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Systematic Review
Oral Medicine

Therapeutic approaches for actinic cheilitis: therapeutic efficacy and malignant transformation after treatment

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Abstract. Actinic cheilitis (AC) is a sun-induced premalignant lesion. AC is a clinical term housing a wide pathological spectrum ranging from hyperkeratosis to invasive squamous cell carcinoma. The aim of this systematic review was to examine the therapeutic efficacy of different approaches in clinical, histological, and cosmetic terms, and the malignization rate after treatment. A systematic search was undertaken in October 2016 and updated in April 2019 at MEDLINE (from 1966), Embase (from 1980), and Proceedings Web of Science (Conference Proceedings Citation Index-Science (CPCI-S) from 1990) databases. The search strategy was ((''actinic'' or ''solar'') AND (''cheilitis'')) using both medical subject headings (MeSH) and freetext. A total of 392 potentially eligible reports were identified. After the selection procedure, 20 articles were included. It was concluded that surgical treatment is the first line of treatment for AC and has proved useful for the clinical and pathological control of the disorder. However, there was no evidence of effective treatment in preventing malignant transformations. Non-surgical procedures showed less consistent results, although drug therapy may improve the results obtained by other therapeutic approaches.

Key words: actinic cheilitis; treatment; malignization; squamous cell carcinoma; systematic review.

Accepted for publication

Actinic cheilitis (AC), also known as 'solar cheilosis' (SC), is a sun-induced premalignant lesion whose main clinical features include variations in the colour of the lips, blurred limits between the vermilion border and the skin, and often atrophic areas, scaly lesions, and pronounced folds together with white spots[1,2]. Ulcerations and crust-making lesions may be also present in the lower lip[1–4].

AC is a clinical term housing a wide pathological spectrum ranging from hyperkeratosis (with or without epithelial dysplasia), carcinoma in situ, or superficially invasive squamous cell carcinoma,

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to an openly invasive squamous cell carcinoma[3,4]. As the clinical aspect of AC gives no hint of its pathological severity, an adequate pretreatment histological diagnosis may well be critical for selecting the most suitable therapeutic approach[3,4].

The precancerous nature of AC[3] has been based on the coexistence of AC and squamous cell carcinoma (SCC) and also on the results of retrospective longitudinal studies[4]. However, the rate of malignant transformation of AC remains unknown due to the lack of observational studies following untreated AC lesions in the long term[5].

AC can be topically treated using imiquimod, 5-fluorouracil, and diclofenac; by photodynamic therapy; or by surgical procedures such as vermilionectomy, CO_2 laser ablation, cryosurgery, including Mohs micrographic surgery[2,5]. Other approaches such as dermabrasion or chemical peels can also be used[7]. However, the evidence supporting these latter treatments is scarce and it is mainly based upon retrospective case series and experimental studies without a control group[2,5].

Several reviews have focused on therapeutic approaches to AC[2,6–9]. However, the pertinence of our investigation is based upon the flaws observed in the two systematic reviews on this topic published so far: one provides untrustworthy evidence and does not consider all important outcomes[6,10], and the other[7] does not include recurrence and malignization rates after treatment among its outcomes, despite recognizing the AC potential for malignant transformation. These flaws severely limit the usefulness of the information provided to make adequate treatment choices[7]. All these attempts have chosen as outcomes the degree of clinical and/or histological resolution of the lesion, morbidity, and aesthetic results of the treatments[2,6–9]. Besides, bearing in mind that AC is an oral potentially malignant disorder (OPMD), the main therapeutic objective should be to avoid malignant transformations (later expected lip cancer incidence), thus improvements in clinical and histological parameters should not be considered robust outcomes.

Therefore, the aim of this systematic review was to examine the therapeutic efficacy of different approaches in clinical, histological, side effects and cosmetic terms, as well as the rate of AC malignant transformation after treatment.

Material and methods

The review protocol was established in advance and agreed by all authors before being registered in the International Prospective Register of Systematic Reviews (PROSPERO, 2016; CRD420160500323)[11]. This systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines and following the outlines of PICO: (1) population: subjects clinically and/or pathologically diagnosed with AC; (2) intervention: any treatment undertaken with curative intention; (3) comparisons: patients treated by non-surgical approaches (topical treatment or photodynamic therapy) vs. subjects treated by surgical approaches (including LASER devices); (4) outcomes: primary outcome – clinical and histological outcomes after treatment and adverse effects; secondary outcomes – malignant transformation after treatment.

Systematic search

A systematic search was undertaken in October 2016 (updated April 2019) at MEDLINE (from 1966), Embase (from 1980), and Proceedings Web of Science (Conference Proceedings Citation Index-Science (CPCI-S) from 1990) databases. The search strategy was ((''actinic'' or ''solar'') AND (''cheilitis'')) using both medical subject headings (MeSH) and freetext.

Eligibility criteria

Inclusion criteria: all studies reporting original data from AC case series ($\geq$10 patients), with a pathological diagnosis, treated either by surgical or non-surgical procedures considering the clinical and/or pathological response as their outcome. Exclusion criteria: cross-sectional studies with no follow-up after treatment.

Data collection and extraction

Two researchers (Y.L. and J.S.) independently extracted the data in an unblinded manner and entered it into a custom-made form following a standardized procedure. Disagreements were solved by a third researcher, blinded to the study hypothesis. Inter-observer concordance was calculated by means of the Epidat 3.1 statistical package (Programa para Análisis Epidemiológico de Datos Tabulados, Xunta de Galicia, Santiago de Compostela, Spain).

Quality assessment

The methodological quality of the selected studies was assessed using the Downs and Black checklist which included five main domains: reporting (10 items), external validity (three items), bias (seven items), confounding (six items) and power (one item). Each item was given one point when the criterion was fulfilled, except for item no. 5 (principal confounders) in the reporting sub-scale – which scored 0 to 2 – summing up to a maximum of 28 points per study[12]. According to their score, studies were allocated a grade of 'excellent' (24–28 points), 'good' (19–23 points), 'fair' (14–18 points), or 'poor' (<14 points)[13]. Quality was independently assessed by two authors (Y.L. and J.S.), who solved disagreements by discussion until a consensus was reached.

Results

A total of 392 potentially eligible reports were identified and 323 of them were discarded after assessing both titles and abstracts because they did not deal with treatment and follow-up of AC ($k = 0.903$).

Another 49 papers did not meet the inclusion criteria. Finally, 20 studies reporting on AC were included in the qualitiative synthesis (Fig. 1), and their relevant information is summarized in Tables 1–3.

Surgical approaches

Ten papers published between 1987 and 2011 in the USA ($n = 6$), Israel ($n = 1$), Brazil ($n = 2$), and Germany ($n = 1$), reporting on surgical treatments for 227 patients were identified (Table 1)[14–23]. The quality of these papers was moderate (four were good/fair and six were poor), and reported mainly on retrospective/prospective interventional case series, and only four were comparative in nature (randomized trials) and met the eligibility criteria[16,21–23].

Both vermiliectomy with cold blade/CO_2 laser or vaporization with CO_2 laser demonstrated excellent clinical outcomes with complete resolution of the lesion[14,16,21–23]and functional preservation of the lip[14,17,23]. Besides, three studies including pre- and postoperative biopsies proved that vermiliectomy by cold blade[16] and CO_2 laser vaporization[15,19]can completely eliminate epithelial dysplasia, whereas low-morbidity, CO_2 laser vaporization one-pass protocols only solves about 53.8–61.5% of dysplastic cheilitis[22].

Lip dysaesthesias were reported as the most frequent adverse effect linked to these techniques, ranging from 0%[14,17,19,21] to 33%[23], being more com-

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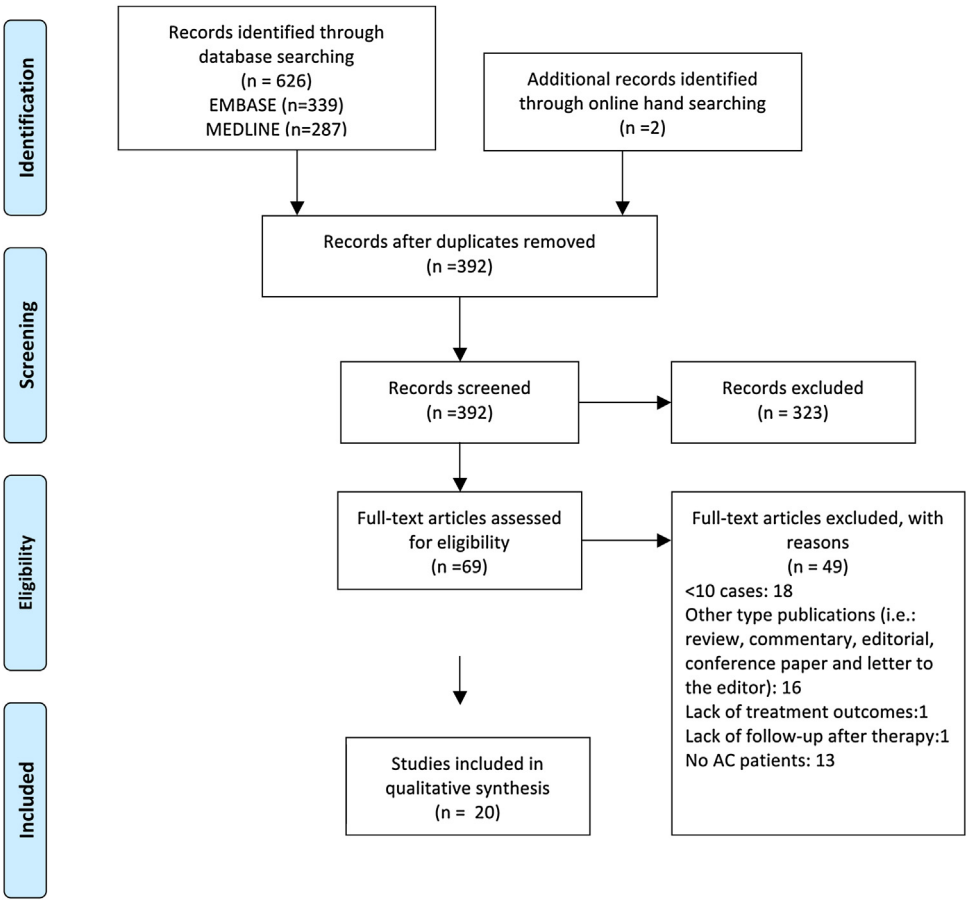

Fig. 1. Flow chart of the study.
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.
For more information, visit www.prisma-statement.org.

mon after vermilionectomy with cold blade when compared with laser vaporization. Prevalence was also higher among those treated by w-plasty vermilionectomy compared with classic vermilionectomy[23].

Eight reports analysed the recurrence rate of AC after treatment and mainly reported either no recurrences[14,16,19] or low rates[20,21]. However, the highest reported recurrence rates were observed in patients treated by one-pass protocols for CO_2 laser vaporization (12.5%)[23].

Non-surgical approach

Another 11 studies investigated non-surgical approaches for AC treatment (Tables 2,3). Nine of them assessed photodynamic therapy[24–32] and the other one evaluated different topical pharmacological approaches: imiquimod[33]. An additional prospective study comparing the outcomes of surgical and non-surgical therapies (fluorouracil and trichloroacetic acid) also fulfilled the inclusion criteria[16].

Information on the therapeutic efficacy of this non-invasive procedure was obtained from papers reporting on 187 AC patients diagnosed using clinical and pathological criteria (Table 2)[24–32]. The protocols of these studies included a series of sensitizing agents, such as MAL (methyl aminolaevulinate)[27–32], ALA (5-aminolevulinic acid)[25,26], and MAOP (methylaminoxipentanoate)[24] activated either by red, or day lights, as well as by Er:YAG laser at a 37–40 J/cm^2 irradiation dose[24–32].

This procedure elicited excellent cosmetic outcomes[25,26,30,31] and a moderate clinical therapeutic efficacy, with complete healing percentages ranging from 30% after 45 min[29] to >70% after 12 min[25]. In this sense, the relevant outcomes were obtained by protocols using combinations of imiquimod and red light: 40 J/cm^2/MAL[25]. However, photodynamic therapy also showed high recurrence rates[30] and persistence of epithelial dysplasia after treatment[24,28,32].

Pain was the most frequently reported unwanted effect, which disappeared after a short period of time after photodynamic therapy[26–28,30,31].

Articles on AC medical treatments gathered 35 USA patients[16,33], all of them with a previous pathological diagnosis. Despite trichloroacetic-acid-treated lesions having been reported to show the highest recurrence rates[16], 5% imiquimod cream showed a high clinical effectiveness, but investigations on malignant transformations after treatment are scarce[16,33]. In addition, pathological studies undertaken after medical treatment have shown these drugs to be unable to eliminate epithelial dysplasias[16] (Table 3).

Malignant transformation after treatment

Malignant transformation rates after surgical treatments were assessed in six longitudinal studies, and four of them did not

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Table 1. Summary of surgical treatments for actinic cheilitis.

First author, Year Country	Patients (M/F)	Diagnostic criteria for AC	Surgical treatment	Clinical outcomes Clinical AC after treatment	Histological outcomes (after surgery on follow-up)	Cosmetic outcomes	Adverse events	Follow-up	Recurrence rate	Malignization (lip cancer)	QS
Whitaker[14] 1987 USA	$n = 16$ (1/15)	Clinical & histological**	CO_2 laser ablation (4–8 w)	CR at 2 w. No sensitivity or function changes	3–6 m after treatment: ND	No hypertrophic scarring	No adverse events (except 1 patient)	24 m	1 recurrence (at 14 m)	None	6
Dufresne[15] 1988 USA	$n = 13$ (8/5)	Histological* (8 ED, 1 SCC)	CO_2 laser vaporization (3–5 w)	No functional restrictions	CR at 4 w	Focal scarring ($n = 3$)	4–7 d: minor pain = 3 Dysesthesia = 1	11 m	No recurrences	None stated	7
Robinson[16] 1989 USA	1. $n = 10$ 2. $n = 10$	Histological (ED)	1.Vermilionectomy 2. CO_2 laser vaporization (5 w)	2. Blurred appearance	1 & 2: No dysplasia	Not assessed	1. Paraesthesias = 1; haematoma = 1	1.54 m 2.50 m	1. No recurrences 2. No recurrences	1. None 2. None	14
Zelickson[17] 1990 USA	$n = 43$ (38/5)	Histological (ED)	CO_2 laser Vaporization (5–7 w)	Function: Improved = 18		Unchanged = 22 Worse = 1	Not assessed		Improved = 26 Unchanged = 16 Worse = 1	No pain Mild postoperative swelling ($n = 3$)	31 m
Recurrences ($n = 3$) leukoplakia ($n = 1$)	SCC ($n = 1$)	7									
Neder[18] 1992 Israel	$n = 16$	Histological*	CO_2 laser vermilionectomy with (8 w)	No scars, more elastic lip	CR at 4 w	Similar lip configuration as prior to surgery	Minimal discomfort	1 y	None stated	None stated	5
Johnson[19] 1992 USA	$n = 14$ (12/2)	Clinical & histological (ED)	CO_2 laser vaporization (2–3 w)	CR after 2–4 w	100% CR	No evidence of scars	No pain after 2–3 w	12 m	No recurrences	None stated	6
Hohenleutne[20] 1999 Germany	$n = 19$	Clinical & histological	CO_2 laser vaporization	Erosion 2 m post-treatment ($n = 1$)	Not assessed	Excellent cosmetic results	Minor scarring ($n = 1$)	16 m	Recurrence ($n = 1$)	None	5
Laws,[21] 2000 USA	$n = 14$ (13/1)	Histological (ED)	1. E (5 w to 4.3 w) 2. CO_2 Laser (18 W;360mj/cm^2)	Improved all patients (ND)	$n = 5$. 3 m follow-up biopsy	ND	Minimal pain (ND)	3 m	Recurrence (n = 1)	1 SCC (1 LSCC 3-m previous)	16
de Godoy[22] 2009 Brazil	$n = 40$ (36/4)	Histological (ED)	1. CO_2 laser 250 mJ, 5 w 2. CO_2 laser 350 mJ, 3.5 w	CR: 35	1. ND = 53.8% 2. ND = 61.5%	No visible scarring	$n = 12$ moerate pain.	6–30 m	Recurrences 1.(12.5%) 2. (12.5%)	None	22
Rossoe[23] 2011 Brazil	$n = 32$ (13/19)	Clinical & histological (ED)	1. Classic vermilionectomy 2. W-plasty vermilionectomy	No function abnormality	Surgical specimen: 2 SCC 1 BCC	Association between no scar retraction and W-plasty procedure	1.				

Paraesthesia = 23.5%
2. Paraesthesia = 33.3%
19 m
Non stated
None stated
17

AC, actinic cheilitis; BCC, Basal Cell Carcinoma; CR, complete re-epitelization; d, days; ED, epithelial dysplasia; Er:YAG, erbium:ythrium-aluminium-garnet; F, female; M, male; m, months; NCR, non-complete re-epithelialization; ND, Not determined; QS, qualitative score; SCC, squamous cell carcinoma; w, weeks; y, years.

* Incisional biopsy.

** Excisional biopsy or surgical specimen after incisional diagnostic biopsy.

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Table 2. Summary of studies reporting on photodynamic therapy.

First author Year Country	Patients (M/F)	AC diagnostic criteria (*)	PDT light/laser	Photosensitizing agent	Treatment protocol light dose	Clinical outcomes Clinical AC after treatment: CR vs. non-CR	Histological outcomes (after treatment on follow-up) (**) (***)	Cosmetic outcomes	Adverse events	Follow-up	Malignization rate (lip cancer)	QS
Berking[24] 2007 Germany	$n = 15$ (9/6)	Histological (ED)	Red light	MAOP	37 J/cm^2	CR: 47% after 3 m	CR: 38%*** (ED = 8)	Very good: 33%	All resolved within 4 d	3 m	None stated	13
Sotiriou[25] 2008 Greece	$n = 10$ (10/0)	Histological (ED)	Red light	ALA	40 J/cm^2	CR: 90% after 3 m	CR: 80%	Excellent: 80–60%	All resolved within 13 d	3 m	None stated	6
Sotiriou[26] 2010 Greece	$n = 40$ (40/0)	Histological (ED)	Red light	ALA	40 J/cm^2	CR: 22/26 after 18 m	CR: 17/22 after 18 m	Excellert: 81.8% (18/22)	Pain & burning (mild to moderate)	18 m	None	14
Sotiriou[27] 2011 Greece	$n = 34$ (33/1)	Histological	Red light + imiquimod	MAL	40 J/cm^2	CR: 90% after 3 m	CR: 73% after 12 m	Not assessed	Mild–moderate All resolved within 8 d	12 m	None stated	8
Ribeiro[28] 2012 Brazil	$n = 19$ (10/9)	Histological (ED)	Red light (LED)	MAL	37 J/cm^2	CR: 47–68%	CR: 16% ED: 84%	85% satisfaction	Moderate pain All resolved within 7 d	51–94 d	None stated	14
Kim[29] 2013 Korea	$n = 10$ (6/4)	HIstological	Red light	MAL	37 J/cm^2	CR: about 30% after 45 m ($n = 2$ recurrences)	Not stated	Not assessed	Well tolerated	45 m	None stated	6
Choi[30] 2015 Korea	$n = 33$ 1: $n = 14$ (9/5) 2: $n = 19$ (11/8)	Histological	1: Er:YAG AFL + red diode light 2: Red diode light	MAL	37 J/cm^2	1: CR = 12 after 3 m 2: CR = 10 after 3 m ($P = 0.040$) Still significant after 12 m	12 m recurrences 1: 8% 2: 50%	Excellent or good 1: 73% 2: 60%	Mild/moderate pain All resolved within 7 d	12 m	None stated	23
Suárez-Pérez[31] 2015 Spain	$n = 10$ (8/2)	Histological	Red LED light	MAL	20 J/cm^2 + 80 J/cm^2	CR = 8 after 3 m 2 recurrences	AC = 5 after 3 m***	Excellent or good 80%	Minor: $n = 7$ Moderate: $n = 3$ All resolved within 14 d	1 m	None stated	8
Chaves[32] 2016 Brazil	$n = 16$ (10/6)	Histological	Red LED light	MAL	37 J/cm^2	CR = 10 (62.5%)	Persistence of dysplasia after treatment	Not assessed	Erythema & oedema Herpes labialis ($n = 1$)	3 m	None stated	12

AC, actinic cheilitis; ALA, 5-aminolevulinic acid; CR, complete curation; d, days; ED, epithelial dysplasia; Er:YAG, erbium:ythrium-aluminium-garnet laser; F, female; h, hours; M, male; m: months; MAL, methyl aminlevulinate; MAOP, methylanomoxopentanoate; PDT, photodynamic therapy; QS, qualitative score.

* Incisional biopsy.

** excisional biopsy or surgical specimen after incisional diagnostic biopsy.

*** incisional biopsy after treatment.

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Table 3. Summary of papers reporting on topical drug therapy.

First author Year Country	Patients (M/F)	Criteria for AC diagnosis (*)	Drug employed	Protocol	Length of treatment	Clinical outcomes Clinical AC after treatment	Histological outcomes (after treatment on follow-up) (**)	Cosmetic outcomes	Adverse events	Follow-up	Recurrences	Malignization (lip cancer) *n* (%)	QS
Robinson[16] 1989 USA	1. $n = 10$ 2. $n = 10$	AC pathological diagnosis (ED)	1. FU 5% solution 2. TCA (50%)	1. 3 times a day for 14 days	1. 14 d 2. Chemical peeling (twice)	Not assessed	Biopsy after 1 y 1. ED ($n = 5$) 2. ED ($n = 10$)	Not assessed	1. Irritation & soreness 2. No	1. 50 m 2. 49 m	1. $n = 5$ 2. $n = 7$	None	14
Smith[33] 2002 EEUU	$n = 15$ (12/3)	Clinical & histological	5% imiquimod cream,	3 times weekly	4–6 w	All CR; 11 patients required 2 additional weeks	Not assessed	Not assessed	Moderate–marked inflammation	$n = 15$, 4 w $n = 7$, 1 y	No recurrences	Not stated	11

AC, actinic cheilitis; CR, complete curation; ED, epithelial dysplasia; FU, fluorouracil; m, month; PR, partial curation); QS, qualitative score; TCA, trichloroacetic acid; w, weeks; y, years.
* Incisional biopsy.
** Excisional biopsy after treatment.

report any case of malignization[14,16,20,22], whereas studies using different protocols for CO_2 laser vaporization reported low rates of malignant transformations in the treated areas: 1/43[17]. Case series with smaller sample sizes also reported malignizations after CO_2 vermilionectomy (1/14)[21] (Table 1). Conversely, neither of the other two reports[16,25] which had undertaken non-surgical treatment for AC with long follow-up periods (18–50 months) could identify a single case of malignization after treatment.

Discussion

Limitations of this systematic review

Certain limitations inherent to the moderate quality of the individual studies considered, together with the potential selection biases, should be taken into account despite the fact that only patients with a pathological diagnosis of AC were included in this systematic review. Data on malignant transformations of AC should also be interpreted with caution because of the reduced number of studies investigating this variable[14,16,17,20–22,25], and also because it can behave as a censored observation due to a hypothetical insufficient observation time for malignization to occur, thus resulting in an underestimation of its frequency.

Besides, pre-treatment diagnosis has mainly been established upon incisional biopsies despite the well-known non-homogenous, multifocal nature of AC[3]. Thus, incisional biopsies may result in underdiagnosis of dysplastic lesions and also masking non-contiguous foci of squamous cell carcinomas, even in diffuse and poorly demarcated lesions[1,3]. These possibilities are somehow reinforced by the widely reported findings of squamous cell carcinomas in surgical specimens obtained by vermilionectomy (excisional biopsy for AC diagnosis) from patients with clinical diagnosis of AC or who had undergone previous incisional biopsies[3,21,34].

The papers included in this review were mainly retrospective/prospective observational case series and prospective quasi-experimental studies. However, seven studies were categorized as of good or fair quality (Supplementary data)[16,21–23,26,28,30], and offer a moderate level of evidence. Besides, the current investigation is the first systematic review to compare different therapeutic approaches to AC which includes studies with patient follow-up and post-treatment malignization outcomes.

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Surgical vs. non-surgical treatments for AC

Vermilionectomy with cold blade[16,23] and CO_2 laser with secondary intention healing allow an adequate clinical-pathological control of the lesion[18]. Regarding non-surgical approaches, photodynamic therapies provided not very effective clearance rates[35] and poorly consistent results[29]. However, daylight photodynamic therapy with MAL proved to be better tolerated than the conventional one[15] and it may be specifically indicated for AC cases associated with multiple actinic keratoses of the face.

Topical drug therapies are poorly studied[16,33] and seem to provide acceptable clinical results. Moreover, topical drug therapies may help in controlling the cancerization field and its association with other therapeutic approaches may increase their clinical efficacy[2,8,9].

AC malignization after treatment

The main therapeutic intention when dealing with pre-malignant oral lesions is to reduce the risk of oral cancer in the affected area in the future. Most squamous cell carcinoma cases were reported in series using clinical diagnostic criteria exclusively[34,36] (where diagnostic uncertainty is higher), and were not considered in this systematic review. In these cases, the lip carcinoma may well have already been there before the treatment was started. The other case series[17,21] reporting malignant transformations of AC lesions have selected patients with epithelial dysplasia, particularly those moderate and severe[17].

This can be explained by the fact that the presence and severity of epithelial dysplasia condition the potential for malignization[37]. In any case, well-designed clinical trials considering malignization rate among their outcomes are required to render stronger evidence on the different treatment options, particularly for non-invasive procedures.

Clinical implications

Therapy selection should be made on an individual basis and be guided by the pathological findings and the potential for malignant transformation taking into account the side-effect profiles[8], the patient cosmetic wishes, and the available scientific evidence[2,8]. Therefore, vermilionectomy techniques may be reserved for diffuse AC with severe dysplasia whereas laser vaporization techniques may be used in diffuse or multicentric lesions with mild dysplasia provided a high preoperative diagnostic certainty is achieved. AC circumscribed lesions suspicious for malignancy should be removed by excision or vaporization if moderate/severe dysplasia is detected, or under oncological criteria if squamous cell carcinoma is diagnosed in the previous (one or more) incisional biopsies. Although photodynamic therapy continues with unclear indication of use, non-dysplastic AC lesions –either circumscribed or diffuse – may be treated using drug therapy[16,33], avoiding the recommendation of 5-fluorouracil and imiquimod for treating clinically suspicious areas (>0.5 cm) with mild to severe dysplasia, or when dealing with diffuse lesions, leukoplakia, or atrophy, with mild to moderate dysplasia.

In any case, preventive measures and regular follow-up after treatment are mandatory.

It is concluded that surgical treatment is the first line of treatment for AC and has proved useful for the clinical and pathological control of the disorder. However, there is no evidence of effective treatment in preventing malignant transformations. Non-surgical procedures have shown less consistent results, although drug therapy may improve the results obtained by other therapeutic approaches.

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Competing interests

None.

Ethical approval

Not required.

Patient consent

Not required.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijom.2020.02.014.

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