

Review

# Prevention of Recurrence of Oral HPV-Related Lesions: Systematic Review of the Literature and Meta-Analysis

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**Abstract:** (1) Background The incidence of oral cavity lesions related to human papillomavirus (HPV) is 3%. There are no reliable data in the literature on recurrence rates of HPV-related oral cavity lesions. The only data available concern gynecological infections, which have a recurrence rate of ~30%. Recurrence may be due to a failure to completely eradicate the lesion, persistence of the viral infection, or persistence of an immune-compromised state. Therefore, the study aimed to ascertain the most effective therapeutic strategy to achieve complete eradication of the virus and avoid a possible recurrence of lesions, based upon the long-term behavior of the virus with the type of treatment. (2) Methods: Systematic searches of the Cochrane Library, EMBASE, Pubmed, Web of Science, clinicaltrials.gov, and SCOPUS were performed. Restrictions were placed on the date of publication and language. Only English or Italian language articles published between Jan 1990 and Dec 2019 were included in the meta-analysis. The following keywords and/or corresponding medical subject heading terms were used: “oral papillomavirus lesions” and “oral HPV lesions” or “treatment”, “therapy”, “therapeutics,” and “management”. (3) Results: Upon systematic literature review of all analyzed HPV-lesion treatment techniques, 36 studies on laser and cold scalpel eradications were selected. These studies document an excellent success rate from excisional treatments using both laser and cold scalpel and report low recurrence rates with both techniques, respectively 5.98% and 4.07%. (4) Conclusions: The meta-analysis revealed that additional studies with greater sample sizes are needed for these two treatment methods. It would also be appropriate to carry out case-controlled studies, preferably RCTs, to determine the best treatment for eradicating HPV-related lesions.

**Keywords:** oral HPV-related lesions; human papillomavirus; meta-analysis; treatment strategies; oral HPV treatment



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## 1. Introduction

The majority of human papillomavirus (HPV) infections of the oral cavity are latent or subclinical and spontaneously regress between 1 and 2 years (on average 6 months) of infection [1]. Although the literature does not give a well-defined prevalence, some studies show persistent infection in up to 23.1% of those with oral HPV [2]. The overall incidence of HPV-related oral cavity lesions in the general population is 3% [3].

Benign HPV-related lesions of the oral cavity include verruca vulgaris (VV) (the common wart), squamous papilloma (SP), condyloma acuminatum (CA), and multifocal epithelial hyperplasia (MEH). These lesions share clinical and histological features with one another, as well as with other lesions of inflammatory, syndrome-associated, or malignant etiologies. Some authors argue that SP and CA should be categorized together due to a shared causality by both HPV 6 and HPV 11, as well as overlapping histological and clinical presentations [4].

VV, although common on the skin, is relatively uncommon intraorally. Autoinoculation is the main mode of VV transmission. Clinically, VV mucosal lesions appear similar to

their cutaneous counterpart. The labial mucosa and palate are the most common intraoral sites of VV infection. The lesions are pink to white, sessile, usually less than 1 cm in size, and display exophytic fronds [5].

SP is a common lesion and the most frequent benign oral epithelial entity in both children and adults. The palate and tongue are most affected, but any site may be involved. Clinically, SP is characterized by exophytic “finger-like” projections. SPs are usually pedunculated, with colors ranging from white to pink/red. The lesions are rarely larger than 5 mm in dimension and usually solitary [6].

CA is uncommon in the oral cavity. Adults in their 30s and 40s are most affected by CA. Clinically, CA may present as a solitary lesion or in multiples, some of which may fuse to form larger growths. The lesions may be pedunculated but are more often sessile with cauliflower-like or a moruloid surface texture and pink to white coloration. The tongue and upper lip are the most common intraoral locations for CA [7].

MEH lesions are associated with a genetic susceptibility due to human leukocyte antigen subtype HLA-DR4. MEH is most often reported in particular populations, such as Navajo and Alaskan Eskimo children, indigenous children in the Americas, and AIDS patients. MEH is characterized by multiple lesions of varying sizes and affects various sites. Two clinical presentations are described in the literature: the more common papulonodular variant and a papillomatous one. The papulonodular lesions tend to occur on the buccal and labial mucosa and are mucosal-colored and flat. Those papillomatous presentations occur more often on the masticatory mucosa of the tongue and gingiva, with white and pebbly surfaces. Lesions of both variants range in size from 1 mm to 1 cm, often with coalescence [8]. Occurrences on the palate are rare, and the floor of the mouth is spared.

Spontaneous regression of benign HPV-related oral lesions has been reported with an average of 2 years for regression of VV and 18 months for regression of MEH. However, a biopsy is necessary to make a definitive diagnosis. In addition, treating the lesions is necessary to lower the viral load and limit the virus' spread in the individual or transmission to others. There are no reliable data in the literature on recurrence rates of HPV-related oral cavity lesions. The only data available are for gynecological infections, which have a recurrence rate of ~30% [9]. Recurrence may be due to a failure to complete excision of the lesion, persistence of the viral infection, or persistence of an immune-compromised state. Recurrence rates occur more frequently in HIV-positive patients or those on antiretroviral therapy (HAART) [10].

Therefore, the study aimed to ascertain the most effective therapeutic strategy to achieve a better removal of the virus and avoid a possible recurrence of lesions, based upon the long-term behavior of the virus with the type of treatment. A systematic review of the literature with meta-analysis is the most appropriate method to analyze previous research results and determine a new evidence-based trial approach. Papillomavirus infection is an important issue for gynecologists, anogenital surgeons, and epidemiologists. Additionally, odontostomatologists must consider the epidemiological importance of HPV infection to determine the most effective therapeutic strategies [11].

## 2. Materials and Methods

The PRISMA statement was followed during the preparation of this meta-analysis [12].

### 2.1. Search Strategy

Systematic searches of the Cochrane Library, EMBASE, Pubmed, Web of Science, clinicaltrials.gov, and SCOPUS were performed by two investigators to identify all relevant studies for the meta-analysis. Restrictions were placed on the date of publication and language when searching the electronic databases. Only English or Italian language articles published between January 1990 and December 2019 were included. The bibliographies of the included studies were also scanned to identify additional relevant studies not identified in the database search. The following keywords and/or corresponding medical subject

heading terms were used: “oral papillomavirus lesions” and “oral HPV lesions” or “treatment”, “therapy”, “therapeutics,” and “management”.

## 2.2. Study Inclusion Criteria

The first clinical question underlying our research was, “Which treatments are effective for the resolution of HPV-related oral cavity lesions?” The elements taken into consideration for selecting studies to be included in the systematic review were determined according to the reference patient and problem, intervention, comparison, outcome methodology (PICO):

- Patients or problem: patients with HPV-related oral cavity lesions;
- Intervention: pharmacological (systemic and topical) and non-pharmacological treatments;
- Comparison: between different types of intervention and between active intervention and placebo;
- Outcome: clinical resolution of the lesion and possible recurrence after treatment.
- Eligibility criteria included;
- Randomized controlled trials (RCTs) and crossover trials that employed different treatment strategies for the management of HPV-related lesions;
- Case reports and case series employing different treatment strategies for the management of HPV-related injuries;
- Patients with clinical and histopathological manifestations of HPV-related oral cavity lesions;
- Articles in English or Italian language;
- Articles accessible in full form.

Many treatments lack clinical trials. In fact, in the literature, only case series and case-control studies can be found. Nevertheless, the authors decided to pursue this investigation to highlight the need for more thorough analyses of benign HPV-related lesions treatments.

This study was conducted following the guidelines recommended by the Cochrane Collaboration.

The second clinical question underlying the research was, “Which treatment, laser or scalpel excision, is most effective in achieving the removal of HPV-related lesions of the oral cavity?”

The elements of patient and problem, intervention, comparison, outcome (PICO) taken into consideration for selecting studies to be included were:

- Patient and problem: patients with diagnosed HPV-related oral cavity lesions;
- Intervention: laser or scalpel excision;
- Comparison: between the different types of intervention mentioned above;
- Outcome: the disappearance of the lesions in the absence of recurrence at follow-up.

The literature search was conducted using the Pubmed database between 1 January 1990 and 31 December 2019. Studies involving multiple types of HPV-related lesion treatment, both pharmacological and non-pharmacological, were considered.

## 2.3. Exclusion Criteria

The exclusion criteria were:

- Articles not accessible in full form;
- Studies and case reports that did not report the follow-up of the lesion after excision.

## 2.4. 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. Two reviewers independently extracted the data from each article, including the authors, year published, country in which the study was performed, number of cases, length of the follow-up period, presence of recurrence, related risk factors, type of HPV lesion, and treatment strategy. If

the two reviewers disagreed about whether a study met the inclusion criteria, a consensus was reached by a third reviewer.

### 2.5. Statistical Analysis

The meta-analysis of data from the selected studies was performed using the IBM SPSS program (Spss Inc., Chicago, IL, USA) version 25.0. A single-arm meta-analysis was performed to calculate the pooled proportion (PP) of recurrence of HPV-related laser-treated and cold-blade lesions. The estimated effect of each treatment was expressed as an odds ratio (OR). ORs were determined for each study and summed using a Der-Simonian Liard random-effect model. The total variation between the conclusions of the various studies was analyzed according to the Cochran test for heterogeneity and the  $I^2$  index. The  $I^2$  index shows the percentage of observed differences between study indices that are attributable to heterogeneity between studies. This index was classified according to Cochrane guidelines as follows: 0–40% is non-significant heterogeneity; 30–60% is moderate heterogeneity; 50–90% is relevant heterogeneity; 75–100% is remarkable heterogeneity.

## 3. Results

### 3.1. Search Results and Studies Selection

The pre-established document search strategy initially yielded 305 results. After the removal of duplicates, the search yielded 251 results. Following evaluation of titles and abstracts, this number was narrowed to 129 documents. Subsequently, an additional 41 documents were excluded because they did not focus on the treatment or recurrence of the lesions, including some studies that did not include a retrospective analysis of treatment outcome and others that did not meet the inclusion criteria for the clinical and histopathological characteristics of the lesions. At the end of the study selection process, 59 documents were considered suitable for review (Figure 1).

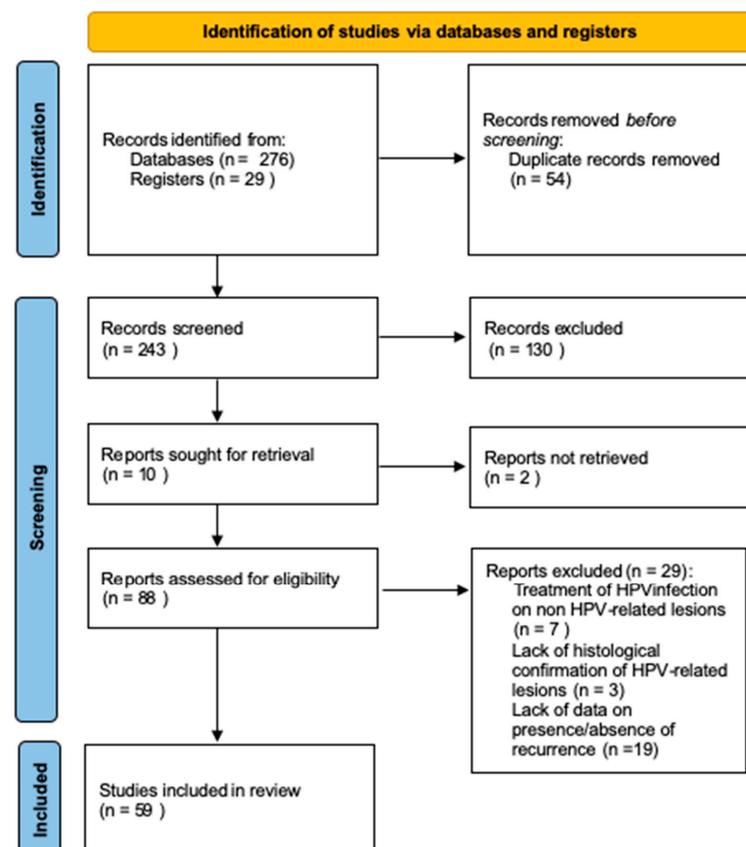


Figure 1. Flowchart systematic review.

At the end of the selection process, the studies were divided according to the type of treatment into pharmacological and non-pharmacological therapies (Table 1).

**Table 1.** Studies included.

Pharmacological Treatment				
Treatment	Studies			
Imiquimod	Wenzel et al., 2003	Maschke et al., 2004	Esquivel-Pedraza L et al., 2015	
Cidofovir	Calista D 2000	De Rossi et al., 2004	Husak et al., 2005	Collette et al., 2011
Bleomycin	Girao L et al., 2000			
Imidazoquinoline	Curi D et al., 2017			
Interferon	Kose et al., 2001	Steinhoff et al., 2001	Kyol et al., 2003 (con CO <sub>2</sub> )	Collangelettes et al., 2009 (con laser)
	NCT00454181, 2011			
Trichloroacetic acid	Carmona Lorduy M et al., 2017			
Non-Pharmacological Treatment				
Treatment	Studies			
Cryotherapy	Ledesma-montes et al., 2005			
Surgical excision Cold scalpel	Aboulafia D 2001	Dos Reis et al., 2009	Jaju et al., 2009	Puriene et al., 2011
	Moroglu et al., 2014	Jaiswal et al., 2014	Frigerio et al., 2015	Nayak et al., 2016
	Mattoo et al., 2018	Orenouga et al., 2018	Sen r et al., 2018	Sudhakar et al., 2019
	Hilal 2019			
Electrosurgery	Wenzel et al., 2003	Goodstein et al., 2012	Ural et al., 2014	Ghazal 2019
Surgical excision Laser	Luomanen et al., 1990	Luomanen M et al., 1992	Squires et al., 1999	Bassioukas et al., 2000
	Moerman et al., 2001	Casariego et al., 2002	Akyol A et al., 2003 (con interferone)	Maschke et al., 2004
	Marangoni et al., 2005	Boj J et al., 2007	Bombeccari et al., 2009	Collangettes et al., 2009 (con interferone)
	Pereira et al., 2010	Misir 2013	Galanakis et al., 2014	Angiero 2015
	Akerzoul et al., 2018			
Mohs micrographic surgery	Lacoture et al., 2006			
Follow-up (after incisional biopsy)	Viraben et al., 1996	Jayasooriya P et al., 2004	Falaki F et al., 2009	Saunders et al., 2010
	Liu et al., 2012	Ghalayani et al., 2014		

A summary of all studies included was compiled.

For each treatment found in the literature, the following parameters were examined (Tables 2–12):

- Type of treatment and study (authors and year);
- Dosage and therapy administration;
- Number of patients;
- Type of benign lesion;
- Treatment length;
- Follow-up length;
- Presence of recurrence;
- Side effects;
- Number of immunocompromised patients.

**Table 2.** Imiquimod studies.

Study	Dosage and Administration	Num of Patients	Type of Lesions	Treatment Length/No of Application	Follow-Up (months)	Side Effects	Recurrence	Immunocompromised Patients	Healed Lesions
Wenzel et al., 2003	Imiquimod 5%, topical admin	1	SP	3 per week/ 4 months	24	Malignant transformation	0	0	1
Maschke et al., 2004	Imiquimod 5%, topical admin	1	FEH	3 per week/ 2 months	5	0	0	0	1
Esquivel-Pedraza L et al., 2015	Imiquimod 5%, topical admin	1	SP	2 per day/ 5 weeks	20	erosion	0	1	1
Esquivel-Pedraza L et al., 2015	Imiquimod 5%, topical admin	1	FEH	2 per day/ 3 weeks	22	0	0	1	1

**Table 3.** Cidofovir studies.

Study	Dosage and Administration	Num of Patients	Type of Lesions	Treatment Length/No of Application	Follow-Up (months)	Side Effects	Recurrence	Immunocompromised Patients	Healed Lesions
Calista D 2000	Cidofovir 1% topical admin	1	SP	1 per day for 5 days/ 2 weeks	12	0	0	1	1
De Rossi et al., 2004	Cidofovir 1% topical admin	1	SP	1 per day/ 4 weeks	12	0	0	1	1
Husak R et al., 2005	Cidofovir 1–3% topical admin	3	VV	1 per day/ 10 weeks	18–24	0	1	3	2
Collette et al., 2011	Cidofovir 1% topical admin	1	FEH	1 per day/ 4 weeks	12	0	0	1	1

**Table 4.** Bleomycin studies.

Study	Dosage and Administration	Num of Patients	Type of Lesions	Treatment Length/No of Application	Follow-Up (months)	Side Effects	Recurrence	Immunocompromised Patients	Healed Lesions
Girao L et al., 2000	0.5/4 mg	1	AC	2	12	Pain and local necrosis	0	1	1

**Table 5.** Imidazoquinoline studies.

Study	Dosage and Administration	Num of Patients	Type of Lesions	Treatment Length/No of Application	Follow-Up (months)	Side Effects	Recurrence	Immunocompromised Patients	Healed Lesions
Curi D et al., 2017	Imidazoquinoline 5%	1	AC	3 per week/ 2 months	24	0	0	1	1

**Table 6.** TCA studies.

Study	No of Patients	Type of Lesions	Treatment Length/No of Application	Follow-Up (months)	Side Effects	Recurrence	Immunocompromised Patients	Healed Lesions
Carmona Lorduy M et al., 2017	13	FEH	1/9 applications	12	0	0	0	13
Carmona Lorduy M et al., 2017	4	VV	1/9 applications	12	0	0	0	4
Carmona Lorduy M et al., 2017	3	AC	1/9 applications	12	0	0	0	3
Curi D et al., 2017	1	AC	30 days	1	0	1	1	0

**Table 7.** Interferon studies.

Study	Dosage and Administration	Num of Patients	Type of Lesions	Treatment Length/No of Application	Follow-Up (months)	Side Effects	Recurrence	Immunocompromised Patients	Healed Lesions
Calista 2000	INF alpha	1		nd	12	0	1	1	0
Kose et al., 2001	INF alpha 2a 4.5 million IU/IM	1	FEH	3 per week/ 14 weeks	2	0	Partial regression	0	0
Steinhoff et al., 2001	INF beta, topical	1	FEH	5 per day/ 12 weeks	7	0	0	0	1
Akyol A et al., 2003 (con Co2)	INF alpha 2b	1	FEH	8 months	24	0	0	0	1
Collangelettes et al., 2009 (con laser)	INF alpha 2a 3 mill U	1	Papillomatosis	3 per week/ 3 months	48	0	0	0	1
NCT00454181 2011	500 IU interferon-alpha lozenges for oral dissolution	36	VV	3 times per day/ 24 weeks	6	1	18	36	18

Table 8. Cryotherapy studies.

Study	Dosage and Administration	Num of Patients	Type of Lesions	Treatment Length/No of Application	Follow-Up (months)	Side Effects	Recurrence	Immunocompromised Patients	Healed Lesions
Ledesma-montes et al., 2005	nd	9	FEH	nd	24	0	0	0	1
Curi D et al., 2017	nd	1	AC	nd	1	0	1	1	0

Table 9. Mohs Micrographic surgery studies.

Study	No of Patients	Type of Lesions	Treatment Length/No of Application	Follow-Up (months)	Side Effects	Recurrence	Immunocompromised Patients	Healed Lesions
Lacoture et al., 2006	1	AC	1	8	0	0	0	1

Table 10. Electrosurgery studies.

Study	No of Patients	Type of Lesions	Treatment Length/No of Application	Follow-Up (months)	Side Effects	Recurrence	Immunocompromised Patients	Healed Lesions
Wenzel et al., 2003	1	FOP	nd	48	Malignant transformation	1	0	0
Goodstein et al., 2012	1	SP	1	2	0	0	0	1
Beder et al., 2012	5	AC	1	2	0	0	5	5
Ural et al., 2014	1	VV	1	6	0	0	0	1
Gazal 2019	1	VV	1	4	0	0	0	1

Table 11. Follow-up studies.

Study	No of Patients	Type of Lesions	Treatment Length/No of Application	Follow-Up (months)	Side Effects	Recurrence	Immunocompromised Patients	Healed Lesions
Viraben et al., 1996	1	FEH	-	36	0	1	1	0
Falaki F et al., 2009	7	FEH	-	1–8	0	5	0	2
Liu et al., 2012	2	FEH	-	16	0	0	0	2

Table 12. Cold blade surgery.

Study	No of Patients	Type of Lesions	Treatment Length/No of Application	Follow-Up (months)	Side Effects	Recurrence	Immunocompromised Patients	Healed Lesions
Abouafia D 2001	1	AC	1	6	0	0	1	1
Dos Reis et al., 2009	1	SP	1	24	0	0	0	1
Jaju et al., 2009	1	SP	1	12	0	0	0	1
Puriene et al., 2011	3	FEH	1	6	0	0	0	3
Collette et al., 2011	1	FEH	1	12	Pain	1	1	0
Jaiswal et al., 2014	1	AC	1	9	0	0	0	1
Moroglu et al., 2014	1	GAC	1	6	0	0	0	1
Frigerio et al., 2015	205	SP	1	24	0	6	0	199
Nayak et al., 2016	1	SP	1	24	0	0	0	1
Sen r et al., 2018	4	AC	1	6	0	0	0	4
Orenouga et al., 2018	1	SP	1	24		1	0	0
Mattoo et al., 2018	1	VV	1	12	0	0	0	1
Sudhakar et al., 2019	1	AC	1	6	0	0	0	1
Hilal 2019	2	SP	1	12	0	0	0	2
Toledano et al., 2019	22	SP	1	15	0	2	0	20
TOT	246				1	10	2	236

### 3.2. Meta-Analysis Results

Of the 59 studies included in the initial systematic review, those related to trials that included pharmacological treatments were eliminated because of poor numbers of cases. Additionally, all studies that did not include excision with laser or cold-blade scalpel were eliminated. Therefore, only studies that included treatment of oral HPV-related lesions by excision using laser or scalpel were retained for meta-analysis purposes (Figure 2 and Table 13).

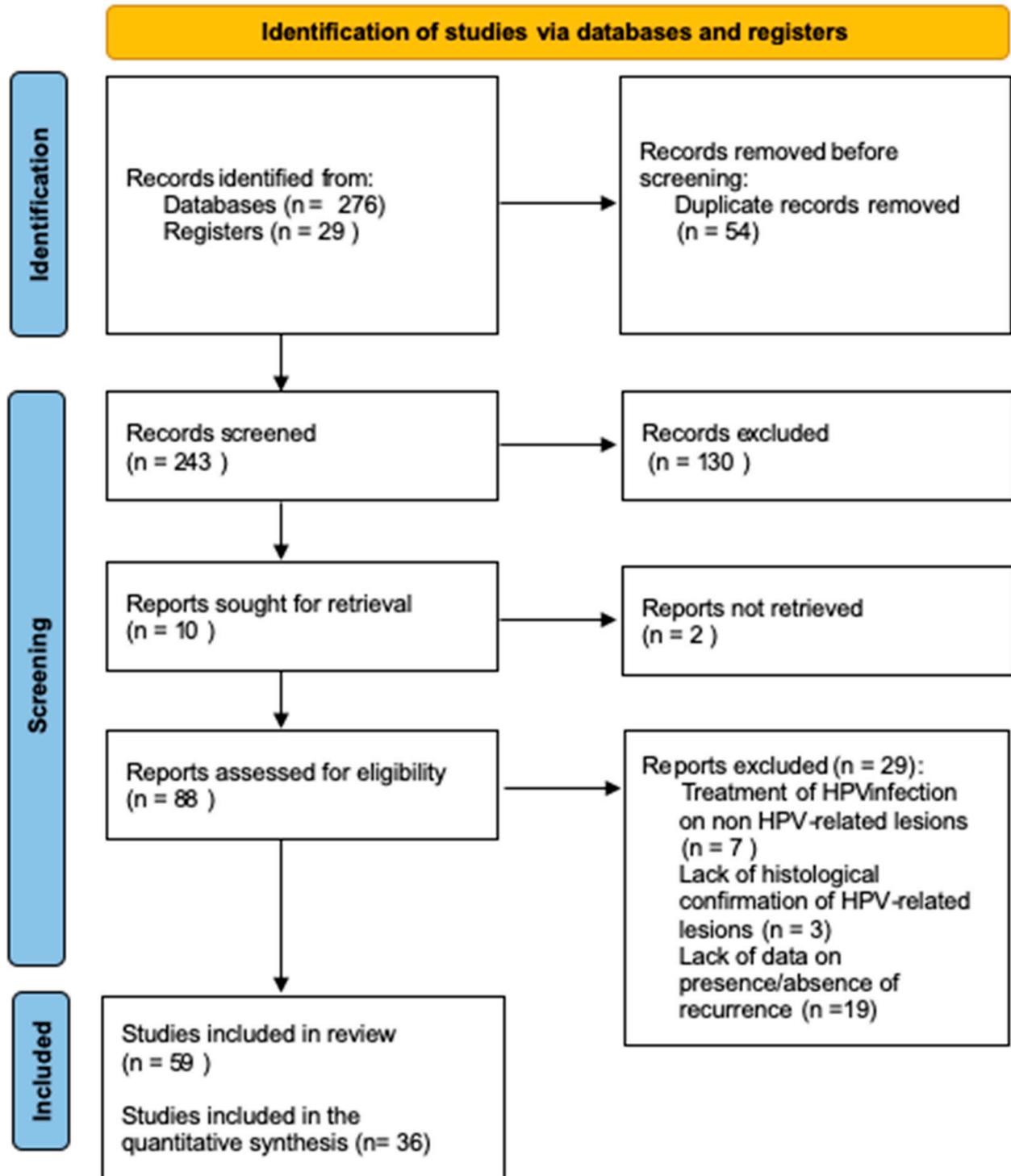


Figure 2. Flowchart meta-analysis.

Table 13. Laser excision studies.

Study	No of Patients	Type of Lesions	Treatment Length/ No of Application	Follow-Up (months)	Side Effects	Recurrence	Immunocompromised Patients	Healed Lesions
Luomanen et al., 1990	1	FEH	1	18	0	0	0	1
Luomanen M et al., 1992	2	AC	1	23	0	0	0	2
Luomanen M et al., 1992	11	SP	1	30	0	0	0	11
Squires et al., 1999	3	AC	2	4	0	3	0	0
White et al., 1999	5	SP	1	3	0	2	0	2
Bassioukas et al., 2000	1	FEH	1	20	0	0	0	1
Calista 2000	1	SP	1	12	0	1	1	0
Moerman et al., 2001	1	FEH	3	8	0	1	1	0
Casariago et al., 2002	1	AC	3	4	Malignant transformation	1	1	0
Akyol A et al., 2003 (w/interferon)	1	FEH	1	24	0	0	0	1
Wenzel 2003	1	SP	1	36	Malignant transformation	1	0	0
Maschke et al., 2004	1	FEH	1	18	0	1	0	0
Marangoni et al., 2005	3	AC	1	12	0	0	0	3
Boj J et al., 2007	1	AC	1	6	0	0	0	1
Collangelettes et al., 2009	1	Papillomatosis	6	36	0	0	0	1
Bombeccari et al., 2009	1	FEH	1	6	0	0	0	1
Pereira et al., 2010	1	SP	1	6	Worsening	1	1	0
Collette et al., 2011	1	FEH	1	12	Pain	1	1	0
Beder et al., 2012	5	AC	1	2	0	0	5	5
Misir 2013	1	SP	1	12	0	0	0	1
Galanakis et al., 2014	17	FEH	1	12	0	0	17	17

Table 13. Cont.

Study	No of Patients	Type of Lesions	Treatment Length/ No of Application	Follow-Up (months)	Side Effects	Recurrence	Immunocompromised Patients	Healed Lesions
Angiero 2015	129	SP	1	12	0	0	0	129
Angiero 2015	17	VV	1	12	0	0	0	17
Angiero 2015	13	SP	1	12	0	0	0	13
Angiero 2015	2	FEH	1	12	0	0	0	2
Akerzoul et al., 2018	1	SP	1	1	0	0	0	1
Toledano et al., 2019	12	SP	1	15	0	2	0	10
TOT	233				6	12	27	221

The results of the meta-analysis of the laser excision studies are summarized in the forest plot in Figure 3. The area of the square is proportional to the weight of the study. To evaluate the presence of heterogeneity, the Higgins  $I^2$  index equal to 16.61%, low heterogeneity, with a  $p$  value of 0.268, was used.

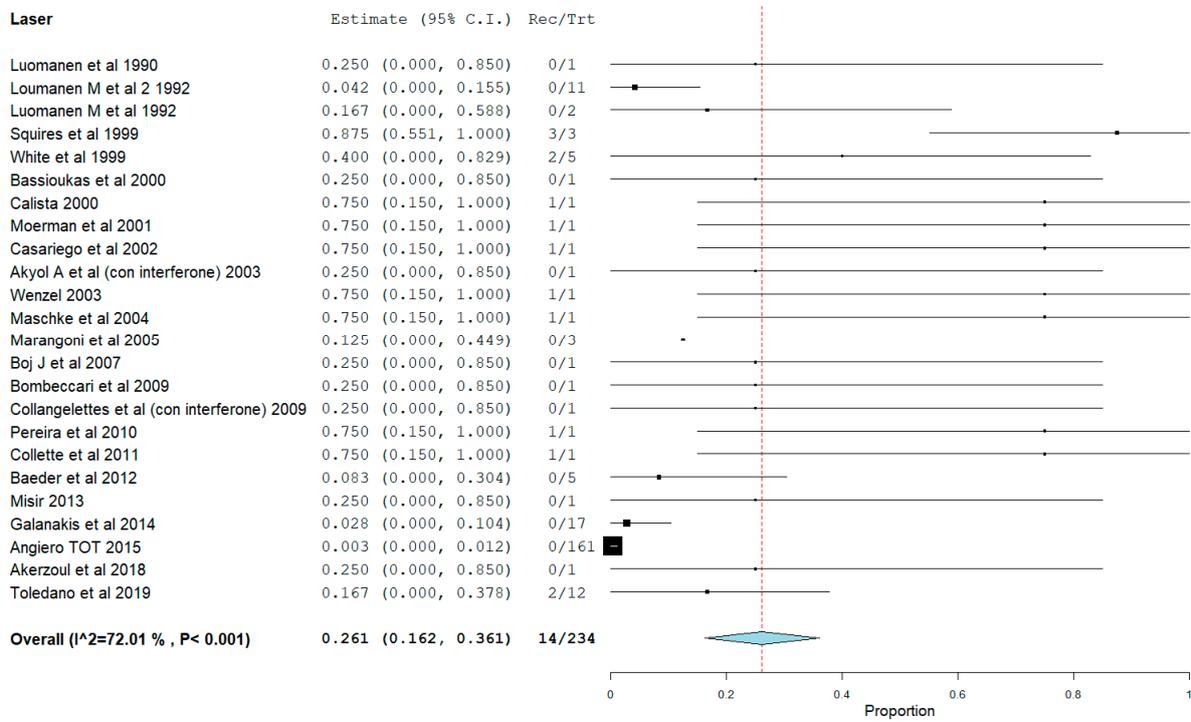


Figure 3. Forest-plot, laser excision studies.

When heterogeneity occurred, a random-effects model was used. The results show that the pooled proportion was 4.07% (95% CI 0.030–0.182).

The results of the meta-analysis of the cold-blade excision studies are summarized in the Forest plot in Figure 4. The area of the squares proportional to the weight of the study. To evaluate the presence of heterogeneity, a Higgins  $I^2$  index equal to 72.01%, high heterogeneity, with a  $p$  value of 0.001, was used.

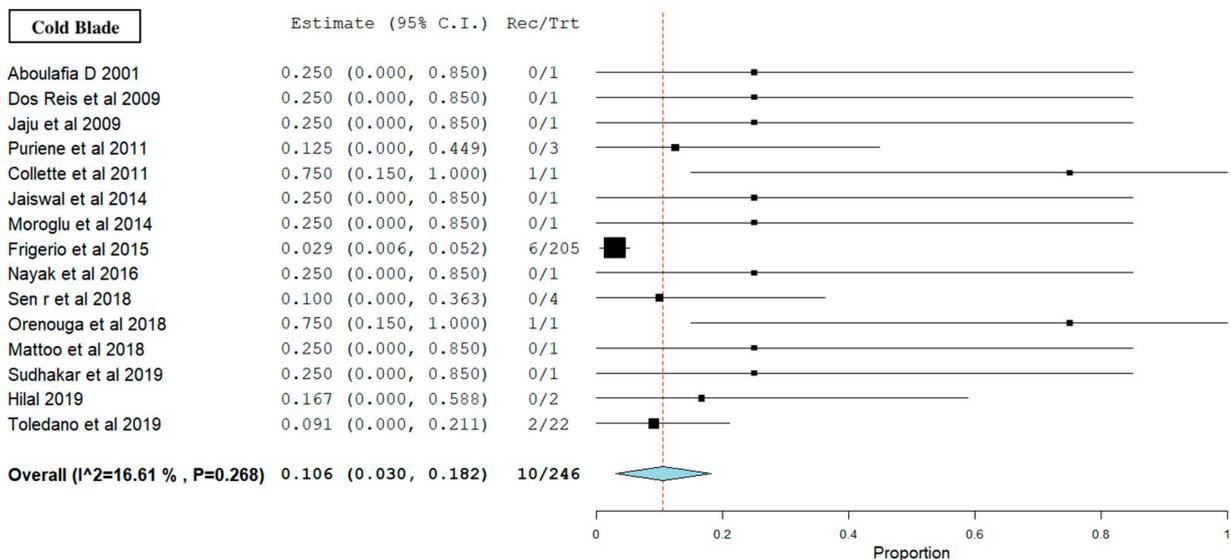


Figure 4. Forest-plot, cold-blade excision studies.

When heterogeneity occurred, a random-effects model was used. The results show that the pooled proportion is 5.98% (95% CI 0.162–0.361).

The examined studies document an excellent success of excisional treatments using laser or cold-blade techniques, and low recurrence rates were reported with both laser and cold-blade treatments, 5.98% and 4.07%, respectively. The only study that previously examined both treatments was the 2019 study by Toledano-Serrabona et al., which reported similar results. Their reported difference in recurrence rate was 10% for cold-blade treated lesions than 18% for laser-treated lesions. However, this difference was not statistically significant [13].

#### 4. Discussion

The objective of this research was to combine data from various studies conducted on the treatment of benign HPV-related lesions of the oral cavity, thereby generating a single conclusive piece of data on the most effective treatment for the management of these lesions. Oral benign HPV-related lesions are relatively common. There are many treatment strategies proposed in the literature. However, a definitive and validated standard therapy has not yet been defined to achieve a low recurrence rate and low viral load.

Regarding the current systematic review of the scientific literature of pharmacological and non-pharmacological treatment of oral HPV-related lesions, some considerations should be made. Due to this analysis's inclusion and exclusion criteria, many of the included studies had small sample sizes, short duration of treatments, insufficient follow-up, and inhomogeneity of the treatment outcomes. Additionally, several new targeted treatments are still under investigation, with no RCTs or case-control studies currently available. Therefore, available data on the effectiveness of these new treatments is lacking.

Research is moving toward more targeted therapies, especially for lesions that have appeared in immunocompromised patients undergoing highly active antiretroviral therapy (HAART), such as imiquimod [14–16] and cidofovir, [17–20]. For these, RCTs and case-control studies with large patient sample sizes and longer follow-up periods, as well as standardization of treatment duration and modalities, are needed. Additional HPV-related drug treatments, such as bleomycin, imidazoquinoline, and trichloroacetic acid, do not have application in the oral cavity and scientists appear to have no interest in experimenting with their application [21–23]. Furthermore, additional study is needed for applying interferon for long-term prevention of oral HPV recurrence.

What can safely be inferred from this systematic review of the literature is that lesion excision is the first line of therapy to be adopted, regardless of the instrument used. In cases of multiple relapses, especially in immunocompromised or HAART patients, topical drug therapies, such as imiquimod and cidofovir, can be applied for several weeks with a high probability of success. The management of these lesions is important, both for limiting the spread of the virus and preventing the appearance of malignant lesions within the oral cavity. Therefore, new, randomized, case-controlled studies with large patient samples, adequate treatment duration, long-term follow-up, study of recurrence rate, and uniform result detection criteria are necessary to define a standard treatment of HPV-related oral cavity lesions.

The most commonly recommended treatment of oral HPV-related lesions is surgical excision with a cold-blade scalpel. This instrument allows the complete excision of the lesion, therefore, lowering the viral load. It also allows an achievement of tissue fragment, characterized by defined peri-incisional margins, without any other structural alterations. However, this surgical intervention involves anesthesia, sutures, and bleeding. Laser excision can be performed using various wavelengths, thereby minimizing interaction with soft tissues while allowing for the collection of tissue samples. Biopsies performed with lasers have some advantages compared to those performed with a scalpel. Generally, these operations do not require suturing, and the healing at the collection site is faster in the initial stages [24].

Of the studies that we selected for analysis, 22 involved excision by laser, 13 involved excisions by cold blade, and one compared both techniques. The recurrence rate of laser-treated lesions is 5.98%, while the recurrence rate of cold-blade excision is 4.07%. The most extensive studies on cold-blade excision are the 2015 study by Frigerio et al. and the 2019 study by Toledano-Sarrabona et al. [13,25]. Frigerio et al. presented a retrospective study of 205 cases of SP in immunocompromised patients, with only 6 relapses occurring in a 24 month follow-up period. Toledano-Sarrabona et al. published a case-controlled study of immunocompromised patients for which surgical excisions were performed by cold blade (22 patients with SP) and CO<sub>2</sub> laser (12 patients with SP). After 15 months, two recurrences occurred in both groups. Toledano-Sarrabona et al. stated that the treatment of choice for HPV-related lesions of the oral cavity is surgical excision, primarily with traditional surgery, and secondarily with any other method, among which laser is an excellent alternative.

In Calista's reports in 2000, Moerman et al. in 2001, and Casariego et al. in 2002, three different lesions were treated in immunocompromised patients [17,26,27]. Relapses occurred in all three studies, and Casariego reported the malignant transformation of the lesion. In 2003, Wenzel et al. also reported the malignant transformation of an SP in an immunocompromised patient after 36 months [14]. However, in studies using larger sample size, different outcomes were reported. In 1992, Luomanen et al. did not report recurrence in 13 immunocompromised patients treated with laser excision. In 2012, Baeder did not report recurrence after treatment of five immunocompromised patients. In 2015, Angiero et al. reported the absence of complications and only one recurrence (with the lesion disappearing after a second application) in treating 174 lesions in 170 immunocompromised patients. In the larger sample size studies, the authors reported excellent patient tolerance and a short duration of surgical sessions [28–30]. Interestingly, a split-mouth study conducted by Beder et al. in 2012 of 10 lesions in 5 patients treated with both CO<sub>2</sub> lasers and electrocautery reported that the viral load three weeks after surgery was significantly lower or absent in laser-treated areas [29]. The viral load may influence the recurrence of lesions and infections, from which potentially malignant lesions could arise. Furthermore, it would be appropriate to assess the viral load in immunocompromised patients and in those lesions that tend to recur, perhaps due to an ineffective immune response.

The therapeutic approach to benign HPV neoformations is to completely remove the lesions. However, other factors should be considered from the patient's pharmacological and systemic history to better identify the causes of infection. Factors, such as the need to attenuate any risk behaviors; repeated mechanical trauma; irritative stimuli that may result from sharp edges of fillings, teeth, rough or abrasive surfaces, and incongruous prostheses should be identified to help the patient adopt an accurate oral hygiene program to reduce the potential risk of malignant transformation. Particular attention to gum disease and avoiding risky behaviors, such as cigarette smoking and alcohol consumption, should be advised.

We subjected numerous therapeutic strategies, adopted by clinicians and reported by scholars in the scientific literature, to a systematic review and meta-analysis. The limitations of the studies analyzed were primarily small samples, short duration of treatments, absent or insufficient follow-up, absence of overlapping and reliable standard verification questionnaires, and inhomogeneity in treatment outcomes.

The limit of this study is clearly the presence of small sample papers and case reports, but the authors thought it could be interesting to include different therapeutic strategies, such as targeted therapies.

Research is moving toward more targeted therapies, especially for lesions that have appeared in immunocompromised patients undergoing highly active antiretroviral therapy (HAART), such as imiquimod and cidofovir. For these, RCTs and case-controlled studies with large patient sample sizes and longer follow-up periods and standardization of treatment duration and modalities are needed.

Lesion excision is the first line of therapy to be adopted, regardless of the instrument used. In cases of multiple relapses, especially in immunocompromised or HAART patients, topical drug therapies, such as imiquimod and cidofovir, can be applied for several weeks with a high probability of success. The management of these lesions is important, both for limiting the spread of the virus and preventing the appearance of malignant lesions within the oral cavity. Therefore, new, randomized, case-controlled studies with large patient samples, adequate treatment duration, long-term follow-up, study of recurrence rate, and uniform result detection criteria are necessary to define a standard treatment of HPV-related oral cavity lesions. Furthermore, the benefit–risk profile and costs are important when choosing between the various options.

## 5. Conclusions

Despite many treatment options available, a systematic review of the scientific literature has shown that defining a standard, comprehensive, and effective treatment for the excision HPV-related infection and lesions is still a goal for clinicians today.

It can be concluded from the meta-analysis of the available and relevant scientific literature that both excisions by cold-blade scalpel and excision by laser can be considered effective treatment options. Many treatment strategies have been proposed in the literature. However, a definitive and validated standard therapy has not been defined.

From this meta-analysis, it can also be concluded that more in-depth studies with a greater number of samples are necessary. It would also be appropriate to carry out case–control studies or RCTs to assess the best treatment to eradicate HPV-related lesions.

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