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## Oral leukoplakia: Diagnosis and treatment

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### Review Article

#### Abstract

**BACKGROUND AND AIM:** Oral leukoplakia (OL) is a common premalignant lesion. The possible benefits of specific interventions in preventing a malignant transformation of OL are not well understood. This review assesses different invasive treatment techniques for OL and evaluate the optimal treatment possibilities.

**METHODS:** A Medline (PubMed) search was conducted and heterogeneity between the studies was found, e.g., with regard to the OL lesions, patient groups, follow-up time, and definition of recurrence.

**RESULTS:** The recurrence and malignant transformation rate after the different treatment methods were evaluated. The mean overall recurrence rate varied with the treatment method.

**CONCLUSION:** A surgical treatment appears to decrease the risk of transformation but does not fully eliminate it. Follow-up should be done regardless of the surgical treatment.

**KEYWORDS:** Oral Leukoplakia; Squamous Cell Carcinoma; Chemotherapy; Laser Ablation; Cryosurgery

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The incidence of oral cancer varies among countries and is generally increasing.<sup>1-3</sup> The most common type is the squamous cell carcinoma (SCC), which in the United States accounts for 96% of the oral cancers.<sup>1</sup> The etiological basis for the SCC is not known-human papilloma virus and the use of marijuana has been suggested.<sup>4</sup> An increased focus on premalignant conditions, risk factors, and relevant treatment opportunities is imperative. In spite of decreasing the incidence of developing oral SCC, this review will base on the treatment of the premalignant condition and oral leukoplakia (OL).

A premalignant condition is a pathological process that possesses the ability to develop into a malignancy. In 1967, the World Health Organization (WHO) established a center for

characterizing and defining which oral lesions should be considered premalignant and to determine the risk of these lesions becoming malignant.<sup>5</sup> One of the most common lesions is leukoplakia. OL was defined by the WHO in 1978 as: "a white patch or plaque that cannot be characterized clinically or pathologically as any other disease."<sup>5</sup> The definition of OL has changed over the years and in 2005 it was defined as: "white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer."<sup>6</sup>

OL has the potential risk of a malignant transformation into SCC. The prevalence of OL varies from 0.9 to 3%<sup>7-9</sup> with a malignant transformation rate of 0.13-37%.<sup>9-15</sup> The incidence of OL displays geographic and demographic variations thus resembling the

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incidence of oral cancer.<sup>16</sup> The reported proportion of OL that transforms into carcinoma varies depending on several factors, e.g., the definition of OL, the study population, and the length of observation time. The main risk factors for developing OL are tobacco smoking, betel quid chewing, and alcohol consumptions.<sup>11,17-23</sup> It is unclear whether these risk factors play a role in the malignant transformation of OL. The studies show that there is a higher risk of malignant transformation of OL in older persons than in younger persons when the OL is located on the lateral/ventral tongue, and non-homogenous lesions have a higher transformation rate than homogenous lesions.<sup>10-12,21,24,25</sup>

The high-risk sites for developing SCC might be explained on the basis of a higher exposure to carcinogens than other areas of the oral cavity and the lower degree of keratinization.<sup>26,27</sup> Holmstrup et al.<sup>28</sup> showed that the risk of non-homogenous OL undergoing malignant transformation was seven times greater than it was for homogenous OL. Furthermore, they showed a 5 times increased risk for malignant development when the size of the OL exceeded 20 cm<sup>2</sup>.<sup>28</sup> Another study reported a higher potential for malignant development of widespread OL than for smaller, localized OLs.<sup>27</sup>

The histological presence of epithelial dysplasia is often correlated with a higher risk of cancerous transformation.<sup>11,21,24,29</sup> A meta-analysis from 2009 showed that the malignant transformation rate of lesions with oral dysplasia was 12.1%.<sup>30</sup> Holmstrup et al.<sup>28</sup>

showed that 11-14% of lesions exhibiting slight epithelial dysplasia, developed into cancer.

## Methods

This article focuses on OL treatment methods and their outcome. A web-based search was done using the National Center for Biotechnology Information (NCBI) to search Medline (PubMed). The use of PubMed was chosen according to the searching procedure and references. The keyword "OL" was used. A total number of 4315 titles were identified, and 252 titles and abstracts were recognized as potentially appropriate. The articles containing human immunodeficiency virus (HIV) and those not in English were excluded. Inclusion criteria were malignant transformation, diagnostic, treatment, and outcome. Furthermore, a thorough bibliographic hand search identified further studies. Due to the fact that only a few randomized clinical trials (RCTs) exist, retrospective non-RCTs were included.

## Results

A full-text screening of 175 papers was performed according to the inclusion and exclusion criteria. 30 papers were included (Tables 1-4). Data from clinical articles were compared with regard to number of patients, clinical resolution of OL, follow-up, recurrence, and malignant transformation.

### *The clinical and histological appearance of OL*

Clinically, OL varies in size, shape, and consistency. OL is often divided into homogenous and non-homogenous lesions.

**Table 1.** Results of observation in oral leukoplakia (OL) in the literature

Author	Year	Number of patients	Follow-up (months)	Clinical resolution (%)	Malignant transformation (%)
Silverman et al. <sup>12</sup>	1984	196	6-468	NR	17.5 (including 61 patients treated surgically)
Holmstrup et al. <sup>28</sup>	2006	175	18-223.2	16.0	4.00
Banoczy and Csiba <sup>31</sup>	1976	23	12-240	0.0	30.40
Saito et al. <sup>32</sup>	2001	51	7-192	NR	7.80
Silverman et al. <sup>33</sup>	1976	4762	24	31.6	0.13
5 studies			7-468	0-31.6	0-30.4

NR: Not report

**Table 2.** Results of surgical excision in oral leukoplakia (OL) in the literature

Author	Year	Number of patients	Follow-up (months)	Recurrence (%)	Malignant transformation (%)
Silverman et al. <sup>12</sup>	1984	61	6-468	34.4	17.5 (including 196 patients non-treated)
Holmstrup et al. <sup>28</sup>	2006	94	18-223.2	13.0	12.0
Vedtofte et al. <sup>34</sup>	1987	46	Average 46.8	17.4	6.5
Pandey et al. <sup>35</sup>	2001	59	12-37	10.1	0.0
Hogewind et al. <sup>36</sup>	1989	46	12-100	0.0	3.6
Banoczy and Csiba <sup>31</sup>	1976	45	12-240	NR	2.2
Hsue et al. <sup>37</sup>	2007	166	Mean 43.2	NR	4.8
Saito et al. <sup>32</sup>	2001	75	7-192	NR	1.3
del Corso et al. <sup>38</sup>	2015	30	6-112	13.3	0.0
9 studies			6-223.2	0-34.4	0-12

NR: Not report

Homogenous leukoplakia is flat and may exhibit superficial irregularities. The non-homogenous lesion is mostly white but can be white and red with an irregular texture that can be flat, nodular, or speckled. The homogenous lesion may be white, whitish yellow, or gray, and can vary greatly in size.<sup>5,57,58</sup> Non-homogenous OL may compromise about 10% of all OL.<sup>59</sup> etiologic factors associated with OL, e.g., candidiasis, smoker's lesions, frictional lesions, and dental-restoration associated lesions and can show white plaques or patches and must be identified before making the diagnose of OL.<sup>58,60</sup>

Histologically, OL shows variable degrees of hyperorthokeratosis, hyperparakeratosis, acanthosis, and atrophy. Furthermore, a diffuse chronic inflammatory infiltration in

the lamina propria is often seen. Dysplasia may be seen occasionally.<sup>59</sup> Apart from the nodular type of OL, there is not a strong correlation between clinical appearance and dysplasia.<sup>5</sup> The presence of dysplasia may indicate an increased risk of the malignant transformation. The dysplasia is graded as mild, moderate and severe dysplasia and carcinoma in situ.<sup>13,59</sup> Currently, no reproducible criteria exist that can be used to divide the dysplastic spectrum into mild, moderate or severe.<sup>61</sup> The grade of dysplasia is subjective and dependent on the pathologist.<sup>24,61,62</sup> Silverman et al.<sup>12</sup> showed that 8.6% of the patients with OL had a diagnosis of epithelial dysplasia. The benefit of a subdivision of epithelial dysplasia is not known.<sup>5,59,61</sup>

**Table 3.** Results of cryosurgery in oral leukoplakia (OL) in the literature

Author	Year	Therapy	Number of patients	Clinical resolution (%)	Follow-up (months)	Recurrence (%)	Malignant transformation (%)
Yeh <sup>39</sup>	2000	Cryosurgery (open) (liquid nitrogen)	25	NR	3-46	32.0	NR
Kawczyk-Krupka et al. <sup>40</sup>	2013	Cryosurgery (closed) (nitrous oxide)	37	89.2	6	24.3	5.4
Yu et al. <sup>41</sup>	2009	Cryosurgery (open) (liquid nitrogen)	47	All	5-31	8.3	0.0
Lin et al. <sup>42</sup>	2012	Cryosurgery (closed) (liquid nitrogen)	54	All	7-38	8.3	0.0
Saito et al. <sup>32</sup>	2001	Cryosurgery (closed) (liquid nitrogen)	12	All	7-192	25.0	25.0
5 studies				89.2-100%	3-192	8.3-32	0-25

NR: Not report

**Table 4.** Results of laser treatment in oral leukoplakia (OL) in the literature

Author	Year	Therapy	Number of patients	Follow-up (months)	Recurrence (%)	Malignant transformation (%)
Yang et al. <sup>21</sup>	2011	CO <sub>2</sub>	114	21-110	17.5	11.4
Chandu and Smith <sup>22</sup>	2005	CO <sub>2</sub>	43	2-102	28.9	7.3
Schoelch et al. <sup>43</sup>	1999	CO <sub>2</sub>	70 (55)	6-178	38.2	9.0
Thomson and Wylie <sup>44</sup>	2002	Nd: YAG CO <sub>2</sub>	57	1-44	33.3	7.0
Frame <sup>45</sup>	1985	CO <sub>2</sub> (vaporization or evaporation)	75	3-45	8.0	NR
Horch et al. <sup>46</sup>	1986	CO <sub>2</sub> (evaporation)	32	37	22	NR
Ishii et al. <sup>47</sup>	2003	CO <sub>2</sub>	82	6-288	29.3	1.2
White et al. <sup>48</sup>	1998	Nd: YAG KTP	17	1-36	23.5	NR
		CO <sub>2</sub>				
		Nd: YAG				
López-Jornet and Camacho-Alonso <sup>49</sup>	2013	CO <sub>2</sub> Kirurgi	48	1-40	NR	0
Vivek et al. <sup>50</sup>	2008	Nd: YAG	28	60	7	3.5
van der Hem et al. <sup>51</sup>	2005	CO <sub>2</sub>	200	1-219	9.9	1.1
Flynn et al. <sup>52</sup>	1988	CO <sub>2</sub>	14	12-41	15	NR
Chiesa et al. <sup>53</sup>	1990	CO <sub>2</sub> (vaporization or evaporation)	145	12-36	10 (12 months) 21 (24 months) 27 (36 months)	1.4
Roodenburg et al. <sup>54</sup>	1991	CO <sub>2</sub>	70	6-144	9.7	NR
Lim et al. <sup>55</sup>	2010	CO <sub>2</sub> KTP	75	41-43	39.5 (CO <sub>2</sub> ) 25 (KTP)	4 (CO <sub>2</sub> ) 5.4 (KTP)
Mogedas-Vegara et al. <sup>56</sup>	2015	CO <sub>2</sub> (vaporization)	65	0.3-38.7	33.8	15.4
del Corso et al. <sup>38</sup>	2015	Nd: YAG	47	6-112	38.3	3.9
17 studies				0.3-288	7-39.5	0-15.4

KTP: Potassium-titanyl-phosphate; Nd: YAG: Neodymium: yttrium-aluminum garnet; CO<sub>2</sub>: Carbon dioxide; NR: Not report

### Malignant transformation

Clinically, almost all oral cancers have two characteristic features: ulceration and an indurated margin, although these features may not be present in the early stages of oral cancers.<sup>59</sup> A diagnose of SCC is made histopathologically when the nests of epithelial cells have invaded the underlying lamina propria and deeper submucosa.<sup>5,59</sup>

The most important predictor of recurrence and mortality in patients with SCC is the clinical stage at the time of diagnosis.<sup>13,59</sup> The early detection and treatment of premalignant lesions can help

prevent transformation into oral carcinoma. Several methods are available for the screening of oral cancer and precancerous lesions. Unfortunately, most methods present limitations that make them more or less useful.<sup>13,59,63,64</sup>

Conventional oral examination and palpation remain the standard method for screening of oral cancer and premalignant lesions.

Biopsy and histopathological examination are the gold standard in diagnosing and grading oral premalignant lesions.<sup>13,63,65-67</sup> Invasive methods can be painful and can result in complications. Non-invasive tests

would be preferable as a diagnostic tool, and various tests are now being investigated. Toluidine blue (tolonium chloride) can be used to identify premalignant and carcinomatous lesions. The dye is a member of the thiazine group and it selectively stains acid tissue components such as DNA and RNA. Theoretically, dysplastic and malignant cells have a higher RNA and DNA content than normal cells, which is the rationale for its use.<sup>63</sup> Toluidine blue can help identify the presence of dysplastic or carcinomatous lesions, but due to a low specificity, it cannot replace biopsy.<sup>68</sup>

Histological diagnosis of epithelial dysplasia has a disadvantage because the analysis is based on a static snapshot.<sup>13,62</sup> The malignant transformation is a dynamic process in which several molecular changes are taking place simultaneously.

Optical imaging systems, saliva, and exfoliated cells can be used as a source for biomarker-based risk assessment.<sup>63</sup> Several studies have investigated changes as a method to identify when dysplastic lesions will develop into SCC.<sup>13,15,62,69-75</sup> Many molecular changes are associated with the transformation from dysplasia to malignancy in OL and include loss of heterozygosity, aberrant DNA expression, dysregulation of apoptosis, and altered expression of tissue markers.<sup>58,62</sup>

### *Treatment methods*

Various treatment modalities for OL have been suggested. Overall, the treatments can be categorized as observation, chemotherapy, and surgical excision/ablation. Currently, the most appropriate treatment remains to be found. The outcome of the treatment modalities appears to vary, and long-term follow-up studies are few. A surgical excision has been considered the gold standard with regard to the treatment of small local lesions with severe dysplasia or carcinoma in situ.<sup>13,30</sup> Recently, the use of cryosurgery, laser evaporation, and laser excision has been recommended in the literature.<sup>39-44,76-79</sup> OL with a low to moderate malignant risk may

either be surgically removed or not.<sup>5,13</sup> Non-dysplastic OL lesions have been shown to respond to changes in lifestyle factors such as reduction of alcohol and tobacco use.<sup>28,66,67</sup> In addition, chemoprevention has shown a positive effect on precancerous lesions.<sup>64</sup>

### *Non-surgical treatment/chemoprevention*

Non-surgical treatment is a possibility when surgical removal is difficult because of, e.g., the location of the lesion, its size, or the patient's medical status.<sup>57</sup> Overall, the non-surgical treatment can be divided into carotenoids, vitamins, bleomycin, and photodynamic therapy. Ribeiro et al.<sup>64</sup> published a review in 2009 on the non-surgical treatment of OL. RCTs for chemotherapy of OL failed to demonstrate an effective treatment in preventing transformation to SCC and recurrence. No recommendation can be provided for specific non-invasive and invasive treatments of OL.

### *Surgery*

The surgical excision of OL is defined as removal of the entire lesion. It is recommended that the lesion is excised with a margin of 3-5 mm of the clinical normal mucosa. The lesion is separated from the underlying tissue by blunt dissection. Subsequently, the defects are closed directly. This can be done by transposition of local mucosa flaps or with free mucosal grafts, depending on the size of the surgical defect.<sup>28,34</sup>

Recurrence rates between 0 and 34.4% are reported following surgical excision,<sup>12,28,31,32,34-38</sup> and 0-12% of surgically treated lesions develop carcinoma within a follow-up period of 7-223.2 months.<sup>12,28,31,32,34-38</sup> No RCTs have been reported so far.<sup>80</sup> A retrospective study of 269 lesions investigated the long-term outcome of premalignant lesions after surgical excision and after a follow-up without surgery.<sup>28</sup> 94 lesions were surgically removed, and no surgical intervention was undertaken in 175 lesions. Malignant transformation was seen in 12% of the surgically treated lesions after a mean follow-

up period of 7.5 years, whereas 4% of the non-surgical treated lesions transformed malignantly after a mean follow-up period of 6.6 years. The two groups were not directly comparable due to a greater number of cases of non-homogenous OL, OL with epithelial dysplasia, and carcinoma in situ in the group that underwent surgical intervention. Thus, the study did demonstrate that surgical intervention of premalignant lesions did not prevent malignant development.<sup>28</sup>

Post-operative complications after surgical excision of OL are described in the literature and include infections, nerve injuries, reduction in the mobility of the mouth, obstruction of salivary flow, etc.<sup>34</sup> In the treatment of large OL lesions, surgical excision can cause a considerable scar contraction during healing with both functional and aesthetic consequences.<sup>45</sup> In addition, the use of skin grafts can interfere with proper diagnosis and early signs of recurrence.<sup>34,45</sup>

### *Cryosurgery*

A cryosurgery is a treatment option for various skin and mucosal diseases. In the early 1960s, the method was used as a treatment for oral lesions such as hyperplasia, angiomas, and leukoplakia.<sup>81,82</sup> Cryosurgery is a simple, weakly invasive technique in which rapid freezing destroys a lesion in situ.<sup>39,81</sup>

The positive advantages of the therapy include a bloodless treatment and a relative lack of scarring and pain. In addition, a very low incidence of secondary infection has been noted.<sup>39</sup> Furthermore, it is very safe, relative inexpensive, and easy to perform. A disadvantage of the therapy is that a biopsy should be taken before the OL is treated because after treatment the true lesion is destroyed. It is non-specific in its destructive effects and due to lack of precision; it can be difficult to judge the volume of tissue necrosis afterward.<sup>39,40,67,81</sup> Complications include pain, hyperemia, and edema.<sup>39-41,67</sup> The treatment can be done with adjuvant

therapies and if there is no response to one freezing cycle, another cycle can be given.<sup>39,81</sup>

In only a few studies has cryosurgery been used for the treatment of OL. One study treated 60 OL lesions with the use of cotton swabs and liquid nitrogen. All lesions showed a complete response after an average of 6.3 cryosurgeries, and 5 out of 60 OL recurred in the follow-up period of 1-5 months. The recurred lesions underwent cryosurgery again. The study demonstrated that OL with epithelial dysplasia required a significantly fewer number of cryosurgeries than lesions without dysplasia.<sup>41</sup> The same authors investigated the use of cryogun cryosurgery in 60 OL lesions. All lesions showed complete regression after an average of 3.1 treatments. The cryogun therapy required fewer treatments to achieve complete regression than cryosurgery with cotton swabs. Perhaps this can be explained by the large amount of liquid nitrogen delivered by the cryogun, which maintains a constant low temperature, whereas the temperature increases quickly with the use of cotton swabs.<sup>42</sup>

The recurrence of OL after cryosurgery has been reported to be 8.3-32.0% after a follow-up period of 3-192 months.<sup>32,39-42</sup> Unfortunately, the malignancy rate following treatments has, unfortunately, only been reported in few studies with numbers varying from 0 to 25%.<sup>32,40-42</sup>

### *Laser*

Lasers have been increasingly used in oral and maxillofacial surgery since the 1970s, and it has become a well-accepted treatment of OL.<sup>76,77,83</sup> Laser therapy for the treatment of OL was first described in 1978.<sup>83</sup> It can be used for evaporation, excision, and coagulation of tissue. The effect of various laser types is determined by their wavelength and the specific absorption in the tissue.

Different kinds of lasers have been used for oral surgery, including carbon dioxide (CO<sub>2</sub>), neodymium:yttrium-aluminum garnet, and potassium-titanyl-phosphate (KTP) lasers. The most common and suitable for use in the

mouth is the CO<sub>2</sub> laser, which generates energy at a wavelength of 10.6 μm.<sup>22,46</sup>

Laser excision is preferable because it allows histological examination, but some difficulty in the histopathological interpretation can occur because of collateral thermal damage.<sup>45</sup> Vaporization does not allow histological examination of the lesion, and there is a risk that small fragments of OL may not be completely eliminated by the beam.

In the literature, several advantages of the use of laser in the maxillofacial region have been described. The laser affords a hemostatic effect by sealing off the blood vessels, creating a virtually bloodless field. Incision of the oral mucosa can be made with minimal bleeding.<sup>45,47,78</sup> This is very useful in highly vascularized areas. The risk of damage to the tissues is small, which reduces acute inflammatory reactions and post-operative pain, swelling, edema, and infection owing to the cauterization of nerve endings and blood vessels.<sup>45,47,78,84</sup> Wound healing after laser treatment is good because of limited tissue contraction and produces satisfactory mobility of the oral mucosa.<sup>47-49,84</sup> There is no need for sutures with the laser technique, which shortens the surgical time.<sup>48,78</sup>

One of the disadvantages with laser evaporation is that the lesion is not available for histological study. Therefore, an incisional biopsy must always be obtained before the treatment.<sup>67</sup> Wound healing is delayed compared with surgical excision and closure with sutures because of secondary healing with epithelial regeneration. Complete healing is described to take around 2-3 weeks.<sup>46</sup> Safety precautions are another consideration.<sup>78,82</sup>

Post-operative complications after laser treatment include pain, bleeding, difficulties with speech, paresthesia, difficulty swallowing, obstructive swelling of the submandibular gland and tethering of the tongue. In one study, 78% of patients treated by laser reported one or more of these complications.<sup>50,85</sup>

The recurrence rate of OL after laser

treatment is 7.0-39.5% within a mean follow-up period of 1-288 months.<sup>21,22,38,43-48,50-56,76</sup> Recurrence of OL is more likely, especially in deeper tissue layers, which are not completely eradicated.<sup>33</sup> The malignant transformation rate has been reported to be 0-11.4% after a follow-up period of 1-288 months.<sup>21,22,38,43-48,50-56,76</sup>

Few studies have compared the different types of lasers. Lim et al.<sup>55</sup> compared the use of the KTP and CO<sub>2</sub> laser in the treatment of OL in a retrospectively study of 75 patients. No significant difference was found between the two groups treated either by KTP or CO<sub>2</sub> laser. A statistically significant reduction in recurrence rate was demonstrated in the patients treated with the KTP laser (P = 0.049). The recurrence rates for the KTP and CO<sub>2</sub> laser groups were 25.0 and 39.5%. The reduction in recurrence might be explained by the greater thermal damage from the KTP laser.

## Discussion

One of the approaches for diagnosing SCC is to detect premalignant lesions and prevent their malignant transformation either by invasive or non-invasive treatment methods. It seems redundant to treat all OL lesions surgically, as only 0.13-37% develop into SCC.<sup>9-15</sup> Furthermore, several studies have shown that some OL lesions can regress spontaneously without any treatment.<sup>28,34</sup> It is, therefore, important to determine the risk for malignant transformation of each OL lesion.

It is possible to identify lesions with a high risk of developing malignancy using the clinical and histological picture.<sup>11,12,21,24,25,34,79</sup> Carcinomas may develop in OL lesions with no signs of epithelial dysplasia.<sup>12,28,32</sup> A study showed malignant development in 11-14% of lesions exhibiting slight epithelial dysplasia.<sup>28</sup> Instead, clinical characteristics like the location, size, and homogeneity of the OL may be used to identify risk.<sup>11-13,21,24,25,28,62,79</sup>

Another important factor is the reliability of the biopsy that is taken for histological evaluation. Lack of correlation between

histological features and outcome of the lesions can probably be explained by the site and size of the biopsy. Vedtofte et al.<sup>34</sup> found that four of 61 OL lesions had superficial carcinomas in the excision specimen that were undiagnosed in the incisional, pre-operative biopsy. Lee et al.<sup>86</sup> investigated the reliability of incisional biopsies. In 200 cases receiving a single-site biopsy, 29.5% of the patients were underdiagnosed (the definitive diagnosis was more serious). Also, overdiagnosis (the definitive diagnosis was less serious) did occur in 32.9% (with CO<sub>2</sub> laser) and 20.0% (with KTP laser) of their biopsies. In 12.0% of the cases, resection specimen showed malignancy undetected by incisional biopsy. Thus, the study showed that incisional biopsies have limitations regarding the assessment of OL. Patients receiving multiple-site biopsies had significantly lower rates of under diagnosis and unexpected carcinomas. It is possible to histopathologically examine the entire OL lesion with an excisional biopsy, but this entails the risk of incomplete treatment of malignant lesions and overtreatment of benign lesions. In general, excisional biopsy is not cost-effective.<sup>86</sup> Other methods for predicting the potential for malignant transformation are needed. The use of gene markers seems promising as a method of assessing the prognosis with regards to malignant transformation. Currently, no studies have demonstrated methods that are applicable for routine diagnostic work.<sup>13,15,62,69-75</sup>

Several treatment options to prevent OL developing into SCC are described in the literature. Invasive techniques such as surgical excision, cryosurgery, laser excision, and laser ablation have been investigated with regard to preventing OL from developing into carcinoma. Few studies have compared the recurrence and malignant transformation after treatment between the different treatment options.<sup>32,40</sup> Significant heterogeneity between follow-up studies is seen in the literature, which makes it difficult

to compare the trials.<sup>30,62</sup> The definition of recurrence differs in different studies, which results in different rates of recurrence. Thus, it is not possible to determine the influence of exposure to causative agents in treated patients, and the selection of the proper treatment method remains difficult.

A Cochrane review failed to show a high level of evidence regarding an effective treatment in preventing OL from transforming into carcinomas. Treatments of OL can be effective but recurrence and adverse effects are common.<sup>80</sup> Holmstrup et al.<sup>28</sup> showed that surgical interventions did not prevent all premalignant lesions from malignant development. Further, they showed a higher rate of malignant development of surgically treated OL (13%) compared with non-surgically treated lesions (4%), which is in contrast to other reported study results.<sup>12,30-32,34</sup> The two groups in the study of Holmstrup et al.<sup>28</sup> were not completely comparable due to the retrospective nature of the study and because the groups were not randomized. However, they still showed that surgical interventions could not prevent OL lesions from developing into carcinomas. Further investigations are needed.

Saito et al.<sup>32</sup> investigated patients with OL who underwent surgical excision, cryosurgery, cryosurgery followed by surgical excision and observation. The malignant transformation rate was lower among patients that received surgical excision (1.3%) than among patients who underwent cryosurgery (25.0%) and among patients who did not receive any treatment (7.8%). The study groups were not completely comparable because of the unequal numbers of patients in each group, the number of severe dysplasia was higher in the group that underwent surgical excision, and the location of OL was different between the groups. However, their data still indicate that the rate of malignant transformation is higher in patients that undergo cryosurgery than among patients who receive surgical excision in those in whom



surgical excision is performed.

The time for the occurrence of malignant transformation in OL is not clear. Pandey et al.<sup>35</sup> did not show any carcinoma after surgical excision 1 year after treatment. Holmstrup et al.<sup>28</sup> showed that carcinomas developed 2.7-15.1 years after surgical intervention. In 257 patients with OL, Silverman et al.<sup>12</sup> found the greatest occurrence of malignant transformation in the second follow-up year (24%). The malignant transformation was also seen 20-39 years after the initial diagnosis of OL. There is currently no consensus regarding the treatment and follow-up required for patients with OL. Reported follow-up periods vary from immediate discharge to lifetime follow-up.<sup>87</sup> However, in general, the literature suggests a close and prolonged follow-up of patients who have undergone surgical treatment.<sup>12,22,28,34,54</sup>

Yang et al.<sup>21</sup> investigated the risk for recurrence after laser surgery. Patients with non-homogenous OL had a higher risk for recurrence compared to patients with homogenous OL. Lifestyle factors such as cigarette smoking and betel quid chewing affected the outcome. Patients who did not quit smoking cigarettes or chewing betel quid were 9.6 and 19.5 times more likely to develop recurrence than those who did quit. Thus, the curative effect of the treatment is not only dependent on the treatment method, but also the lifestyle factors, that might serve as causative agents.

In tables 2-4, the recurrence and malignancy rates reported in several studies of invasive treatments are listed. The rates vary between the studies, and as mentioned, the study outcomes are not completely comparable. The main studies are retrospective with small patient groups. It is not possible to give specific evidence-based recommendations regarding the surgical treatment of OL lesions because of a lack of RCTs in the literature. In non-RCTs, the effectiveness of various surgical interventions has resulted in various outcomes.

Furthermore, the literature contains no studies of sufficient quality for evidence-based recommendations for the use of non-surgical treatment modalities.

OL lesions are not lethal in themselves and the risk of developing carcinomas is low. Therefore, adverse effects and complications in the proposed treatment must be kept very low. Non-invasive treatments are often preferable for the patient. Side effects such as headache, muscular pain, erythema, and erosions have been reported.<sup>80</sup> No study has compared the recurrence, the malignancy rate, and the objective and subjective (patients) side effects and complications of chemotherapy with the invasive treatment modalities.

López-Jornet and Camacho-Alonso<sup>49</sup> compared the pain and swelling after removal of OL with CO<sub>2</sub> laser and a cold knife. They found statistically significant differences during the first 3 days after treatment. The patients treated with CO<sub>2</sub> laser showed a lower level of post-operative pain ( $P = 0.021$ ) and swelling ( $P = 0.019$ ) compared with the patients treated with surgery. The study group was small and the follow-up period was brief, but their results were interesting and showed that the CO<sub>2</sub> laser could be an interesting alternative to conventional surgery, considering the apparent reduction of side effects. Furthermore, another study showed a significant difference in the use of post-operative analgesic. 90% of the patients treated with a conventional surgery used analgesics postoperatively, compared to 29% patients treated with CO<sub>2</sub> laser used them ( $P < 0.001$ ).<sup>78</sup> Chee and Sasaki<sup>77</sup> compared the operating time and blood loss between surgical excision and CO<sub>2</sub> laser excision in 45 patients. The visualization of the operative field was better in the CO<sub>2</sub> group, but there was no improvement in operating time. Another study reported shorter surgical time when CO<sub>2</sub> laser was used compared to that associated with surgical excision because of less bleeding and no need for sutures.<sup>78</sup> Thus, CO<sub>2</sub> laser can be a good alternative to

surgical excision owing to its favorable features like a clearer surgical field because of its hemostatic effect and probably also reduced post-operative pain and swelling.<sup>49</sup>

So far no study reveals any evidence that non-surgical and surgical treatments are protective against the malignant transformation of OL. There is no evidence of the opposite effect either. It appears that recurrence and malignant transformation of OL might be independent of the treatment regime. The number of OL lesions that are prevented from development into cancer is unknown. A follow-up by the clinician responsible for the treatment should be done regardless of the treatment. No strict guidelines can be given with regard to follow-up, but lifelong follow-up is recommended at intervals of < 6 months.<sup>88</sup>

### Conclusion

The detection, diagnosis, and management of OL remain complex. The risk of malignant transformation of OL varies from 0.13 to 37% depending on location, etiological factors, clinical features, and degree of dysplasia. Promising technologies for determining the

risk of malignant transformation are currently being investigated. Several medical and surgical treatment protocols have been recommended. However, no high-level, evidence-based study exists that recommends one specific treatment. Some treatments of OL may be effective in healing but no treatments have been shown to be able to prevent recurrence and malignant transformation. Surgical treatment appears to decrease the risk of transformation but does not eliminate it. Future research is needed to identify better prognostic markers for the progression from OL to SCC, a more effective and less invasive treatments, and the length of follow-up periods.

### Conflict of Interests

Authors have no conflict of interest.

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