

Safety of Different Surgical Modalities for Recurrent Respiratory Papillomatosis Resection: A Systematic Review and Meta-Analysis

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Abstract

Abstract Background: Currently, the most common surgical modalities used for recurrent respiratory papillomatosis resection are microdebrider, CO2 laser, and KTP laser. However, complication rates vary among different surgical modalities and have been controversial in different studies. **Objective of review:** This study systematically reviews the available studies which reported intraoperative and postoperative complications, aiming to compare the safety of microdebrider, CO2 laser, and KTP laser. **Type of review:** Meta-analysis. **Search strategy:** Seven electronic databases (PubMed/MEDLINE, EMBASE[Ovid], Scopus, Cochrane Library, and Web of Science) were searched from inception through April 28th, 2022. Randomized controlled, prospective or retrospective observational studies that recorded the complications of three different surgical modalities for recurrent respiratory papillomatosis resection were included in the meta-analysis. **Evaluation method:** Outcomes of interest were intraoperative and postoperative complications, and complication rate was calculated to evaluate the safety of surgical methods. **Results:** Twenty different studies were included in quantitative synthesis. Only one study compared outcomes of those three kinds of treatment modalities simultaneously, two studies compared microdebrider and CO2 laser, and the remaining studies focused on only one of three treatments. The weighted average complication rate for microdebrider was 0.03 (95% confidence interval [CI] 0.00-0.21), n = 6, for CO2 laser treatment was 0.16 (95% confidence interval [CI] 0.09-0.25), n = 14, and for KTP laser treatment was 0.04 (95% CI 0.00-0.14), n = 4. **Conclusion:** The limited evidence demonstrated that CO2 lasers in the surgical treatment of RRP may lead to more surgical complications, and microdebrider and KTP lasers may be safer. However, the heterogeneous data limits any strong comparison of outcomes of different treatment of laryngeal papillomas. Future randomised controlled trials that directly compare the safety of different surgical modalities are needed.

(The ethical institution name and any affiliation or author identifying information were blinded with the following statement “Blinded for review”).

Key points:

- We compare the safety of various surgical modalities (microdebrider, CO2 laser, and KTP laser) for recurrent respiratory papillomatosis resection using the intraoperative and postoperative complication rate.
- As far as we know, this is the first meta-analysis to safety of various surgical modalities.
- Twenty different studies were included in quantitative synthesis.
- The weighted average complication rate for microdebrider was 0.03, for CO2 laser treatment was 0.16, and for KTP laser treatment was 0.04.
- The limited evidence demonstrated that CO2 lasers in the surgical treatment of RRP may lead to more surgical complications, and microdebrider and KTP lasers may be safer.

Introduction

Recurrent respiratory papillomatosis(RRP) and its potential malignant degeneration have a clinical history of about 100 years, and we have gradually recognized that the etiology of RRP is related to HPV virus infection^[1]. Epidemiological investigations have found three peaks in the age distribution of onset: 7, 35, and 64 years^[2]. However, RRP has usually been subdivided into juvenile-onset RRP and adult-onset RRP, with the variable age of demarcation used in different studies^[3-6]. The juvenile-onset RRP is generally more aggressive than the adult-onset RRP, with a high recurrence rate and a stronger propensity to spread^[7]. RRP is characterized by recurrent papillomatous lesions that occur primarily in the larynx but occasionally involve other parts of the aerodigestive tract^[8].

At present, there is still no cure for RRP^[9]. The main treatment for Recurrent respiratory papillomatosis is still repetitive surgery, which aims to maintain airway patency without effectively preventing recurrence^{[10][11]}. Surgical treatment with traditional cold instruments, microdebriders, 10,600nm carbon dioxide(CO₂) laser, 532-nm pulsed potassium-titanyl-phosphate(KTP) laser is usually preferred^[12]. But there is no standard guidelines for the choice of surgical technique. Factors that can influence decision-making are the effectiveness and safety of surgical techniques, patient factors, and surgeon preferences^[13].

As for the efficacy, according to the outcomes of studies, different surgeries appear to be comparable in removing lesions and preventing recurrence. Papaioannou^[14] reported that conventional cold instrument and laser surgery both had no effect on postoperative recurrence time or the number of surgeries per year, regardless of whether the JORRP and AORRP populations were analyzed separately. Hock^[15] analyzed the efficacy of RRP treated with three surgical modalities(KTP, CO₂, and microdebrider) in a large retrospective study, and found no significant difference in mean intervals among the three treatment groups when analyzing people with AO-RRP. Preuss^[16] also suggests that there is no correlation between different surgical modalities and the recurrence rate of RRP. In other words, these commonly used surgical modalities seem to have the equally effective on RRP.

Therefore, safety should be taken into account before making a decision on the choice of surgical method. The common complications of surgery were scar tissue and web formation in the anterior commissure of the larynx, and Laryngeal stenosis et al. Due to the high recurrence rate of RRP, repeated surgery is required to reduce tumors, and delayed complications during or after surgery will affect the quality of breathing and voice, which in turn will affect the quality of life^[17].

However, complication rates vary among different surgical modalities and have been controversial in different studies. Preuss^[18] reported the overall incidence of soft tissue complications after CO₂ laser surgery is significantly lower and the rate of tracheostomy is lower compared to laryngeal microsurgery with cold instruments. On the contrary, Hermann^[19] found a statistical trend towards an association between the use of laser and the presence of sequelae lesions. Similarly, Rasmussende^[20] argue that lasers are not optimal choice, in contrast to microdebriders that are simple to operate and result in less scar tissue. Scatolini^[21] reported that a higher rate of sequelae was found in patients in whom laser was used together with microlaryngeal instruments. However, unlike the results of the studies mentioned above, Papaioannou supports the view that there is no significant difference in complications after conventional cold surgery and laser surgery^[3]. As can be seen from the data on the available instruments above, the rate of complications reported for each is variable. On the one hand, cold steel instruments (like microdebrider) avoid heat transfer to the surrounding tissue and thereby the possibility of scar retraction. On the other hand, hot methods (laser) allow for better hemostasis and vaporization of the flat superficial lesions while preserving normal tissue. Therefore, this study will conduct a literature review to compare the types and incidence of surgical complications between different surgical modalities, and provide evidence for making decisions on surgical modality.

Methods

A systematic literature review and meta-analysis was performed in accordance with the guideline Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement^[22]. The review protocol has been registered in the International Prospective Register of Systematic Review (PROSPERO; registration No. CRD42022328001).

Systematic Literature Search

Five electronic databases (PubMed/MEDLINE, EMBASE[Ovid], Scopus, Cochrane Library, and Web of Science) were searched from inception through April 28th, 2022. Literatures searched from the Chinese Clinical Trials Registry and ClinicalTrials.gov were classified as literature from other sources. A Population, Intervention, Comparison, Outcome, and Study (PICOS) design strategy was adopted. The target population of the study was patients with recurrent respiratory papillomatosis. The intervention was surgery with microdebrider or CO2 laser or KTP laser. The effectiveness of the procedural setting was based on these primary outcomes of interest: intraoperative and postoperative complications, and complication rate. A comprehensive search strategy using PubMed's MeSH and EMBASE's Emtree subject headings and keywords consisting of three main concepts was developed: recurrent respiratory papillomatosis, treatment modality or surgical technique applied or instruments used in the surgical procedures (Appendix, Table 1). The search was limited to humans only. The strategy was designed for ease in replication across databases, and it was adapted as needed for additional searches across the table of contents searches and unique features in Ovid databases.

Study Selection and Quality Assessment

A total of 801 studies identified from the literature search were exported into EndNote software, along with 5 additional records identified through other sources. Duplicates were removed automatically and manually, leaving 351 studies to screen. The selection of the studies was performed independently by two authors (Liu and Wang.). Publications were evaluated dependent on predefined inclusion and exclusion criteria.

Inclusion criteria were as follows: (1) Randomized controlled, prospective or retrospective observational studies; (2) Patients were diagnosed with recurrent respiratory papillomas by histological pathological examination; (3) Patients agreed to undergo surgical treatment with microdebrider or CO2 laser or KTP laser; (4) Outcomes of interest were intraoperative and postoperative complications, and complication rates.

The following exclusion criteria were adopted: (1) Case reports, editorials, reviews and short communications; (2) Adjuvant therapies simultaneously; (3) Sample size[?]5; (4) The target outcomes is not available. Data extraction from each included study was performed on the basis of study characteristics and predefined outcome variables. The following variables were retrieved from each study: year of publication, study design, surgery modality (microdebrider or CO2 laser or KTP laser), number of surgeries, intraoperative and postoperative complications, complication rates. Discrepancies were resolved by discussion. The methodological quality assessment was performed following the Newcastle Ottawa Scale^[23].

Statistical Methods and Synthesis of Results

A meta-analysis of aggregate data was performed to generate a pooled estimate using outcomes of individual studies reported in the published literature. The data were analyzed using STATA software. Dichotomous outcomes from each study were expressed as percentage of complications, with a 95% confidence interval (CI). Heterogeneity between studies was reported with the I^2 statistic. A "hybrid" Mantel-Haenszel random-effects model with inverse-variance weighting was used in meta-analyses if any heterogeneity was detected, whereas a fixed effect model was used if no heterogeneity was identified. A value of $p < 0.05$ was considered statistically significant.

Results

Study Characteristics

The systematic review resulted in 806 articles with 351 screened after duplicates were removed (Figure 1). Following the criteria described above, a total of 305 studies were excluded. Forty-six full-text articles were assessed. Among them, 26 were excluded as they conducted adjuvant therapy studies and did not provide relevant outcomes. Twenty different studies fulfilled the predefined inclusion criteria. The main details of the included articles are shown in Table 1.

No randomized control trials were available to be included in this review. Two studies met the criteria as good quality studies. The remaining 18 studies were of poor quality(Table 2.).

Synthesis of Results

Of the 20 studies, only one directly compared three kinds of treatments of RRP,and two studies compared microdebrider to CO2 laser treatment of RRP, analyzing the complications tape and complication rate between the two treatment settings. The remaining 17 studies analyzed the outcome measures in one of the three treatment modalities only. In the study which compared three kinds of treatments, patients in the KTP laser group had been treated in the hospital multiple times prior to inclusion in the study, and calculating postoperative complication rate data on this basis was unreliable and therefore excluded from the KTP group study. Overall, 14 studies were CO2 laser treatment, while 6 studies were microdebrider treatment, and 5 studies assessed KTP laser. There are 161 patients with RRP were treated by microdebrider, a total of 605 patients with RRP were treated by CO2 laser, while a total of 106 were treated by KTP laser.

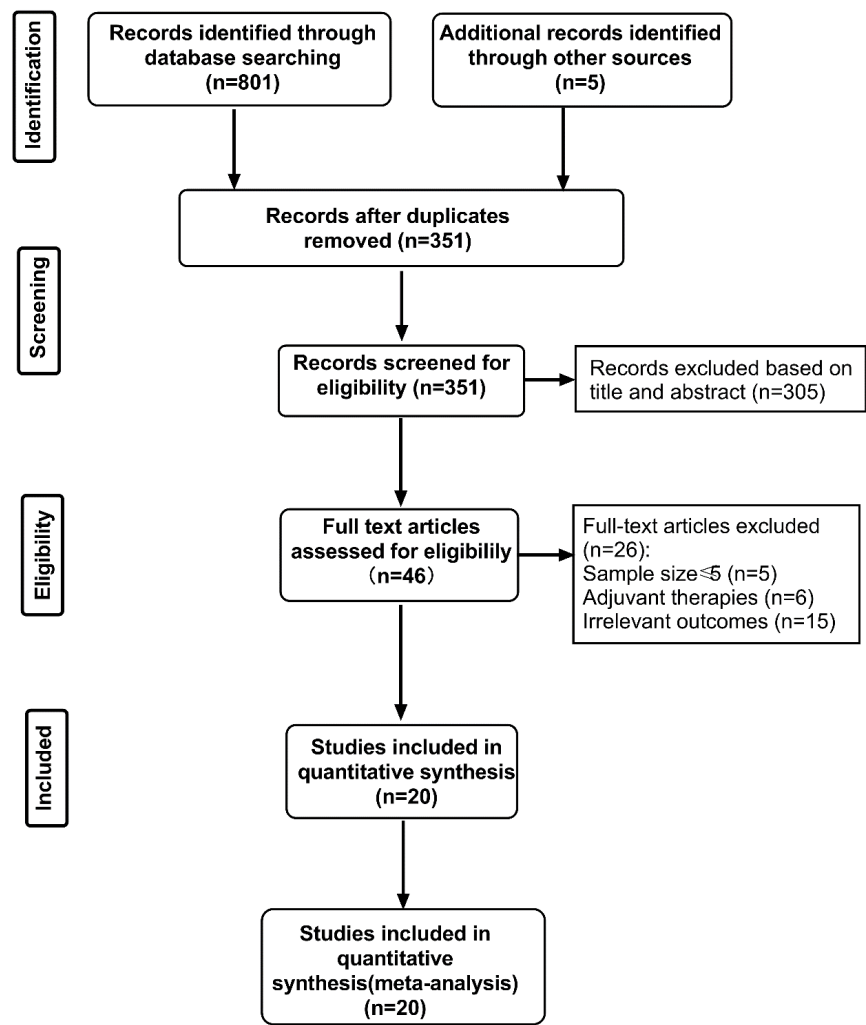


Figure 1. PRISMA diagram.

Table 1. Available Outcome Measures from the Included Studies on Different Treatment Modalities used in

NO
NO.1

NO.2
NO.3
NO.4

NO.5

NO.6
NO.7
NO.8
NO.9
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NO.17
NO.18
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NO.20

Abbreviations: CO2, carbon dioxide; KTP, potassium-titanyl-phosphate; AoRRP, adult-onset recurrent resp

Table 3. Complications of on CO2 laser, microdebrider and KTP laser used in the Surgical Procedures for RRP.

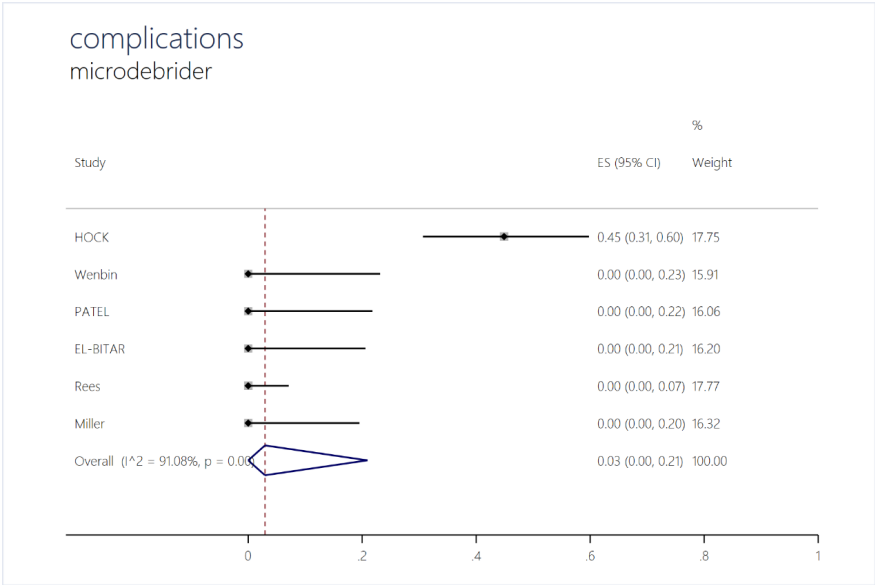
Study, Year	Treatment Modality	Sample Size	Mean Number of Procedures	Complication rate	Delayed complications(n)	Intraoperative complications(n)
HOCK. 2022 ^[15] .	CO2 laser	21	15.5	38.10%	2 vocal scar	
					6 anterior commissure web	
PATEL.2003 ^[5]	CO2 laser	17	7.47	0.00%		
EL-BITAR. 2002 ^[25]	CO2 laser	16	1.44	31.25%	1 vocal scar	1 Glottic edema
					3 anterior commissure web	
Hao-Chun.2017 ^[27]	CO2 laser	6	1.67	0.00%		
Papaspyrou. 2016 ^[9] .	CO2 laser	37	1.22	8.11%	3 anterior commissure web	
Ossoff.1991 ^[30]	CO2 laser	14	4.43	21.43%	2 vocal scar	

						1 anterior commissure web	
Ossoff.1991 ^[30]	CO2 laser	8	5.38	0.00%			
Araki.2019 ^[31]	CO2 laser	7	1.71	0.00%			
Papaioannou.2018 ^[14]	CO2 laser	44	2.16	15.91%		1 vocal scar 4 anterior commissure web 2 Granulation polyp 7 Glottic stenosis	
Zhao.2007 ^[32]	CO2 laser	30	NA	23.33%		2 vocal scar	2 Glottic edema
Preuss.2007 ^[16]	CO2 laser	64	2.14	12.50%		4 anterior commissure web 2 vocal scar 61 anterior commissure web 16 Glottic stenosis	
Dedo.2001 ^[35]	CO2 laser	227	NA	34.80%		23 Glottic stenosis	1 Burning in the tracheobronchial
Cui.2001 ^[36]	CO2 laser	60	5.58	40.00%		6 Glottic stenosis 5 vocal scar	
Shah.1994 ^[37]	CO2 laser	54	3.98	11.11%		17 anterior commissure web	
HOCK. 2022 ^[15] .	microdebrider	49	17.3	44.90%			
Wenbin.2006 ^[6]	microdebrider	14	4.71	0.00%			
PATEL.2003 ^[5]	microdebrider	15	3.33	0.00%			
EL-BITAR. 2002 ^[25]	microdebrider	16	3.13	0.00%			
Miller.2019 ^[26]	microdebrider	17	13.53	0.00%			
Rees.2005 ^[34]	microdebrider	50	NA	0.00%			
HUNG. 2021 ^[24]	KTP laser	16	4.94	18.75%		3 anterior commissure web 1 vocal scar	
Del Signore.2016 ^[28]	KTP laser	34	NA	8.82%			
Kuet.2013 ^[29]	KTP laser	19	NA	0.00%			
Burns.2007 ^[33]	KTP laser	37	1.49	0.00%			

Abbreviations: CO2, carbon dioxide; KTP, potassium-titanyl-phosphate; AoRRP, adult-onset

recurrent respiratory papillomatosis (RRP);JoRRP, juvenile-onset RRP; NA, not available.

The weighted complication rate for microdebrider treatment of RRP was 0.03 (95% CI 0.00-0.21, n = 6, I2 = 91.08%, P <0.1). The weighted complication rate for CO2 laser treatment was 0.16 (95% CI 0.09-0.25, n =14, I2= 79.19%, p <0.1). The weighted complication rate for KTP laser treatment was 0.04 (95% CI 0.00-0.14, n =4, I2=67.76%, p=0.03). Of the included literature, only three studies reported intraoperative complications, all occurring during surgery using CO2 lasers. Complications in these procedures included vocal cord edema in 3 patients and intratracheal burning in one case. As for postoperative delayed complications, included cases, reported anterior commissure web, vocal scar, glottic stenosis, granulation polyp and atrophy. Among the postoperative complications reported, the largest number of cases was anterior commissure web, regardless of the surgical method used. Specific information on complication types and complication rates is presented in Figure 2.and Table 3.



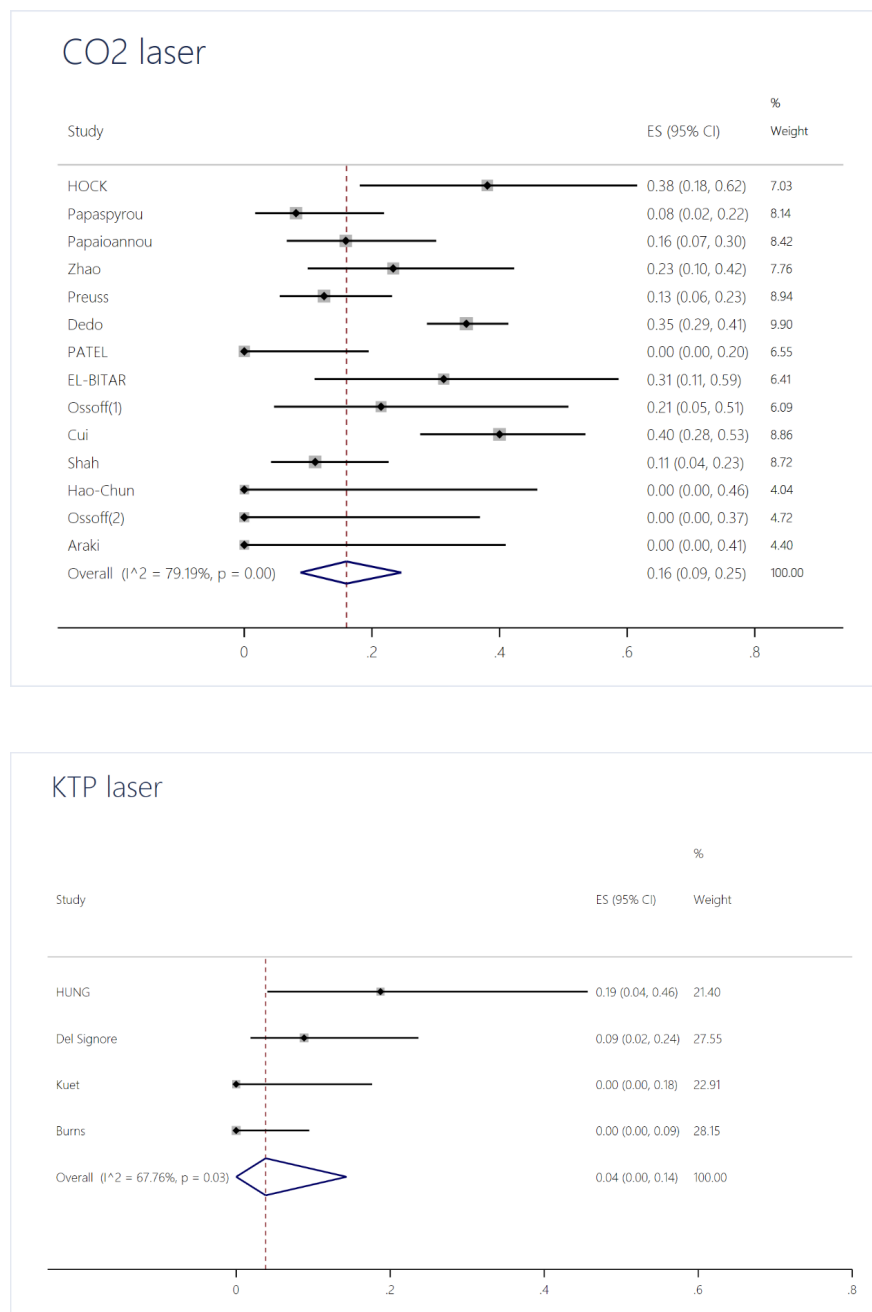


Figure.2. Weighted complication rates for three treatment modalities undertaken to treat RRP, with straight lines depicting 95% confidence intervals for individual studies and diamond depicting 95% confidence intervals for the weigh.

Discussion

This systematic review and meta-analysis is the first to summarize the existing literature on complication rate of different Treatment Modalities of RRP. Heterogeneity precluded a direct comparison between studies within the same surgical techniques.

Benboujja^[38] investigated the depth of RRP using optical coherence tomography and found that the tumor was limited to above the basement membrane. In other words, removing the upper layer of the lesion above the surface is sufficient to remove RRP. Such microsurgery is essential to preserve the layered structure of the vocal cords, avoid fibrosis or scarring, and restore normal vocal function.

The rate of complications reported for each is variable, the reason can be explained by the working mechanism of surgical instrument itself. On the one hand, cold steel instruments (like microdebrider) avoid heat transfer to the surrounding tissue and thereby the possibility of scar retraction. On the other hand, hot methods (laser) allow for better hemostasis and vaporization of the flat superficial lesions while preserving normal tissue.

Due to the blood-rich nature of RRP, KTP laser, which belongs to the angiolytic laser, seems has great advantages in RRP resection^[15]. Unlike the CO₂ laser, the angiolytic laser uses the peak in the absorption spectrum of the oxygen hemoglobin rather than water, which helps to selectively ablate the vascularized lesion without excessive thermal damage^[39]. In other words, the KTP laser can better preserve the surrounding tissue and hemostasis control^[40]. Burns^[41] also argues that diseases in the anterior commissure of glottis can be treated with minimal risk of scarring or adhesions, whether using KTP lasers alone or as a complement to other surgical modalities, with minimal preservation of the potential superficial intrinsic layer.

The wavelength of the CO₂ laser (10 600 nm) is absorbed by water, allowing the lesion to evaporate with a high percentage of intracellular water. CO₂ laser was applied to the treatment of RRP as early as the early 1970s, which replaced the traditional micro-cold device, and gradually become a recognized treatment method for laryngeal diseases due to the better hemostasis effect, lesion clearance and other characteristics^[37, 42, 43]. In 2015, Muroso published a questionnaire to the department of otolaryngology at all 80 Chuo University hospitals in Japan with regard to the use of surgical instruments. A trend was observed towards lasers (50 hospitals) rather than micro devices (16 hospitals) or cold instruments (20 hospitals). Among the 50 hospitals that regularly undergo laser surgery, the most commonly used carbon dioxide (CO₂) laser is followed by titanium-based potassium phosphate laser^[44]. In 2016, a Germany multicenter cohort study reported that CO₂ laser remained the most common surgical modality used alone or in combination with other treatment modalities^[9]. At present, CO₂ laser fiber is available, and outpatient-based CO₂ laser surgery provides great benefits for RRP patients who need multiple surgeries to control the disease, the time and cost of treatment are greatly reduced, and the need for general anesthesia is reduced^[27]. However, CO₂ laser operation is time-consuming, expensive, and potentially dangerous. If the intraoperative procedure is improper may lead to serious complications, such as airway combustion, normal tissue burns and medical staff damaged, which limit its development.

Microdebrider is a dynamic rotational dissection device with suction assist, was initially used in plastic surgery and rhinology. In 1999, Myer first reported the use of microdebrider in the larynx for the treatment of recurrent respiratory tract tumors^[45]. Under the endoscopic auxiliary support laryngoscopy, microdebrider can easily reach the throat, trachea and other parts, with its continuous suction cutting effect. Therefore, it can easily push the mass away from the base and suck up, remove the mass accurately, and has gradually become the preferred treatment for handling JO-RRP in recent years^[18, 32]. Wenbin^[6] retrospectively analyzed the case series of RRP, microdebrider can quickly remove tumors, with few complications and satisfactory postoperative short-term sound quality. El-Bitar^[25] conducted a retrospective study of seventy-three operations, the microdebrider was proved to be less time-consuming than the carbon dioxide laser when used in patients with juvenile-onset recurrent respiratory papillomatosis, whit soft tissue complications were nonexistent. Pasquale^[46] was the first to compare microdebrider with CO₂ laser, there was no significant difference in postoperative pain between the two groups, but this was a short-term study that provided initial data in a relatively small patient population. Similarly, in a retrospective study collaborated by Patel^[5], it was noted that since the CO₂ laser switched to microdebrider, the operation time was significantly shortened without affecting the accuracy of the operation, saving surgical costs, avoiding the risk of airway burns that may occur during laser surgery and the possibility of vaporization of virus particles. Rees^[34] found no statistically significant difference in postoperative pain scores between the microdebriders or CO₂ laser treatment

groups. Unlike in the case of lasers, microdebrider has some drawbacks, where hemostasis is an issue with cold techniques, but due to the suction of the connection, the surgical field could remain clear most of the time^[34]. Rare complications of microdebrider include mediastinal emphysema and retroperitoneal air^[47] and subglottic injuries^[48]. Granulomas that occur after vocal cord polyps have also been reported^[49]. Because of these advantages above, microdebrider may replace CO2 lasers, the preferred method of airway clearance in these patients, and become the surgical modality of choice for RRP^[50]. In addition, since microdebriders are more effective at removing bulky diseases than lasers alone, microdebriders may be a more cost-effective tool for removing tumors^[15].

For bulky exogenous tract tumors, several surgical methods are often combined to learn from each other's strengths and improve surgical efficiency. But there is currently insufficient data to prove whether combined surgery can reduce the occurrence of surgical complications. Huang^[24] notes that the surgeons prefer to use microdebrider for bulky tumors and use KTP laser peeling technique for near-normal structure. This mixing mode can help surgeons shorten surgery time and make it easier to control bleeding, and it may avoid injury to the stratified structure of the vocal cords.

Improvements in surgical modalities may reduce the complications associated with surgical treatment of RRP. The recent introduction of blue laser to office-based laryngology presents potential advantages, which includes a desirable combination of cutting and photoangiolytic qualities and a lightweight, shock-resistant design. Miller^[51] present a case series (thirty-six cases) and overview of office 445 nm blue laser transnasal flexible laser surgery, which support conclusion that blue laser is safe and effective in the treatment of RRP and a range of benign laryngeal lesions. Future research should compare the efficacy and safety of blue laser with potassium titanyl phosphate laser in office-based treatment of these conditions. In addition to improving surgical instruments, the development of imaging technology may also help. The use of OCT imaging for simultaneous monitoring alongside laser treatment may provide the best, patient-specific treatment to improve postoperative prognosis for patients with RRP in the future^[38].

There are several limitations to this systematic review. First, due to the lack of adequate literature, this study did not conduct a meta-analysis of other influencing factors of complications. For example, the location of the lesion, surgeon surgical techniques and the number of surgeries the patient undergoes may also be the influencing factors of complications. Huang^[24] reported three patients with RRP developed anterior glottis after continuous KTP laser surgery in his retrospective case analysis, but all three patients received RRP treatment near the front at the same time. They then performed a staging procedure for papillomas of the bilateral vocal cords, reducing the incidence of anterior commissure web. As mentioned earlier, the discovery of Benboujja^[38] proves that the upper layer of the lesion above the surface is sufficient to remove RRP, except which requires surgeons to have superb surgical skills in order to precisely control the depth of resection. Finally, a higher number of surgeries may be associated with a higher rate of surgical complications. PAPAIOANNOU^[14] believes that patients who undergo more surgeries are more likely to develop complications than patients with fewer surgeries. Scatolini^[21] conducted a retrospective analysis of 74 patients with adolescent RRP and found that patients who had undergone more than 10 surgeries or who had previously had a history of surgery in an external institution had a higher frequency of throat scarring. However, El-Bitar^[25] argued that the incidence of postoperative complications of RRP was related to the surgical technique used, not to the number of surgeries or the interval between surgeries. Due to the fact that most of the existing studies are retrospective studies, made it difficult to control these variables.

Studies in the future would require detailed reporting of disease burden, so that patients could be risk stratified by group. Pre- and post-op Derkay scores or other consistent quantitative metrics are necessary, to accurately stage the bulk and severity of disease to allow for more standardized reporting of disease. Complications in these groups could then be compared to help determine the security of instruments used in the surgical procedures, so that we can provide data support for patients to make the best choice.

Conclusion

This systematic review summarizes the complications and complication rate of RRP patients treated by

surgery using three kinds of surgical modalities as an independent way. Only one study compared outcomes of those three kinds of surgical modalities simultaneously, two studies compared microdebrider and CO2 laser, and the remaining studies focused on only one of three treatments. While definitive conclusions cannot be drawn from the available literature, it is possible that CO2 lasers in the surgical treatment of RRP may lead to more surgical complications, and microdebrider and KTP lasers may be safer. However, the heterogeneous data limits any strong comparison of outcomes of different treatment of laryngeal papillomas is needed. Future Randomised controlled trials that directly compare the safety of different surgical modalities are needed.

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Table 2. The methodological quality assessment outcome performed following the Newcastle Ottawa Scale.. available at <https://authorea.com/users/484739/articles/570381-safety-of-different-surgical-modalities-for-recurrent-respiratory-papillomatosis-resection-a-systematic-review-and-meta-analysis>