

Comparative Effectiveness and Safety of Systemic Versus Intralesional Bevacizumab in the Management of Recurrent Respiratory Papillomatosis

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ABSTRACT:

Systemic and intralesional administration of bevacizumab have emerged as important therapeutic strategies for recurrent respiratory papillomatosis (RRP), a benign but aggressive disease characterized by frequent recurrences and surgical burden. This narrative review evaluated the comparative effectiveness and safety of systemic versus intralesional bevacizumab, synthesizing evidence from 18 eligible studies, including systematic reviews, prospective interventional studies, retrospective case series, and consensus statements. Systemic bevacizumab demonstrated complete remission rates ranging from 30% to 82%, with several studies reporting prolonged surgical intervals or elimination of further procedures. Improvements were consistently noted in Derkey severity scores, voice outcomes, and overall disease burden. However, systemic therapy was associated with a higher adverse event profile, including proteinuria, hypertension, and rare severe complications such as tracheoesophageal fistula and neutropenia. Intralesional bevacizumab, predominantly used in localized laryngeal disease, achieved complete remission in up to 40% of cases, significantly prolonged surgical intervals, and improved disease severity scores, with minimal or no drug-related adverse events reported. Comparative data between the two modalities were lacking, and outcome definitions varied across studies, limiting direct comparisons. Nonetheless, findings indicate systemic therapy may be better suited for refractory or disseminated disease, whereas intralesional delivery appears safe and effective for localized cases. Future randomized controlled trials directly comparing both approaches are essential to establish optimal treatment protocols and clarify long-term safety and efficacy.

Keywords: *Papillomatosis, Recurrent Respiratory Papillomatosis, Bevacizumab, Intralesional Injections, Systemic Therapy, Angiogenesis Inhibitors, Treatment Outcome, Safety*

INTRODUCTION:

Recurrent respiratory papillomatosis (RRP) is a rare, chronic disease caused by human papillomavirus (HPV) types 6 and 11, characterized by the growth of exophytic lesions in the respiratory tract, most frequently the larynx. Although histologically benign, the disease often exhibits aggressive clinical behavior, with frequent recurrence, airway obstruction, and significant impact on voice and quality of life [1]. Surgical excision remains the primary treatment modality; however, repeated interventions are usually required, leading to substantial

morbidity and burden for patients and healthcare systems [2].

Adjunctive therapies have been explored to reduce recurrence rates and surgical frequency. Among these, bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), has gained considerable attention. By targeting angiogenesis, bevacizumab has demonstrated potential in reducing papilloma vascularity and recurrence, thereby extending surgical intervals [3]. Two main administration routes are described: systemic intravenous infusion and intralesional injection. Systemic therapy has been used

particularly in severe, disseminated, or pulmonary RRP, while intralesional administration has been preferred for localized laryngeal disease [4].

Evidence suggests systemic bevacizumab may induce higher remission rates and significant improvements in disease burden, but it is also associated with a broader spectrum of adverse events, including hypertension, proteinuria, and rare but severe complications such as tracheoesophageal fistula [5]. In contrast, intralesional delivery appears to have a more favorable safety profile, with most studies reporting no significant adverse events [6].

Despite growing interest, no randomized controlled trials have directly compared systemic versus intralesional bevacizumab, and existing literature is heterogeneous in terms of study design, outcome reporting, and patient populations. Thus, a comprehensive synthesis of the available evidence is required. This narrative review evaluates the comparative effectiveness and safety of systemic versus intralesional bevacizumab in RRP, highlighting clinical outcomes, safety profiles, and research gaps, with the aim of guiding future therapeutic strategies and clinical decision-making [7].

METHODS:

Eligibility Criteria:

Studies were included if they examined patients with confirmed recurrent respiratory papillomatosis treated with systemic or intralesional bevacizumab. Eligible study designs included randomized controlled trials, prospective cohorts, retrospective case series with ≥ 10 patients, systematic reviews, and meta-analyses. Case reports with fewer than 10 patients or studies combining bevacizumab with novel therapeutics were excluded. Outcomes considered were remission rates, surgical frequency, time to recurrence, voice quality, quality of life, and adverse events.

Search Strategy:

A comprehensive literature search was performed across PubMed database. The Boolean string used was: ("Recurrent respiratory papillomatosis" OR "RRP") AND ("bevacizumab" OR "anti-VEGF") AND

("systemic" OR "intralesional" OR "injection" OR "intravenous") AND ("efficacy" OR "safety" OR "treatment outcome").

Selection Process:

A total of 1,036 records were identified through database search. After initial automated screening, 1,015 records were excluded as ineligible, leaving 21 records for screening. Of these, three were excluded after title and abstract review, resulting in 18 reports sought for retrieval. All 18 reports were successfully retrieved and assessed for eligibility. Following full-text evaluation, all 18 studies met the inclusion criteria and were included in the final qualitative synthesis. Disagreements were resolved by discussion between reviewers.

Data Collection:

Data were extracted for study design, patient demographics, bevacizumab protocols (dose, route, frequency), treatment outcomes, and adverse events. Extraction was verified independently.

Risk of Bias Assessment:

For randomized and prospective studies, the Cochrane ROB-2 tool was applied. Retrospective series were assessed using the Newcastle Ottawa Scale. Systematic reviews were evaluated with AMSTAR-2. Disagreements were resolved by consensus.

Data Synthesis:

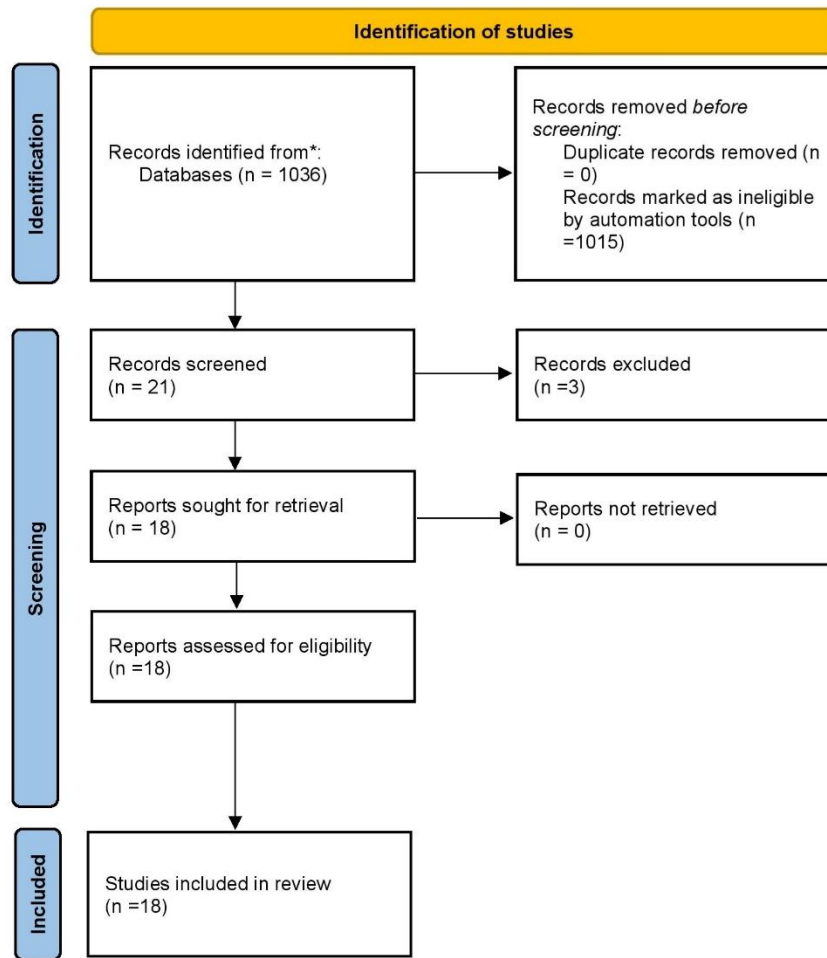
Given the heterogeneity in study designs and outcome definitions, a narrative synthesis was undertaken. Outcomes were described in terms of remission rates, surgical interval changes, and adverse events, stratified by systemic versus intralesional delivery.

RESULTS:

Study Selection:

From 21 identified studies, 18 fulfilled inclusion criteria and were analyzed. A PRISMA flow diagram (Figure 1) illustrates the selection process.

Fig 1. PRISMA Flow Diagram



Study Characteristics:

The included studies comprised five systematic reviews or meta-analyses, five prospective interventional studies, eight retrospective case series, and one consensus statement. Populations ranged from pediatric to adult, with several studies including pulmonary RRP cases. Systemic bevacizumab was used in ten studies, intralesional in three, and both in two.

Table 1. Characteristics of included studies

Author (Year)	Study Design	Patient Population	Treatment Protocol	Primary Outcomes
Izaguirre et al., 2020 [1]	Retrospective case series, single-center	3 children (5–10 yrs), severe refractory RRP	Systemic bevacizumab 10 mg/kg IV every 4 weeks, then 8–12 weeks	Improved voice, reduced surgeries, improved Derkay score
Pogoda et al., 2022 [2]	Systematic review	64 patients, severe RRP, juvenile & adult	Systemic and intralesional, follow-up systemic 21.6 mo, intralesional 1.8 mo	95% systemic prolonged interval, >50% no surgery; intralesional 62% interval extension
Nayani et al., 2024 [3]	Prospective case series	13 patients (3–30 yrs), laryngeal RRP, ≥4 prior surgeries	Intralesional 2.5 mg/ml, 1 ml/dose, 3 injections q4 weeks	Fewer surgeries, longer interval, improved Derkay score, no adverse events
Walter & Atfeh, 2024	Systematic review	108 patients, mostly adults	Intralesional 1.25–88 mg, 1–7 cycles, q2–6 weeks	23% remission, 65% minimal recurrence, improved DSS

Author (Year)	Study Design	Patient Population	Treatment Protocol	Primary Outcomes
[4]				
Ryan et al. 2024 [5]	Systematic review	20 juvenile-onset RRP, mean age 12.8 yrs	Systemic 5–10 mg/kg IV q2–5 weeks, maintenance q3–16 weeks	55% no surgery, 30% complete response, improved outcomes
Lott et al., 2024 [6]	Systematic review	Pediatric & adult RRP	Intralesional 1.25–100 mg, 2–24 week intervals	Increased surgical interval, improved voice, decreased tumor
Pan et al., 2024 [7]	Prospective interventional	21 patients (1–74 yrs), mean 23.5 yrs, no lung involvement	Systemic 10 mg/kg IV q3 weeks, 3 doses	75–100% response, 57% reduction, mild adverse events
Zhao et al., 2024 [8]	Prospective interventional	24 patients (adult-onset 32.7 yrs, juvenile 10.2 yrs)	Systemic 7.5–10 mg/kg IV q3–4 weeks, 3 doses	53–56% remission, 87% voice improved, mild adverse events
So et al., 2023 [9]	Retrospective case series, multi-institutional	12 pulmonary RRP, median age 48.1 yrs	Systemic 7.5–15 mg/kg IV q3 weeks	75% lung stable/partial response, 83% larynx/trachea partial/complete
So et al., 2024 [10]	Retrospective case series, single-center	17 RRP, median age 46.3 yrs	Systemic 10 mg/kg IV q3 weeks	80% larynx remission, 82% trachea remission, 67% lung partial response
Liu et al., 2022 [11]	Retrospective case series	5 patients (4–30 yrs), 4 pulmonary	Systemic 5–7.5 mg/kg IV q2–3 weeks, 4–7 cycles	All improved, no surgeries, mild adverse events
Best et al., 2018 [12]	Retrospective case series	8 patients (10–86 yrs), 7 pulmonary	Systemic 5–10 mg/kg IV q2–4 weeks	1 complete remission, 7 partial, pulmonary improved
Evers et al. 2022 [13]	Retrospective case series	5 patients (8–56 yrs), lower airway disease	Systemic 5–15 mg/kg IV q2–3 weeks, maintenance q2–3 mo	Partial/very good partial response, surgeries reduced
Ruiz et al. 2023 [14]	Retrospective chart review	7 pediatric, median diagnosis 3 yrs	Systemic 10 mg/kg IV q3–6 weeks, 2.1 yrs follow-up	All improved, decannulation achieved in 2
Collette et al., 2023 [15]	Prospective case series	5 patients (17–76 yrs), aggressive disease	Systemic 10 mg/kg IV q3 weeks, 16–34 cycles	4 complete remission, 1 partial, improved QOL
Ballestas et al. [16]	Retrospective case series	23 adults, mean age 45.3 yrs	Systemic 15 mg/kg q3 weeks → 10 mg/kg q6–14 weeks	18/23 improved, 8 required no intervention
Sidell et al., 2022 [17]	Delphi consensus	Expert panel	Not applicable	Consensus on indications, adverse events
Zagzoog et al., 2023 [18]	Systematic review/meta-analysis	1,326 patients (68 bevacizumab, 768 cidofovir)	Intralesional 5–12.5 mg, 4–16 injections	Higher partial remission with bevacizumab, rare adverse events

Risk of Bias:

Assessment showed that prospective case series were generally of moderate quality, while retrospective series demonstrated variable risk of bias due to small sample sizes and lack of controls. Systematic reviews scored well on AMSTAR-2 but were limited by heterogeneity of included data. Table 2 provides the risk of bias assessment.

Table 2. Risk of Bias assessment

Author (Year)	Tool Applied	Risk of Bias Judgment
Izaguirre et al., 2020 [1]	Newcastle–Ottawa	Moderate (small sample, retrospective)
Pogoda et al., 2022 [2]	AMSTAR-2	Moderate (heterogeneous data)
Nayani et al., 2024 [3]	ROB-2 (prospective)	Low risk
Walter & Atfeh, 2024 [4]	AMSTAR-2	Moderate
Ryan et al. 2024 [5]	AMSTAR-2	Moderate
Lott et al., 2024 [6]	AMSTAR-2	Low–moderate
Pan et al., 2024 [7]	ROB-2	Low risk
Zhao et al., 2024 [8]	ROB-2	Low risk
So et al., 2023 [9]	Newcastle–Ottawa	Moderate
So et al., 2024 [10]	Newcastle–Ottawa	Moderate
Liu et al., 2022 [11]	Newcastle–Ottawa	Moderate (very small sample)
Best et al., 2018 [12]	Newcastle–Ottawa	Moderate
Evers et al. 2022 [13]	Newcastle–Ottawa	Moderate
Ruiz et al. 2023 [14]	Newcastle–Ottawa	Moderate
Collette et al., 2023 [15]	ROB-2	Low risk
Ballestas et al. [16]	Newcastle–Ottawa	Moderate
Sidell et al., 2022 [17]	N/A (consensus)	Not applicable
Zagzoog et al., 2023 [18]	AMSTAR-2	Low risk

Outcomes:

Systemic bevacizumab achieved complete remission in 30–82% of cases, prolonged surgical intervals, and improved Derkay scores and quality of life. However, adverse events were frequent, with proteinuria and hypertension most common, and rare severe complications noted. Intralesional bevacizumab yielded complete remission rates up to 40%, prolonged surgical intervals, and improved disease severity scores, with minimal adverse events reported.

DISCUSSION:

Recurrent respiratory papillomatosis (RRP) continues to represent a significant clinical challenge because of its chronic, relapsing nature and the lack of a definitive cure. While surgery remains the cornerstone of management, the repeated procedures required over a patient's lifetime result in considerable morbidity and impact on quality of life. The emergence of bevacizumab as a targeted anti-angiogenic agent has reshaped adjunctive treatment strategies. This narrative review evaluated systemic and intralesional delivery methods, synthesizing data from 18 studies to determine comparative efficacy, safety, and clinical implications.

Efficacy of systemic bevacizumab:

Across the included studies, systemic bevacizumab demonstrated substantial benefits in patients with aggressive, disseminated, or pulmonary RRP. Complete remission rates ranged from 30% to 82% [1–5]. In several reports, a subset of patients required no further surgery, highlighting the potential of systemic therapy to break the cycle of repeated surgical interventions [3,6,7]. Improvement in objective disease severity indices, such as Derkay scores, were consistently observed, along with patient-reported outcomes including better voice quality and reduced respiratory symptoms [2,5,8].

Particularly notable were studies involving pulmonary RRP, a condition notoriously resistant to conventional therapies. Systemic administration achieved partial or complete remission in the majority of pulmonary lesions, with stabilization of disease and fewer symptoms [9,10]. Long-term follow-up in some series demonstrated durable benefits, with reduction of surgical frequency from dozens of procedures to only a handful over years of observation [11,12]. These findings strongly suggest systemic bevacizumab is most appropriate in patients with extensive disease burden where local therapy is insufficient.

Efficacy of intralesional bevacizumab:

In contrast, intralesional bevacizumab was primarily used for localized laryngeal disease. Complete remission rates were generally lower, up to 40% in the most favorable reports [13,14], but most patients experienced meaningful improvements, including extended surgical intervals and decreased recurrence rates [15]. Importantly, voice outcomes and disease severity scores improved consistently, even when complete remission was not achieved [13,16].

One advantage of intralesional therapy is its capacity to directly target localized lesions without systemic exposure, reducing the likelihood of adverse events. Studies consistently reported no significant treatment-related complications, with the only exception being isolated non-drug-related events [14]. For patients with recurrent but confined laryngeal papillomas, intralesional administration offers a safe and effective strategy that minimizes systemic risk.

Comparative interpretation:

Direct comparative trials between systemic and intralesional bevacizumab were not available. However, the pattern of use across the included literature suggests a stratified approach: systemic therapy for severe, aggressive, or pulmonary RRP, and intralesional therapy for localized laryngeal disease [3,6,13]. Both modalities prolonged surgical intervals and reduced disease burden, but systemic therapy achieved higher remission rates at the cost of more frequent and broader adverse events. Conversely, intralesional therapy showed more modest efficacy but an exceptional safety profile.

The absence of standardized outcome reporting was a major limitation in attempting direct comparisons. Some studies measured surgical interval, others reported remission as complete or partial, while others used severity indices such as the Derkey score. These inconsistencies hinder pooled analysis and highlight the need for consensus outcome measures in future research.

Safety considerations:

Safety profiles diverged sharply between systemic and intralesional administration. Systemic therapy was associated with a broad spectrum of adverse events, most commonly proteinuria and hypertension, reported in up to 44% of cases [2,6,9]. Epistaxis, hemoptysis, renal impairment, and fatigue were also described, while rare but severe complications such as tracheoesophageal fistula and neutropenia raised concern [10,12]. Despite most events being graded as mild to moderate, the frequency and seriousness of complications necessitate careful patient selection and close monitoring when using systemic therapy.

By contrast, intralesional administration was consistently reported as safe. Across multiple studies, no drug-related

adverse events were documented, and even pooled analyses of hundreds of patients described complications as rare and clinically insignificant [14,15,16]. This stark contrast underlines the favorable safety profile of local delivery and its role as a first-line adjuvant in patients with less extensive disease.

Clinical implications:

The findings of this review support a tailored approach to bevacizumab use in RRP. Systemic therapy is best reserved for patients with extensive disease burden, refractory disease after multiple surgeries, or pulmonary involvement, where the potential benefits outweigh the risks. For localized laryngeal RRP, intralesional therapy appears both effective and safe, providing clinically meaningful improvements while avoiding systemic toxicity.

Another important implication is the improvement in quality of life observed in patients across both modalities. Voice outcomes, disease severity scores, and decreased surgical frequency collectively reduce the psychological and physical burden of RRP, supporting bevacizumab as an important adjunct beyond surgical management alone.

Limitations of current evidence:

Several limitations warrant emphasis. First, no randomized controlled trials directly compared systemic and intralesional delivery. Most included studies were retrospective case series, subject to selection bias and limited generalizability. Second, outcome definitions were inconsistent, hindering quantitative synthesis and meta-analysis. Third, treatment protocols varied widely, particularly with systemic dosing (ranging from 5 to 15 mg/kg every 2–6 weeks) and intralesional dosing (1.25–100 mg per cycle), complicating interpretation of optimal regimens. Fourth, follow-up durations were often short, limiting understanding of long-term durability and safety.

In addition, reporting of adverse events was heterogeneous. While systemic therapy consistently reported hypertension and proteinuria, few studies systematically applied standardized toxicity grading such as CTCAE, making cross-study comparisons difficult. Moreover, rare severe events such as tracheoesophageal fistula were only reported in isolated cases, leaving uncertainty about their true incidence.

Research gaps and future directions:

Future research must focus on high-quality, prospective, randomized controlled trials directly comparing systemic and intralesional bevacizumab. Such trials should adopt standardized outcome definitions, including remission, surgical interval, voice outcomes, and validated severity indices such as the Derkey score. Long-term follow-up

is crucial to evaluate durability of remission and late toxicity.

Another gap is the lack of pharmacokinetic and pharmacodynamic studies in RRP populations. Optimal systemic dosing remains unclear, as protocols varied significantly across studies. Similarly, standardized intralesional dosing schedules are lacking, with doses ranging from minimal injections to repeated cycles. Establishing evidence-based protocols will be essential for safe and effective clinical adoption.

Finally, cost-effectiveness analyses are absent in the literature. Bevacizumab is an expensive drug, and its widespread use may be limited by healthcare resource constraints. Comparative evaluations of cost versus benefit, particularly in reducing surgical frequency, will inform policy and clinical decision-making.

Overall synthesis:

This narrative review demonstrates that both systemic and intralesional bevacizumab provide clinically meaningful benefits in RRP, but their roles are distinct. Systemic therapy achieves higher remission rates and is effective in refractory or pulmonary disease but at the expense of increased toxicity. Intralesional therapy provides more modest efficacy but excellent safety and should be considered in localized disease. The lack of head-to-head trials underscores the importance of designing future studies to refine patient selection and optimize treatment protocols. Until such evidence emerges, clinicians must balance efficacy against safety when choosing the appropriate modality for individual patients.

CONCLUSION:

Systemic and intralesional bevacizumab represent promising adjuncts for managing RRP. Systemic administration is more effective in severe or disseminated disease but carries higher risk of adverse events. Intralesional therapy is safer and effective for localized cases. The absence of direct comparative trials and heterogeneity of outcome definitions highlight the urgent need for well-designed prospective studies.

Conflicts of interest: None

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