-English and non-Chinese published articles were omitted from the meta-analysis. Thirdly, not every included article was capable of being extracted sufficient data for subgroup analysis and analysis of relevant risk factors. Fourthly, there are still other risk factors that were not investigated in this meta-analysis because of the lack of related numerical data, such as lesion size, the role of infective agents, chewing betel quid, and systematic disease history. Last but not the least; the included literature had a large heterogeneity owing to the differences among study design, study purpose, study subjects, outcome measures, follow-up time, etc. Therefore, the results of this study should be contemplated with caution.

Table 3 The results of calculated OR according to gender, tobacco, and alcohol consumption

Factors	OR	95% Confidence interval	Effects model
Gender	1.7283	0.7380–4.0475	Fixed effects model
Tobacco consumption	0.5529	0.2389–1.2798	Fixed effects model
Alcohol consumption	0.9951	0.1498–6.6121	Fixed effects model

Funding sources This work was supported by grants from the Nonprofit Industry Research Specific Fund of the National Health and Family Planning Commission of China (No. 201502018), National Natural Science Foundation of China (Nos. 81771086, 81470747, 81472533, and 81102060), and International Science and Technology Cooperation Program of China (No. 2012DFA31370). The funding agencies had no role in the study design, collection, analysis, or interpretation of data, writing of the report, or the decision to submit the article for publication.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

References

- Warna Kulasuriya S, Johnson NW, Van der Waal I (2010) Nomenclature and classification of potentially malignant disorders of the oral mucosa. *J Oral Pathol Med* 36(10):575–580
- Petti S (2003) Pooled estimate of world leukoplakia prevalence: a systematic review. *Oral Oncol* 39:770–780
- Bouquot JE, Gorlin RJ (1986) Leukoplakia, lichen planus, and other oral keratoses in 23,616 white Americans over the age of 35 years. *Oral Surgery, Oral Medicine, Oral Pathology* 61(4):373–381
- Charles A, Waldron DDS, William G, Shafer DDS (1975) Leukoplakia revisited. A clinicopathologic study 3256 oral leukoplakias. *Cancer* 36(4):1386–1392
- Silverman S Jr, Gorsky M, Lozada F (1984) Oral leukoplakia and malignant transformation. A follow-up study of 257 patients. *Cancer* 53(3):563–568
- Schepman KP, Meij EHVD, Smeele LE et al (1998) Malignant transformation of oral leukoplakia: a follow-up study of a hospital-based population of 166 patients with oral leukoplakia from The Netherlands. *Oral Oncol* 34(4):270–275
- Wamakulasuriya S, Ariyawardana A (2016) Malignant transformation of oral leukoplakia: a systematic review of observational studies. *J Oral Pathol Med* 45(3):155
- Lodi G, Sardella A, Bez C et al (2016) Interventions for treating oral leukoplakia. *Cochrane Database Syst Rev* 7(4):CD001829
- Ben-Bassat M, Kaplan I, Shindel Y et al (1978) The CO2 laser in surgery of the tongue. *Br J Plast Surg* 31(2):155
- López-Jornet P, Camacho-Alonso F (2013) Comparison of pain and swelling after removal of oral leukoplakia with CO2 laser and cold knife: a randomized clinical trial. *Medicina oral, patología oral y cirugiabucal* 18(1):38–44
- Chee M, Sasaki C (2013) CO2 laser fiber for the excision of oral leukoplakia. *Ann Otol Rhinol Laryngol* 122(9):547
- Tambuwalla A, Sangle A, Khan A et al (2014) Excision of oral leukoplakia by CO2 lasers versus traditional scalpel: a comparative study. *J Maxillofacial Oral Surgery* 13(3):320–327
- White JM, Chaudhry SI, Kudler JJ et al (1998) Nd:YAG and CO2 laser therapy of oral mucosal lesions. *J Clin Laser Med Surg* 16(6):299–304
- Frame JW (1985) Removal of oral soft tissue pathology with the CO2 laser. *J Oral Maxillofac Surg* 43(11):850–855
- MOOSE guidelines for meta-analyses and systematic reviews of observational studies. 2008
- Slim K, Nini ED, Kwiatkowski F et al (2003) Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg* 73(9):712
- Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 25:603–605
- Roodenburg J, Panders AK, Vermey A (1991) Carbon dioxide laser surgery of oral leukoplakia. *Oral Surgery Oral Med Oral Pathol* 71(6):670–674
- Hamadah O, Thomson PJ (2009) Factors affecting carbon dioxide laser treatment for oral precancer: a patient cohort study. *Lasers Surg Med* 41(1):17
- Lim B, Smith AA (2010) Treatment of oral leukoplakia with carbon dioxide and potassium-titanyl-phosphate lasers: a comparison. *J Oral Maxillofac Surg* 68(3):597–601
- Chu FW, Silverman S Jr, Dedo HH (1988) CO2 laser treatment of oral leukoplakia. *Laryngoscope* 98(2):125e130
- Schoelch ML, Sekandari N, Regezi JA, Silverman S Jr (1999) Laser management of oral leukoplakias: a follow-up study of 70 patients. *Laryngoscope* 109(6):949e953
- Chiesa F, Boracchi P, Tradati N, Rossi N, Costa L, Giardini R et al (1993) Risk of preneoplastic and neoplastic events in operated oral leukoplakias. *Oral Oncol Eur J Cancer* 29(1):23e28
- Dunsche A, Härle F (2000) Precancer stages of the oral mucosa: a review. *Laryngorhinotologie* 79(7):423e427
- Pedrosa A, Santos A, Ferreira M et al (2015) Is carbon dioxide laser vaporization a valuable tool in the management of oral leukoplakia? A survey at an oncology hospital. *Lasers Med Sci* 30(5):1629–1630
- Thomson PJ, Wylie J (2002) Interventional laser surgery: an effective surgical and diagnostic tool in oral precancer management. *Int J Oral Maxillofac Surg* 31(2):145–153
- Galletta V, Azevedo L, Lodi G et al (2017) Factors affecting clinical outcomes after treatment of oral leukoplakia with CO2 and diode laser. *J Contemp Dent Pract* 18(9):775
- Deppe H, Mücke T, Hohlweg-Majert B, Hauck W, Wagenpfeil S, Hölzle F (2011) Different CO2 laser vaporization protocols for the therapy of oral precancerous lesions and precancerous conditions: a 10 year follow-up. *Lasers Med Sci* 27:59e63
- Jerjes W, Upile T, Hamdoon Z et al (2012) CO2 laser of oral dysplasia: clinicopathological features of recurrence and malignant transformation. *Lasers Med Sci* 27(1):169–179
- Matsumoto K, Suzuki H, Asai T et al (2015) Clinical investigation of carbon dioxide laser treatment for lingual leukoplakia. *J Oral & Maxillofacial Surgery Med Pathol* 27(4):493–497
- Gooris PJ, Roodenburg JL, Vermey A et al (1999) Carbon dioxide laser evaporation of leukoplakia of the lower lip: a retrospective evaluation. *Oral Oncol* 35(5):490
- Corso GD, Gissi DB, Tarsitano A et al (2015) Laser evaporation versus laser excision of oral leukoplakia: a retrospective study with long-term follow-up. *J Craniomaxillofac Surg* 43(6):763–768
- Ishii J, Fujita K, Munemoto S et al (2004) Management of oral leukoplakia by laser surgery: relation between recurrence and malignant transformation and clinicopathological features. *J Clin Laser Med Surg* 22(1):27–33
- Ps VDH, Nauta JM, Je VDW et al (2005) The results of CO2 laser surgery in patients with oral leukoplakia: a 25 year follow up. *Oral Oncol* 41(1):31–37
- Mogedas-Vegara A, Hueto-Madrid JA, Chimenos-Küstner E et al (2015) The treatment of oral leukoplakia with the CO2 laser: a retrospective study of 65 patients. *J Cranio-Maxillo-Facial Surgery* 43(5):677
- Chandu A, Smith AC (2005) The use of CO2 laser in the treatment of oral white patches: outcomes and factors affecting recurrence. *Int J Oral Maxillofac Surg* 34(4):396–400
- Yang SW, Tsai CN, Lee YS et al (2011) Treatment outcome of dysplastic oral leukoplakia with carbon dioxide laser—emphasis on the factors affecting recurrence. *J Oral Maxillofac Surg* 69(6):e78–e87
- Brouns EREA, Baart JA, Karagozoglu KH et al (2013) Treatment results of CO2 laser vaporisation in a cohort of 35 patients with oral leukoplakia. *Oral Dis* 19(2):212–216

39. Monteiro L, Barbieri C, Warnakulasuriya S, et al. (2017) Type of surgical treatment and recurrence of oral leukoplakia: a retrospective clinical study. *Medicina Oral Patologia Oral Y CirugiaBucal* 22(5)
40. Lodi G, Sardella A, Bez C et al (2002) Systematic review of randomized trials for the treatment of oral leukoplakia. *J Dent Educ* 66: 896
41. van der Waal I (2009) Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. *Oral Oncol* 45:317–323
42. Kuribayashi Y, Tsushima F, Morita KI et al (2015) Long-term outcome of non-surgical treatment in patients with oral leukoplakia. *Oral Oncol* 51(11):1020–1025
43. Holmstrup P, Dabelsteen E (2016) Oral leukoplakia - to treat or not to treat. *Oral Dis* 22(6):494–497
44. Holmstrup P, Vedtofte P, Reibel J, Stoltze K (2007) Oral premalignant lesions: is a biopsy reliable? *J Oral Pathol Med* 36:262–266
45. Vannucci L (2015) Stroma as an active player in the development of the tumor microenvironment. *Cancer Microenviron* 8:159–166
46. Arduino PG, Surace A, Carbone M et al (2010) Outcome of oral dysplasia: a retrospective hospital-based study of 207 patients with a long follow-up. *J Oral Pathol Med* 38(6):540–544
47. Nammour S, Zeinoun T, Namour A, et al. (2017) Evaluation of different laser-supported surgical protocols for the treatment of oral leukoplakia: a long-term follow-up. *Photomed Laser Surgery*