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Short Communication

Evaluating surgical excision to prevent progression of oral precancerous lesions: Highlighting randomized controlled trials and cohort studies

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Abstract Currently, surgical excision remains a common intervention for oral precancerous lesions (OPL). However, the studies focusing on conventional surgery by scalpel for OPL are not analyzed collectively in detail. Therefore, the objective of this short communication is to summarize and evaluate the evidence on scalpel surgery in preventing the progression of OPL patients. There are 16 eligible studies on surgery management of the recurrence (13 studies) or malignant transformation (13 studies) of OPL. The pooled recurrence rate (95% confidence interval) of OPL patients received scalpel surgery and laser therapy is 29.5% (26.3–33.0%) and 32.2% (26.1–38.9%), respectively. The pooled rate of malignant transformation of OPL patients received scalpel surgery, laser therapy, and clinical observation is 8.9% (7.3–10.9%), 6.0% (3.5–10.1%), and 10.2% (8.6–12.1%), respectively. The important limitation of current evidence available for prognosis of dysplastic OPL is based on retrospective observational studies. It highlights that surgical management of OPL needs more randomized controlled trials and cohort studies to explore more reliable methods for routine clinical use

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to facilitate high- or low-risk stratification and further select more appropriate treatment option.

Introduction

Oral squamous cell carcinomas (OSCC) are usually preceded by oral precancerous lesions (OPL), mainly being oral leukoplakia and erythroplakia.[1] From a clinician perspective, the primary purpose of all the intervention for OPL is to prevent the progression, mainly the recurrence and malignant transformation, in order to reduce the cancer morbidity and mortality and to reduce burden on healthcare expenditures.[1] Incisional biopsy and histopathological examination of the suspicious lesion remains the gold standard for diagnosis of OPL. The presence and degree of epithelial dysplasia in a biopsy is still the most important determinant for progression risk in an individual OPL patient.[1] The OPL progression to OSCC is a multistep process that can be challenging to manage. Depending on lesion nature and risk factors, the current treatment for OPL can range from careful observation to surgical intervention. Although various nonsurgical and surgical treatments have been reported, there is no consensus on the most appropriate option.[1]

A Cochrane updated systematic review concluded that randomized controlled trials (RCT) for nonsurgical (medical and complementary) treatment demonstrate no evidence of effective treatment in preventing malignant transformation of oral leukoplakia.[2] Surgical management including conventional resection by scalpel, laser, and cryogun therapy are the most aggressive treatments to remove the affected area of OPL. Recently, a systematic review and meta-analysis concluded that laser excision may decrease recurrence rates but have no effect on the malignant transformation of oral leukoplakia when compared with conventional treatments.[3] Moreover, the studies evaluating the efficacies of close- and open-system cryotherapy treatments on oral precancers were also reviewed.[4] Based on a literature search and to our knowledge, the studies focusing on conventional surgery by scalpel for OPL, however, are not critically examined to determine the efficacy to prevent the potential progression of OPL.

In such a context, the objective of this short communication is to summarize the evidence on conventional scalpel surgery in preventing the recurrence and malignant transformation of OPL patients and analyze collectively in detail as a comprehensive resource for clinicians and investigators.

Materials and methods

A systematic literature search regarding the papers on surgery and OPL from PubMed and Web of Science databases was conducted on 20 Apr 2023. Medical subject term "surg*" in title/abstract and "oral precancerous lesions" and its synonyms in title/abstract were used, according to the search strategy described in Supplementary Table S1. Inclusion criteria was the articles which addressed the issue of OPL patients with the outcome of the recurrence or malignant transformation who received conventional surgery or compared to other interventions or there was no control group.[5–20] Exclusion criteria were case reports, literature reviews, experimental studies, and papers that did not report the patients' outcome. There was no restriction to language and year of publication, and an additional query was identified from cross-referencing. Titles and abstracts or full texts of the articles were screened and re-evaluated to confirm the eligible papers. Data search and extraction were undertaken independently by two investigators (S.Z. and W.L.), and any disagreement was resolved in a consensus symposium. Bibliographical characteristics of the eligible articles were reviewed and recorded the following information: authorship, publication year, country/region of origin, study design, number of subjects, surgical margin, follow-up times, and main results. Descriptive statistics and associations were calculated for these characteristics.

Results

Surgical treatment and the recurrence of OPL

As presented in Table 1, There are 13 eligible studies which addressed the issue of OPL patients with recurrence outcome who received conventional surgery or compared to laser therapy or no intervention. A total of 907 OPL patients, including 705 received conventional surgery and 202 treated with laser therapy, are identified from 9 retrospective studies and 2 prospective RCT. The other 2 retrospective studies report recurrence outcome of scalpel combined with laser surgery, but the respective results of scalpel and laser surgery are not available.[5,7] Those retrospective studies enrolled OPL patients with various grade of dysplasia, while the 2 RCT only enrolled patients with non-dysplasia. There are different follow-up times (mean, 1–11 years; range, 1 month-20.8 years) and surgical margins (1–5 mm of range in 6 studies; unknown in 7 studies). We highlight the recurrence rate of OPL patients received scalpel surgery and laser therapy, and found that the pooled rate (95% confidence interval) is 29.5% (26.3–33.0%) and 32.2% (26.1–38.9%), respectively (Fig. 1A).

Surgical treatment and malignant transformation of OPL

There are 13 eligible studies which addressed the issue of OPL patients with the outcome of malignant transformation

Table 1 Summary of included studies focusing on surgery by scalpel for oral precancerous lesions (OPL) patients with the outcome of the recurrence and malignant transformation.

Author, year	Location	Study design	No. of OPL	Histology type	Mean follow-up (range, y)	Surgical margin	No. (%) of case recurred	No. (%) of case developing carcinoma	Main results
Bagan et al. 2022[5]	Spain	Retrospective	172/224 Surgery 52/224 Laser	24 HGD, 200 LGD	6.4 (1—20.8)	NR	116/224 (51.7%)	19/172 (11.0%) 7/52 (13.5%)	Moderate or severe dysplasia, tongue location, and non-homogeneous increased the risk of malignant transformation (MT)
Arduino et al. 2021[6]	Italy	Prospective RCT	110 Surgery 125 Observation	All nondysplasia	NR (1—5)	1—5 mm	26/110 (23.6%)	1/110 (0.9%) 1/125 (0.8%)	This study failed to show a benefit of surgical excision, in terms of reduction of cancer onset in patients affected by nondysplastic oral leukoplakia
Gilvetti et al. 2021[7]	UK	Retrospective	17 Surgery, 89 Laser 14/120 Observation	All HGD	4.0 (0.7—8.1)	NR	33/95 (34.7%)	13/106 (12.3%) 4/14 (28.6%)	Recurrence was significantly associated with positive excision margins and non-homogeneous. MT was significantly associated with age, non-homogeneous, site, treatment received and positive excision margins.
Chiang et al. 2020[8]	China, Taiwan	Retrospective	202 Surgery 333 Observation 20 Surgery refusal	241 nondysplasia, 15 dysplasia	6.7 (6-NR)	NR	NR	25/202 (12.4%) 17/333 (5.1%) 6/20 (30.0%)	Significant independent risk factors for MT were heavy betel quid chewing, verrucous hyperplasia, and surgery refusal.
Sundberg et al. 2019[18]	Sweden	Prospective	103/180 Surgery 77/180 Observation	17 HGD, 30 LGD, 145 nondysplasia 30 LGD, 145 nondysplasia	4.0 (0.9—6.0)	2 mm	43/103 (41.7%)	NR	Recurrence was significantly associated with snuff use and non-homogeneous.
Arduino et al. 2018[9]	Italy	Prospective RCT	58 Surgery 59 Laser	All nondysplasia	4.8 (2—9)	NR	25/58 (43.1%) 30/59 (50.8%)	0/58 0/59	It seems reasonable to consider the Er:YAG laser as effective as traditional surgery with scalpel.
Ballivet et al. 2018[10]	France	Retrospective	31/31 Surgery	28 HGD, 3 LGD	11 ± 3.7	2 mm	20/31 (64.5%)	13/31 (41.9%)	Recurrence and MT were significantly associated with

									positive or close margins status but not histology grading or lesion size
Monteiro et al. 2017[11]	Italy, Portugal	Retrospective	17/87 Surgery 70/87 Laser	14 HGD, 28 LGD, 45 nondysplasia	1.8 (0.1–12.6)	3 mm	8/17 (47.1%) 16/70 (22.9%)	0/17 1/70 (1.4%)	A significantly better outcome in cases treated with Er: YAG Laser compared with scalpel Surgery
Huang et al. 2015[19]	China	Retrospective	10/32 Surgery 22/32 Laser	NR	1 (0.1–2.0)	Yes	1/10 (10.0%) 2/22 (9.0%)	NR	Laser treatment has the advantages of reduced bleeding, a clear view during surgery, and a shorter operative time.
Kuribayashi et al. 2015[12]	Japan	Retrospective	183 Surgery 218 Observation	64 HGD, 45 LGD, 74 nondysplasia 41 HGD, 72 LGD, 124 nondysplasia	3.4 (1.0–10.5)	NR	NR	NR 7/218 (3.2%)	MT rate in patients with nonsurgical therapy was significantly higher than surgical therapy ($p = 0.022$).
Brouns et al. 2014[13]	Netherlands	Retrospective	60/144 Surgery 35/144 Laser 49/144 Observation	16 severe, 40 mild or moderate, 88 nondysplasia	4.3 (1–14.9)	NR	25/60 (41.7%) 14/35 (40.0%)	5/60 (8.3%) 5/35 (14.3%) 6/49 (12.2%)	A size of >4 cm showed to be the only significant predicting factor of MT in oral leukoplakia.
Arnaoutakis et al. 2013[20]	United States	Retrospective	75/136 Surgery 16/136 Laser 38/136 Observation	27 LGD, 109 HGD	NR	NR	27/75 (36.0%) 3/16 (18.8%)	NR	Surgery excision and/or laser ablation of oral premalignancy is more effective than observation in preventing recurrence and MT of premalignancy
Kuribayashi et al. 2012[14]	Japan	Retrospective	53/53 Surgery	32 HGD 15 LGD 6 nondysplasia	2.6 (0.5–7.4)	3 mm	4/32 (12.5%) 3/15 (20.0%) 1/6 (16.7%)	1/32 (0.3%)	An adequate resection margin (>3 mm) may reduce the risk of recurrence, irrespective of dysplasia grade.
Arduino et al. 2009[15]	Italy	Retrospective	133/207 Surgery 74/207 Observation	72 HGD, 133 LGD	4.5 (1–16)	NR	NR	12/133 (9.0%) 3/74 (4.1%)	There is no eminent benefit of surgical intervention of dysplasia in preventing recurrences and malignant development.
Holmstrup et al. 2006[16]	Denmark	Retrospective	94/269 Surgery 175/269 Observation	44 HGD, 28 LGD, 25 nondysplasia 6 HGD, 14 LGD, 155	7.5 (2.7–15.1) 6.6 (1.0–17.2)	NR	12/94 (12.7%)	11/94 (11.7%) 7/175 (4.1%)	Non-homogeneous and >200mm2 but not dysplasia, site, demarcation, smoking and surgical intervention correlated with malignant

(*continued on next page*)

Table 1 (*continued*)

Author, year	Location	Study design	No. of OPL	Histology type	Mean follow-up (range, y)	Surgical margin	No. (%) of case recurred	No. (%) of case developing carcinoma	Main results
Saito et al. 2001[17]	Japan	Retrospective	75/142 Surgery 16/142 Cryotherapy 51/142 Observation	nondysplasia 43 HGD, 48 LGD, 51 nondysplasia	4.0 (0.6—16.0)	3—5 mm NR	14/94 (14.9%)	1/75 (1.3%) 4/16 (25.0%) 4/51 (6.3)	transformation Surgical excision but not cryosurgery may reduce the risk of malignant development

HGD, high-grade (moderate/severe) dysplasia; LGD, low-grade (mild) dysplasia; NR, not reported; RCT, randomized controlled trial.

who received conventional surgery or compared to other interventions or there was no control group (Table 1). A total of 2514 OPL patients, including 984 treated with conventional surgery, 1172 followed with clinical observation, 216 treated with laser therapy, and 16 received cryosurgery are identified from 11 retrospective studies and 2 prospective RCT. Those retrospective studies enrolled OPL patients with various grade of dysplasia, while the 2 RCT only enrolled patients with non-dysplasia. There are different follow-up protocols (mean, 1.8—11 years; range, 1 month-20.8 years) and surgical margins (1—5 mm of range in 5 studies; unknown in 8 studies). We highlight the malignant transformation rate of OPL patients received scalpel surgery, laser therapy, and clinical observation, and found that the pooled rate (95% confidence interval) is 8.9% (7.3—10.9%), 6.0% (3.5—10.1%), and 10.2% (8.6—12.1%), respectively (Fig. 1B).

Discussion

Given a portion of OPL ultimately develop OSCC, the first step in the management of OPL is diagnosis with risk stratification. It is widely approved that the intervention strategy should be based on histopathological examination in an incisional biopsy of the lesions. Currently, epithelial dysplasia remains the main indicator for clinicians to stratify the progression risk in an individual patient with OPL.[1] However, it is important to understand whether a diagnosis of the presence or degree of oral dysplasia in an incisional biopsy is in fact reliable. One aspect is histological assessment being of high subjectivity in clinical practice, which is the well-known inter-observer and intra-observer variations in the diagnosis of oral dysplasia.[1] Another aspect is that an incisional biopsy sample from a suspicious lesion is not always representative of the whole lesion and so not always reflects the true nature of the entire lesion. The sampling errors during biopsy procedures contribute to misdiagnosis. The issue is further complicated by the fact that 5—10% of OPL contain micro-invasive carcinoma which was not initially revealed by an incisional biopsy but only afterwards on surgical excision.[1] These common errors that may underestimate dysplasia severity or even contributory to missing a carcinoma. Hence, unifocal lesion which is about 2 cm in diameter should be indicated for surgical excision at baseline for purposes of diagnosis. The advantage of surgically excisional biopsy is the availability of the whole specimen for histopathological examination. Besides, the risk of misdiagnosis due to sampling error may be reduced by multiple biopsy samples of large or multifocal lesions, which remains challenging for clinicians to manage.

Secondly, surgical excision using a scalpel can remove visible safety margins, which theoretically reduces the risk of OPL recurrence and malignant transformation. A close surgical margin is often an indicator of a significant risk of disease recurrence. To improving the efficacy of surgical resection, extension of the removal beyond the margin of the visible manifestation and histological examination of all excised lesions. Regrettably, the literature lacks evidence-based guidelines and expert consensus for margin selection, or for intraoperative/postoperative pathological

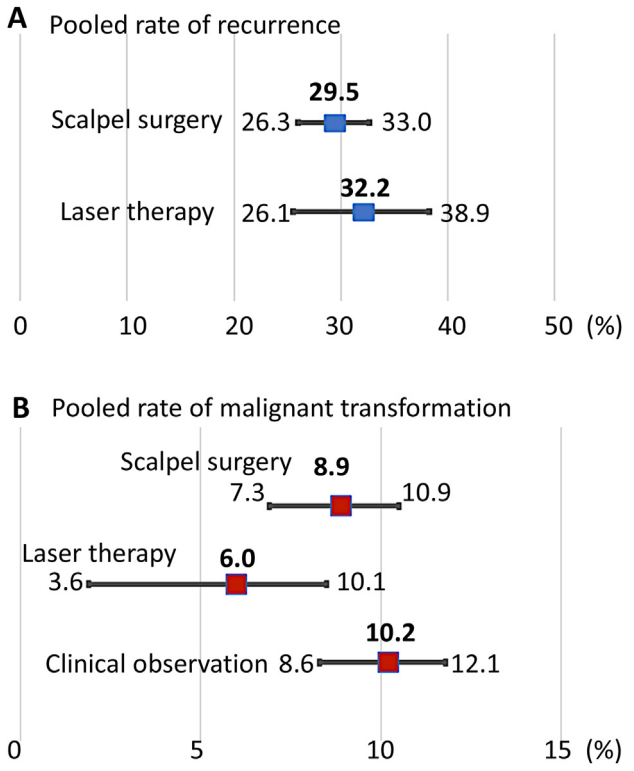

Figure 1 The pooled analysis of the rate (95% confidence interval) of oral precancerous lesions progression. (**A**) The recurrence rate of patients received scalpel surgery (208/705 cases extracted from 12 studies) and laser therapy (65/202 cases extracted from 5 of 12 studies) is 29.5% (26.3—33.0%) and 32.2% (26.1—38.9%), respectively. (**B**) The pooled rate of malignant transformation of patients received scalpel surgery (88/984 cases extracted from 11 studies), laser therapy (13/216 cases extracted from 4 of 11 studies), and clinical observation (120/1172 cases extracted from 8 of 11 studies) is 8.9% (7.3—10.9%), 6.0% (3.5—10.1%), and 10.2% (8.6—12.1%), respectively.

assessment. It is actually unknown whether the width and depth of the margins. For well-defined lesions, a margin of up to 3 mm of apparently unaltered tissue has been advocated removed peripherally. For less demarcated lesions, a margin of 5 mm is taken where anatomically possible and tissue is excised down to superficial striated muscle or periosteum with a depth of 3—5 mm. Notably, surgical excision of the visible abnormal changes is not always commensurate with histologically or molecularly disease-free margins. Field cancerization changes, which characterized by clones of cells even in clinically and histologically surrounding normal oral mucosa with molecular aberrations characterized as hallmarks of malignancy, may account for this phenomenon.

Although we observe the pooled rates of the recurrence and malignant transformation of OPL received scalpel surgery are not superior to laser therapy and clinical observation, surgical removal remains the most common intervention for dysplastic OPL. The rationale is that by removing the lesions, the risk for malignant progression is mitigated. The critical disadvantages of laser ablation/vaporization and cryosurgery are that the tissue is ablated leaving no sample for further histology and the margins are cauterized. These cause a problem that the ability to detect an occult primary in an area of dysplastic epithelium or even micro-invasive carcinoma is lost. The important limitation of current evidence available for prognosis of dysplastic OPL is based on retrospective observational studies. Also, treatment modalities including basis for grouping and ambiguous surgical margins, different clinical and pathological characteristics, small case series, and inadequate follow-up period will inevitably lead to highly heterogeneous or even contradictory results.

With the above-mentioned perspectives in mind, it highlights that surgery management of OPL needs more RCT and cohort studies to explore more reliable methods for routine clinical use to facilitate high- or low-risk stratification and further select more appropriate treatment option. It is our intent for the first time to summarize the current evidence, predominantly low level, on the surgery management of OPL, and to stimulate clinicians and researchers to conduct high-quality RCT and cohort studies on this issue. Collectively, it is sensible to assume that experts still recommend the surgical removal of OPL which are regarded as high risk, until robust evidence is available. Even if there is not clear evidence for the role of surgery in preventing the recurrence and malignant transformation, there may be a role to detect early cancer which was initially undetected by incisional biopsy.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jds.2023.05.033.

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