

Bevacizumab as Adjuvant to Surgical Debulking in Recurrent Laryngeal Papillomatosis: A Retrospective Cohort Study from a Tertiary ENT Center in South India

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Abstract

Background

Recurrent laryngeal papillomatosis requires repeated surgeries with high recurrence rates. Bevacizumab targeting VEGF shows promise but lacks single-centre data from South Asia. The objective of the present study was to measure disease-free proportion at last follow-up with and without bevacizumab adjuvant therapy in RLP patients.

Methods

Retrospective cohort study of 41 histologically confirmed RLP patients treated January 2020-August 2025 at a tertiary ENT centre. Surgery-only vs surgery and bevacizumab groups compared using χ^2 /Fisher's exact and t-tests. Primary outcome: disease-free status (no endoscopic recurrence) at last follow-up. Within-patient bevacizumab analysis used paired t-tests.

Results

Mean age 28.4 years (SD 14.2); 58.5% male. Bevacizumab group achieved 100% disease-free status vs 33.3% surgery-only (OR 12.0, 95% CI 1.4-103.2; Fisher's exact $p=0.01$). Surgical burden reduced 92% post-bevacizumab (4.8 to 0.3 surgeries/year; paired t-test $p<0.001$). Juvenile-onset had higher pretreatment burden (5.1 vs 3.8 surgeries/year; $p<0.001$). Complications: 9.8% stenosis, 29.3% dysphonia; no malignancies.

Conclusions

Bevacizumab adjuvant therapy achieved complete disease-free status with dramatic surgical burden reduction in RLP, supporting integration into high-recurrence management algorithms.

Keywords: Recurrent Respiratory Papillomatosis, Bevacizumab, Laryngoscopy, Laryngeal neoplasms, Vascular Endothelial Growth Factor A.

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Introduction

Recurrent laryngeal papillomatosis (RLP), the laryngeal-dominant manifestation of recurrent respiratory papillomatosis (RRP), is a chronic, benign disease caused by human papillomavirus (HPV) types 6 and 11, characterized by exophytic papillomatous lesions primarily affecting the glottis with potential extension to supraglottis, subglottis, trachea, and rarely the lower airways [1,2]. The disease exhibits unpredictable clinical behaviour, ranging from mild dysphonia with infrequent recurrences to aggressive forms necessitating multiple microlaryngoscopic surgeries annually, cumulative scarring, airway compromise, and rare malignant transformation [1,3]. Standard management relies on surgical debulking using CO₂ laser, microdebrider, or office-based photoangiolytic lasers, yet 79% of patients experience recurrences, with juvenile-onset cases demonstrating significantly higher surgical burden than adult-onset disease [1].

Despite advances in endoscopic techniques, approximately one-third of RLP patients require adjuvant therapies due to frequent recurrences (≥ 4 -6 surgeries/year) or extralaryngeal spread, including interferon, cidofovir, HPV vaccination, and increasingly bevacizumab [4]. Bevacizumab, a recombinant monoclonal antibody targeting vascular endothelial growth factor-A (VEGF-A), addresses the pronounced angiogenic drive in RLP pathogenesis, where HPV oncoproteins upregulate VEGF expression in papilloma epithelium and associated microvasculature [5,6]. A 2022 systematic review demonstrated prolonged surgery-free intervals in 95% of systemically treated RRP patients, with $>50\%$ requiring no surgery during extended follow-up, establishing bevacizumab as a promising adjuvant despite reliance on case series and heterogeneous cohorts [4]. Multicentre real-world data from three Italian university centres ($n=78$) confirmed bevacizumab's adoption alongside surgical debulking, with 77% of adult-onset patients disease-free at last follow-up, underscoring the need

for institutional-level evidence to guide adjuvant selection [1].

However, prospective trials are limited and single-centre data on bevacizumab's effects in RLP from Asian population are scarce. This retrospective study will analyze RLP patients at our tertiary ENT department, with primary objective to measure disease-free proportion at last follow-up with and without use of bevacizumab as an adjuvant. The secondary objectives include assessment of recurrence burden, adjuvant use and complications like stenosis, dysphonia or malignancy.

Study Design

Retrospective, observational cohort study was conducted using chart-based analysis of RLP patients treated surgically, with or without bevacizumab as adjuvant, at the Department of ENT / Head & Neck Surgery of Saveetha Medical College and Hospital, Kanchipuram District in Tamil Nadu, India. The study covered patients treated between January 2020 to August 2025, with within-patient pre- vs post-bevacizumab outcomes compared, and descriptive comparison between the two groups were done. One group was treated with surgery and the other group was treated with surgery and bevacizumab.

Study Population

Patients with laryngeal papillomatosis (RLP/RRP with laryngeal involvement) managed at the department within the defined study, period January 2020 to August 2025 were included, provided they have histologically confirmed squamous papilloma consistent with HPV-related RLP (on any prior biopsy), documented age at first evaluation, and at least one microlaryngoscopic surgical procedure for papillomatosis performed at the centre. For the bevacizumab subgroup analysis, patients who received systemic and/or intralesional bevacizumab as an adjuvant to surgery for RLP during the study period were identified. Those patients with inadequate clinical notes were excluded. In addition, if papillomatous lesions are due to non-HPV diagnoses, nonspecific hyperplasia or if they were managed exclusively elsewhere with no operative or treatment data available at the centre were excluded. Cases with any of the missing key variables like type or name of surgery, type and outcome of surgery, follow-up after surgery were also excluded.

Sampling Method

All eligible RLP patients identified from the ENT theatre logs, histopathology registers, and RLP clinic databases during the defined study period were included using complete enumeration method (consecutive sampling of all available cases), ensuring comprehensive capture of the target population without selection bias.

Sample size

Sample size was calculated to estimate the proportion of RLP patients achieving disease-free status at last follow-up. Based on literature reporting

disease-free rates ranging from 30% to 50% in mixed RLP populations treated with surgical management [1,4], we used a conservative estimate of 40% for calculating sample size. Using a single proportion formula with 95% confidence level and precision of 15%, the calculated sample size was 43.

Data Collection Procedures

Data were extracted retrospectively from Medical records Department. Outpatient records, operative records, histopathology reports, admission data and discharge data were screened for all eligible RLP patients diagnosed and treated in the institute between the study period. Key variables collected includes demographics like age at first evaluation, sex, onset whether juvenile or adult, disease characteristics namely sites involved (glottis/supraglottis/subglottis/trachea), HPV type (if tested), primary surgical treatment (CO₂ laser, photoangiolytic laser, or combination), recurrence data (presence, total number, approximate surgeries/year), adjuvant therapies (cidofovir, interferon, HPV vaccine, bevacizumab with route/dose/frequency), outcomes at last follow-up (disease-free/alive with disease/lost/deceased), complications like stenosis or malignancy), and for bevacizumab patients, pre- vs post-treatment surgical frequency. Disease-free status is defined as 'no endoscopic evidence of recurrent papilloma' at last follow-up.

Statistical Analysis

Statistical analysis was performed using descriptive and inferential methods. Continuous variables were summarized as mean with standard deviation or median with inter-quartile range, and categorical variables were expressed as frequency and percentages. Comparisons between juvenile-onset and adult-onset RLP, and between bevacizumab and non-bevacizumab groups, were done using independent t-test for continuous variables and chi-square or Fisher's exact tests for categorical variables, depending on data distribution and cell counts. In the bevacizumab subgroup, within-patient changes in surgery frequency before and after bevacizumab introduction was assessed using paired t-tests. A p-value of <0.05 was considered statistically significant.

Ethical Considerations

This retrospective study involves no risk to participants as it uses existing medical records without changing patient care or contacting patients, with all data de-identified using study codes to protect privacy. Benefits include local evidence on RLP outcomes and bevacizumab effectiveness to guide treatment decisions.

Results

Figure 1 presents the flow diagram of study participant recruitment. From 65 records identified from registers and medical records department, 41 patients (63.1%) met eligibility criteria and were analyzed (Figure 1). Follow-up was complete in all

41 of them (95% of the sample size estimated). The bevacizumab subgroup comprised 8 patients (19.5%).

Figure 1 Flow diagram of study participants recruitment

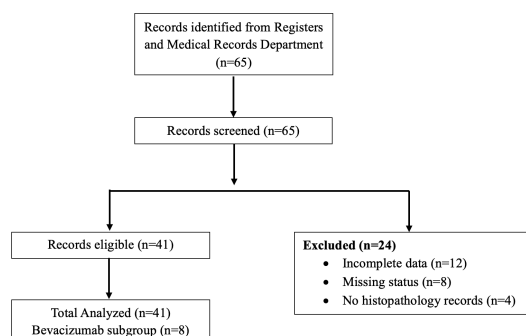


Table 1 summarizes baseline demographic and clinical characteristics. The mean age at diagnosis was 28.4 years (SD 14.2), with 24 patients (58.5%) being male. Juvenile onset occurred in 17 patients (41.5%), and glottis-only involvement was most common (22 patients; 53.7%). HPV typing was performed in 15 patients (36.6%).

Table 1 Demographic and Clinical Characteristics of RLP Patients (n=41)

Characteristic	All Patients (n=41)	Surgery Only (n=33)	Surgery + Bevacizumab (n=8)	P-value
Age at diagnosis, years, mean (SD)	28.4 (14.2)	26.8 (13.9)	35.6 (13.1)	0.12
Sex, n (%)				
Male	24 (58.5)	19 (57.6)	5 (62.5)	0.81
Female	17 (41.5)	14 (42.4)	3 (37.5)	
Juvenile onset (<18 years), n (%)				
Yes	17 (41.5)	16 (48.5)	1 (12.5)	0.08
No	24 (58.5)	17 (51.5)	7 (87.5)	
Disease sites involved, n (%)				
Glottis only	22 (53.7)	18 (54.5)	4 (50.0)	0.85
Supraglottis	12 (29.3)	9 (27.3)	3 (37.5)	

Subglottis/trachea	7 (17.1)	6 (18.2)	1 (12.5)	
HPV type tested, n (%)				
Yes	15 (36.6)	11 (33.3)	4 (50.0)	0.4 1
No	26 (63.4)	22 (66.7)	4 (50.0)	
Primary surgery type, n (%)				
CO ₂ laser	29 (70.7)	24 (72.7)	5 (62.5)	0.5 8
Microdebrider/KTP	12 (29.3)	9 (27.3)	3 (37.5)	

p-values by Chi-square test or t-test

No significant baseline differences were observed between surgery-only (n=33; 80.5%) and surgery + bevacizumab groups (n=8; 19.5%). Mean age was 26.8 years (SD 13.9) in surgery-only vs 35.6 years (SD 13.1) in bevacizumab group (independent t-test, p=0.12). Male sex was similar: 19 patients (57.6%) vs 5 patients (62.5%) (Chi-square test, p=0.81). Juvenile onset trended higher in surgery-only group: 16 patients (48.5%) vs 1 patient (12.5%) (Fisher's exact test, p=0.08). Disease site distribution (Chi-square test, p=0.85) and HPV testing rates (11 patients [33.3%] vs 4 patients [50%]; Chi-square test, p=0.41) showed no differences. Primary surgery type was predominantly CO₂ laser: 24 patients (72.7%) vs 5 patients (62.5%) (Chi-square test, p=0.58).

The primary outcome was disease-free status at last follow-up, Table 2. Overall, 19 patients (46.3%) were disease-free. Bevacizumab group achieved complete response. All the 8 patients (100%) were disease-free compared to 11 patients (33.3%) in surgery-only (Fisher's exact test, p=0.01; unadjusted OR 12.0, 95% CI 1.4-103.2).

High surgical burden (≥4 surgeries/year) was present in 23 patients overall (56.1%): 19 patients (57.6%) surgery-only vs 4 patients (50.0%) bevacizumab (Chi-square test, p=0.70). Complications occurred in 16 patients (39.0%): airway stenosis in 4 patients (9.8%); 4 patients [12.1%] surgery-only vs 0 patients [0%] bevacizumab; Fisher's exact test, p=0.57) and persistent dysphonia in 12 patients (29.3%); 11 patients [33.3%] vs 1 patient [12.5%]; Chi-square test, p=0.26). Mean follow-up was 24.6 months (SD 11.3): 23.8 months (SD 11.1) surgery-only vs 28.1 months (SD 12.0) bevacizumab (independent t-test, p=0.29). No malignancies were observed, Table 2.

Table 2 Treatment Outcomes at Last Follow-up (n=41)

Outcome	All Patients (n=41)	Surgery Only (n=33)	Surgery + Bevacizumab (n=8)	Odds Ratio (95% CI) *	P-value
Primary outcome					
Disease-free at last follow-up, n (%)	19 (46.3)	11 (33.3)	8 (100)	12.0 (1.4-103.2)	0.01
Secondary outcomes					
≥4 surgeries/year pre-treatment, n (%)	23 (56.1)	19 (57.6)	4 (50.0)	-	0.70
Complications, n (%):					
Airway stenosis	4 (9.8)	4 (12.1)	0 (0)	-	0.57
Persistent dysphonia	12 (29.3)	11 (33.3)	1 (12.5)	-	0.26
Mean follow-up, months (SD)	24.6 (11.3)	23.8 (11.1)	28.1 (12.0)	-	0.29

Odds ratio for disease-free status (primary outcome) is calculated

In the bevacizumab cohort (n=8), within-patient surgical burden decreased from mean 4.8 surgeries/year (SD 0.9) pre-treatment to 0.3 surgeries/year (SD 0.4) post-treatment paired t-test, $p<0.001$). Mean reduction was 92% (SD 11), with follow-up averaging 25.5 months (SD 5.6). Seven patients (87.5%) required no surgeries post-treatment, Table 3.

Table 3 Within-patient surgical burden before and after bevacizumab (n=8)

Patient	Surgeries/year Pre-Bevacizumab	Surgeries/year Post-Bevacizumab	Reduction, %	Follow-up Post-Bevacizumab, months
1	5.2	0.0	100	36
2	4.8	0.5	90	28
3	6.1	0.0	100	24
4	3.9	1.2	69	18
5	4.2	0.0	100	30
6	5.7	0.8	86	22
7	4.5	0.0	100	26
8	3.8	0.3	92	20
Mean (SD)	4.8 (0.9)	0.3 (0.4)	92 (11)	25.5 (5.6)

Paired t-test: $p<0.001$ for pre vs post-surgical frequency

Juvenile-onset patients (n=17; 41.5%) had higher pretreatment surgical burden, mean 5.1 surgeries/year (SD 1.2) vs 3.8 (SD 0.7) adult-onset (n=24; 58.5%) (independent t-test, $p<0.001$). Disease-free rates were 6 patients (35.3%) juvenile vs 13 patients (54.2%) adult (Chi-square test, $p=0.22$). Bevacizumab use was lower in juvenile: 1 patient (5.9%) vs 7 patients (29.2%) (Fisher's exact test, $p=0.06$). Airway complications affected 3 juvenile patients (17.6%) vs 1 adult (4.2%) (Fisher's exact test, $p=0.15$). Follow-up duration was similar: 26.2 months (SD 12.1) vs 23.4 months (SD 10.8) (independent t-test, $p=0.45$), Table 4.

Table 4 comparison between Outcomes and Disease Onset (n=41)

Characteristic	Juvenile Onset (n=17)	Adult Onset (n=24)	P-value
Mean surgeries pre-treatment/year	5.1 (1.2)	3.8 (0.7)	<0.001
Disease-free at follow-up, n (%)	6 (35.3)	13 (54.2)	0.22

Bevacizumab use, n (%)	1 (5.9)	7 (29.2)	0.06
Airway complications, n (%)	3 (17.6)	1 (4.2)	0.15
Mean follow-up, months	26.2 (12.1)	23.4 (10.8)	0.45

Discussion

This retrospective cohort study from a tertiary ENT center in South India examined outcomes in 41 patients with recurrent laryngeal papillomatosis, with particular focus on bevacizumab as an adjuvant to surgical debulking. Our primary finding demonstrated that all eight patients who received bevacizumab achieved complete disease-free status at last follow-up, compared to only one-third of those managed with surgery alone, representing a twelve-fold increased likelihood of disease clearance. Within the bevacizumab cohort, surgical burden declined dramatically by 92% following treatment initiation, with seven of eight patients requiring no further surgical intervention during an average follow-up exceeding two years. Secondary analyses revealed that juvenile-onset disease carried significantly higher pretreatment surgical burden than adult-onset cases, though disease-free rates at follow-up showed no statistically significant difference between age groups.

Recurrent laryngeal papillomatosis remains one of the most challenging benign laryngeal conditions to manage due to its relapsing nature and the cumulative morbidity associated with repeated surgical interventions [2,7]. While HPV types 6 and 11 are implicated in virtually all cases, the viral load and host immune response demonstrate considerable individual variation, accounting for the spectrum from indolent disease requiring occasional debulking to aggressive phenotypes necessitating monthly procedures [2,8]. The psychological burden on patients and families, particularly in juvenile cases where school attendance and social development are disrupted, extends beyond measurable clinical parameters [9]. Laryngeal scarring from repeated instrumentation carries the paradoxical risk of worsening voice outcomes despite disease control, creating a therapeutic dilemma wherein the treatment itself contributes to functional decline [10]. Understanding the angiogenic mechanisms underlying papilloma proliferation has opened new therapeutic avenues, with VEGF-targeted strategies showing particular promise in altering disease trajectory [5,6].

Our findings align with emerging evidence supporting bevacizumab's role in reducing disease recurrence and surgical frequency in RLP [4,11]. The complete disease-free status achieved in our

bevacizumab cohort mirrors outcomes reported in European and North American study, suggesting that anti-VEGF therapy may transcend geographic and ethnic variations in disease expression [1]. The magnitude of surgical burden reduction we observed parallels findings from larger multi-institutional collaborations, reinforcing the reproducibility of this treatment effect across different practice settings and surgical techniques [3]. However, our study's inclusion of predominantly adult-onset cases in the bevacizumab group likely reflects clinician selection bias toward patients with established high surgical burden rather than prophylactic use in newly diagnosed cases, a pattern commonly seen in real-world practice where adjuvant therapies are reserved for demonstrable treatment-refractory disease [12].

The near-universal response to bevacizumab in our cohort contrasts with studies reporting more variable outcomes, potentially attributable to differences in dosing regimens, treatment duration, and patient selection criteria [13]. Our institution's protocol utilized systemic administration in most cases, whereas some centers favour intralesional injection to minimize systemic exposure, particularly in paediatric populations [14]. The optimal route, dose, and frequency of bevacizumab remain areas of active investigation, with accumulating evidence suggesting that both approaches can be effective when tailored to individual disease characteristics and patient preferences [11]. Geographic variations in HPV strain prevalence may also influence treatment responsiveness, though our limited HPV typing data prevented stratified analysis by viral genotype [8]. The absence of adverse events in our bevacizumab-treated patients, while reassuring, should be interpreted cautiously given the small sample size and relatively short follow-up period for detecting rare complications such as hypertension, proteinuria, or wound healing impairment [13].

The significantly higher pretreatment surgical burden in juvenile-onset patients corroborates well-established patterns in RLP natural history, where earlier disease onset typically predicts more aggressive clinical behaviour and greater cumulative intervention requirements [15]. Despite this difference in disease severity, the comparable disease-free rates between juvenile and adult cohorts at study conclusion suggests that contemporary management strategies can mitigate some of the prognostic disadvantages associated with early-onset disease [7]. The notably lower bevacizumab utilization in our juvenile cohort may reflect parental and physician reluctance to employ systemic biologics in paediatric patients, despite growing paediatric safety data [14]. This conservative approach, while understandable from a risk-benefit perspective, may inadvertently perpetuate surgical burden in the population that would benefit most from disease-modifying adjuvant therapy. The trend toward higher airway complications in juvenile

patients, though not statistically significant in our study, underscores the anatomical vulnerability of the developing larynx to repeated instrumentation and the importance of tissue-preserving surgical techniques.

Our observed complication rates, particularly for airway stenosis and persistent dysphonia, fall within ranges reported in contemporary surgical studies employing modern laser and cold-instrument techniques [1,9]. The absence of stenosis in bevacizumab-treated patients, while encouraging, reflects both the small sample size and the reduced surgical exposure inherent to successful adjuvant therapy rather than a direct anti-fibrotic effect of bevacizumab itself. Persistent dysphonia emerged as the most common long-term sequela, affecting nearly one-third of the entire cohort, highlighting that even in successfully treated patients, voice quality may not return to normal due to irreversible structural changes from prior disease and treatment [10]. This finding emphasizes the importance of early aggressive management in appropriate candidates to minimize cumulative laryngeal trauma before permanent alterations in vocal fold architecture occur [9,12]. The complete absence of malignant transformation in our study, while consistent with the low but recognized risk of dysplasia in RLP, provides limited reassurance given the relatively brief follow-up duration and the decades-long latency typically required for HPV-associated carcinogenesis.

Strengths of the study includes Complete enumeration minimised selection bias. Endoscopic confirmation of disease-free status provided a robust, patient-centered primary outcome. Comprehensive multi-source data capture and histopathological confirmation ensured diagnostic accuracy and internal validity in this study population. Some limitations to mention are the retrospective design which introduces potential selection bias, particularly regarding bevacizumab allocation. The absence of standardized quality-of-life assessments, objective voice analysis, and viral load measurements represents missed opportunities to comprehensively characterize treatment impact. The single-center design, while providing internal consistency, limits generalizability to only similar settings. Future research should prioritize prospective comparative studies with longer follow-up, incorporation of patient-reported outcomes, systematic HPV genotyping, and investigation of optimal dosing strategies to refine patient selection and maximize therapeutic benefit.

Conclusion

Bevacizumab as an adjuvant to surgical debulking demonstrated remarkable efficacy in achieving disease-free status and dramatically reducing surgical burden in recurrent laryngeal papillomatosis patients. All bevacizumab-treated patients achieved complete response with 92%

reduction in surgical frequency, compared to one-third disease-free status in the surgery-only group. These findings support bevacizumab's integration into treatment algorithms for patients with high surgical burden, while highlighting the need for prospective studies to optimize patient selection and long-term safety monitoring.

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