# Protocol for intralesional injection of bevacizumab for severe recurrent respiratory papillomatosis

Original Article


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## Abstract

Introduction: Recurrent respiratory papillomatosis (RRP) is a chronic condition associated with the growth of papillomas in the airways, with impaired voice and respiratory quality. Recent studies have shown that intralesional injection of bevacizumab increases the interval between surgeries, improves quality of life, and has a virtually zero risk of complications.
Objectives: To establish a protocol for intralesional application of bevacizumab in patients with severe RRP.
Materials and Methods: The search included the PUBMED and Cochrane databases. A review of relevant medical literature was conducted.
Results: The protocol consists of four distinct phases: selection of patients with severe RRP requiring adjuvant therapy and obtaining informed consent, staging and assessment of preoperative disease burden, implementation of adjuvant treatment with intralesional bevacizumab as outlined, and follow-up and efficacy criteria.
Conclusions: For the treatment of severe RRP, this standardized technique provides a systematic method for injecting bevacizumab intralesionally.


Keywords: Respiratory Papillomatosis; Bevacizumab; HPV; Laryngology; Surgery


## Introduction

Recurrent respiratory papillomatosis (RRP) is a benign disease caused by the human papillomavirus (HPV)[1] and is characterized by a growth of papillomas in the respiratory tract, affecting the vocal quality and respiratory function[2]. Despite the recent advances in vaccine development, RRP remains a therapeutic challenge due to its high recurrence rate, elevated risk of airway obstruction, and significantly reduced quality of life[3]. While HPV serotypes 6 and 11 are most often associated with RRP, high-risk serotypes such as 16, 18, 31, 33, and 39 have also been identified[2].

RRP exhibits a bimodal age distribution, with children and young adults being the most affected populations[1]. The disease is generally more aggressive and has higher recurrence rates in children, whereas juvenile-adult RRP tends to be more indolent. Disease severity and recurrence are highly variable, highlighting the challenge of relying solely on surgical excision as a treatment modality. The larynx is the most frequently affected site, particularly the vocal fold-covering layer, including the mucosa and lamina propria[4]. Recurrence rates are higher at the primary site of infection[2].

The Derkay[5,6] staging system can be used for the evaluation of patients with RRP, including the disease location and burden. This system attributes different degrees to the extent of papillomatosis along the aerodigestive tract and assesses the vocal and respiratory capacity of the patient. The final score is the sum of the anatomical and functional evaluation. This system is an important tool for monitoring disease progression, assessing the treatment response, and comparing results between centers.

Currently, there is no cure for RRP, and no single treatment has been proven to be consistently effective in eradicating the disease[7]. The therapeutic gold standard is surgery ($CO_2$ laser, cold steel, or microdebrider excision), which aims to completely remove the papillomas while preserving the structure and functionality. Approximately 20% of patients with RRP require adjuvant therapy to control the disease[7], and it is currently indicated in cases of severe RRP[8], which is defined as:

- Need for more than four surgical procedures in a year;
- Rapid recurrence of papillomas with airway involvement; or
- Extralaryngeal spread.

Bevacizumab (Avastin®) is a monoclonal antibody that binds to vascular endothelial growth factor (VEGF) and inhibits its interaction with receptors[2]. Numerous studies[9–11] have revealed that intralesional injection of bevacizumab in patients with RRP increases the time between surgeries, reduces disease severity, and improves the quality of life. However, some complications of intralesional injection have been documented, particularly the formation of pyogenic granulomas[8].

The protocol presented in this study is a standardized proposal for the intralesional administration of bevacizumab in patients with severe RRP.

## Objective

To develop a standardized protocol for the intralesional administration of bevacizumab in patients with severe RRP.

## Materials and methods

The PubMed database and Cochrane Library were searched for any combination of the following terms: "laryngeal papillomatosis," "recurrent laryngeal papillomatosis," "bevacizumab," "Avastin®," and "human papillomavirus." The references of the included studies were manually reviewed to identify additional literature. All the relevant medical literature was reviewed, particularly the studies by Fortes et al.[1], Benedict et al.[2,4], Derkay et al.[5–7], Zeleník et al.[8], Best et al.[11], Pogoda et al.[12], Nagel et al.[16], and Zeitels et al. [10,17–18].

## Results

The protocol is structured into four distinct phases:

- Careful selection of patients with severe RRP who are eligible for adjuvant therapy, with subsequently procurement of informed consent.
- Preoperative staging and evaluation of disease burden in the selected patients.
- Treatment implementation as outlined in the protocol.
- Post-treatment follow-up and evaluation of the effectiveness criteria, including a possible therapeutic switch of adjuvant agents.

### 1. Patient selection and informed consent

Adjuvant therapy with surgery is indicated in cases of severe RRP[8], which is defined as:

- Need for more than four surgical procedures

in a year;
- Rapid recurrence of papillomas with airway involvement; or
- Extralaryngeal spread.

All patients must sign an informed consent form before starting the treatment (Appendix).

**2. Staging and evaluation of disease burden**

After obtaining informed consent, the upper airway should be endoscopically evaluated and the Derkay staging system (Appendix) should be used for assessment. RRP should be diagnosed by histopathological examination. HPV genotyping should be requested.

**3. Treatment**

Dosage and technique

In this protocol, the recommended dose of bevacizumab is 12.5 mg, delivered in a volume of 0.5 mL (25 mg/mL). The Reinke's space can accommodate 0.3–0.5 mL of the solution, enabling a dose range of 7.5–12.5 mg[11]. Patients with more widespread disease may require a higher dose.

Bevacizumab is injected intralesionally after excision of the papillomas using $CO_2$ laser, cold steel, or microdebrider techniques.

The next two procedures should be spaced three weeks apart, and the injections should preferably be administered at the previously treated sites. In the proposed protocol, we recommend removing the papillomas with $CO_2$ laser because of its hemostatic properties and ability to provide clear visualization during surgery, which helps in optimizing the operative time. Effective hemostasis is crucial for using narrow band imaging (NBI), an endoscopic imaging technique that employs monochromatic light to enhance the visualization of mucosa and blood vessels on the surface of internal organs. NBI is valuable for identifying papillomas because it shows the vascular and morphological characteristics on the lesion surface.

Treatment timeline

Start of treatment:

- Intralesional injection every three weeks for a total of three procedures.
- Treatment discontinuation:
- Allergic reaction (not documented in the literature).
- Severe systemic side effects such as stroke and acute myocardial infarction (documented only with systemic administration[12]).

**Surgical suite procedures**

The following procedures should be implemented in the surgical suite:

- The sealed aluminum container, which holds individual, sterilized, and labeled syringes of bevacizumab, is delivered by the pharmaceutical services operational assistant to the nurse responsible for the operating room.
- In the operating room:
  - ▸ Verify the sealed container and open it under aseptic conditions.
  - ▸ Check the integrity of the sterilized syringes containing bevacizumab and confirm the information provided in the labels.
- Surgical technique:
  - ▸ Perform hand disinfection and don sterile gowns and gloves (surgical team).
  - ▸ Place a sterile surgical drape.
  - ▸ Conduct rigid direct laryngoscopy using a surgical laryngoscope (Kleinasser or Lindholm).
  - ▸ Use additional materials typically required for functional laryngeal microsurgery (Figure 1):
    - Micro-laryngeal forceps.
    - Micro-laryngeal scissors.
    - Fine suction tubes (3, 5, and 7 Fr).
    - Microscope (focal length of 400 nm).
    - Laser $CO_2$ or microdebrider.
    - Butterfly needle 21–27 G and tubing connected to the syringe.
  - ▸ Surgical steps:
  - ▸ Position the patient with the neck flexed and head extended.
  - ▸ Place a mouth guard to prevent dental and mucosal injury.
  - ▸ Introduce the laryngoscope.
  - ▸ Suspend the larynx using a rotating sus-

pension system.

▸ Perform the next steps using a microscope equipped with a 400 nm lens.

▸ Excise papillomatous lesions using $CO_2$ laser, cold steel, or microdebrider techniques. For $CO_2$ laser, use the super-pulsed or ultra-pulsed mode, unfocused, with power between 2–5 W[13].

▸ Confirm hemostasis.

▸ Administer the intralesional injection, preferably into the superficial lamina propria (Figure 2).

▸ Confirm hemostasis.

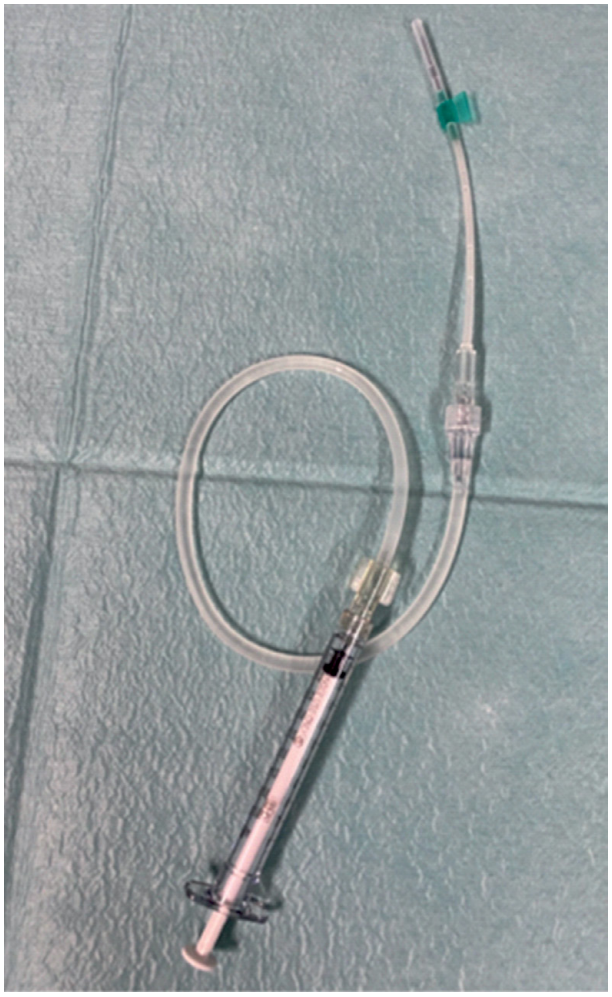
▸ Remove the laryngoscope.

▸ Discard all unused syringes immediately.

At the end of the procedure, the patient is transferred to the recovery room and remains in outpatient care, with an overnight stay. Some basic care measures, common to functional laryngeal surgery, are recommended:

- Vocal rest, typically between 3–5 days.
- Oral hydration.
- Pain medication as needed (ibuprofen 400–600 mg every 8 hours).

**Figure 1**
Butterfly needle and coupling system attached to a syringe containing bevacizumab (original photograph).



**4. Follow-up, effectiveness criteria, and therapeutic switch**

After treatment, the patient should undergo follow-up assessments by an otorhinolaryngologist 1 week, 1, 3, 6, 9, and 12 months postoperatively, and then based on clinical progression.

A new procedure should be considered when the disease burden is at least similar to that observed in the first procedure.

Treatment is considered ineffective if the number of surgeries required to remove the papillomas is equal to or greater than the number performed in the year before the start of adjuvant treatment.

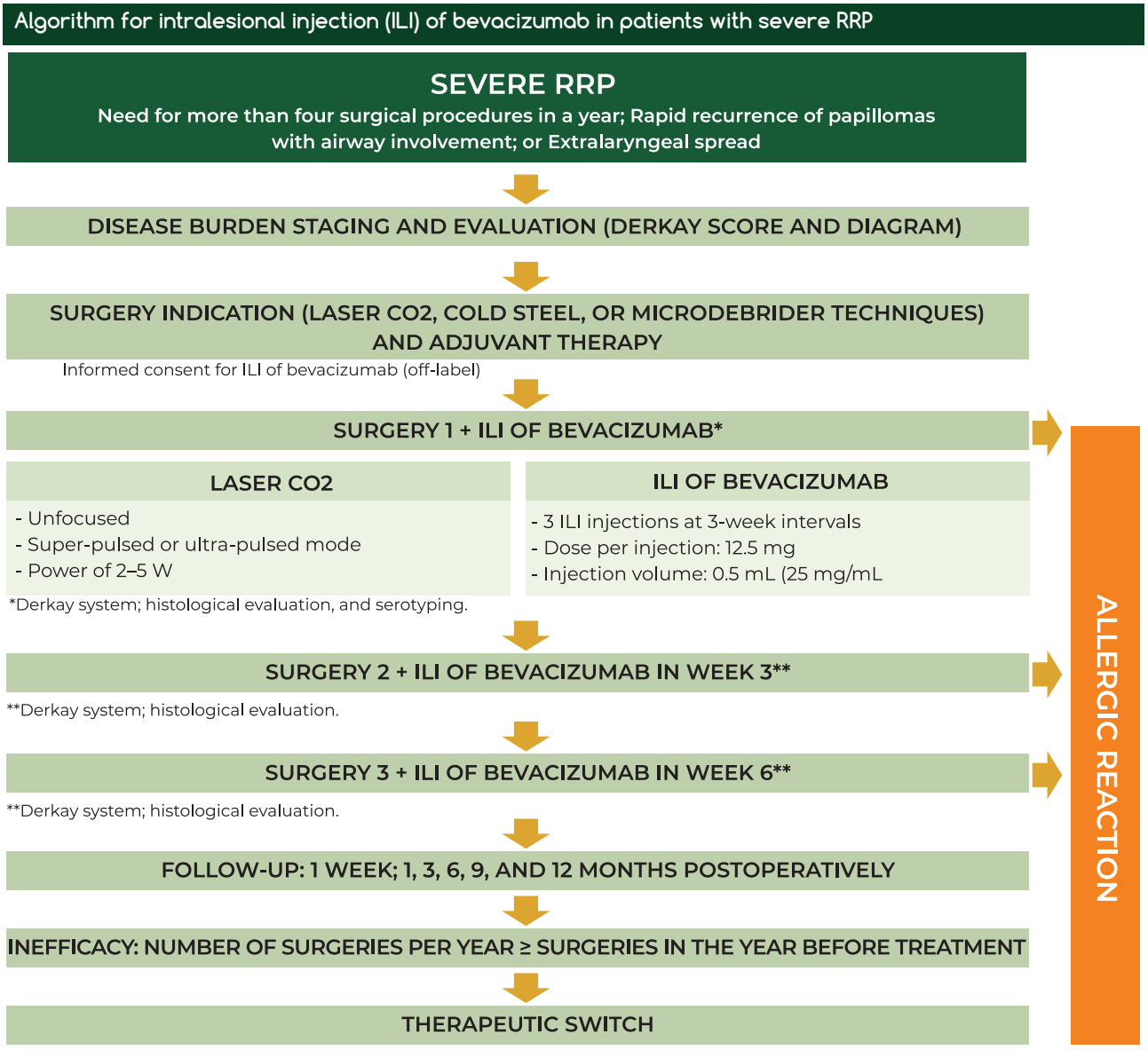
Other adjuvant therapies, such as switching to intralesional cidofovir may be considered in patients with RRP who show an inadequate response to treatment or cannot tolerate intralesional bevacizumab.

Patients with RRP who have not been vaccinated for HPV are advised to undergo the vaccination after completing the treatment cycle[14] (e.g., three doses of Gardasil® 9 at 0, 2, and 6 months).

**5. Use of the protocol (clinical case report)**

A 37-year- non-smoker man, who was a non-smoker, was referred for an otolaryngology appointment to the Pedro Hispano Hospital because of progressive dysphonia for the last few months. He had a history of three laryngeal microsurgeries at another hospital in 2017, 2019, and 2020.

On physical examination, papillomas were observed in the larynx, located at the anterior commissure, posterior third of the left vocal fold, and middle of the right ventricle. His total Derkay score was 5 (4 + 1), and the dysphonia was classified as $G_1R_1B_0A_0S_1$, according to the




RRP, recurrent respiratory papillomatosis

Grade, Roughness, Breathiness, Asthenia, and Strain (GRBAS) scale.

The patient underwent laryngeal microsurgery using the $CO_2$ laser technique set to 5 watts in a super-pulsed mode. A laryngeal needle was used to inject 12.5 mg (0.5 mL) of medication into the affected areas (Figure 2). Histopathological analysis confirmed the presence of squamous cell papillomas. The procedure was repeated after three and six weeks. After each procedure, the patient was discharged the next day. He was prescribed esomeprazole 20 mg once daily before breakfast for two months, amoxicillin with clavulanic acid (875 + 125 mg) every 12 hours for eight days, and analgesics as needed. Follow-up appointments were scheduled for the first week and first month after the end of the treatment cycle. At the final follow-up, three months post-treatment, the patient was asymptomatic, and no papillomas were detected on physical examination. The vocal fold epithelium was intact and appeared normal (Figures 3 and 4).

## Discussion

RRP is a chronic disease characterized by the growth of papillomas within the respiratory tract, including the larynx, trachea, and bronchi. These papillomas are usually caused

**Figure 2**
Narrow band imaging (NBI) at the time of the third bevacizumab injection shows no papillomas.

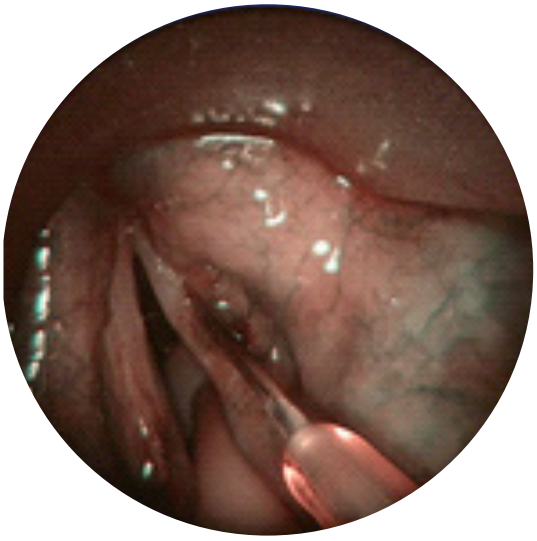
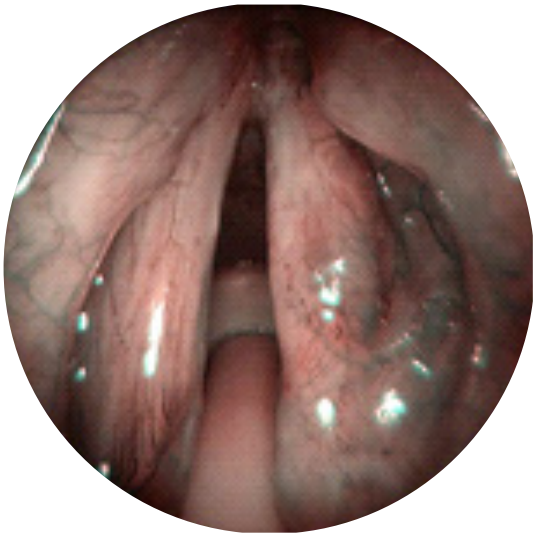
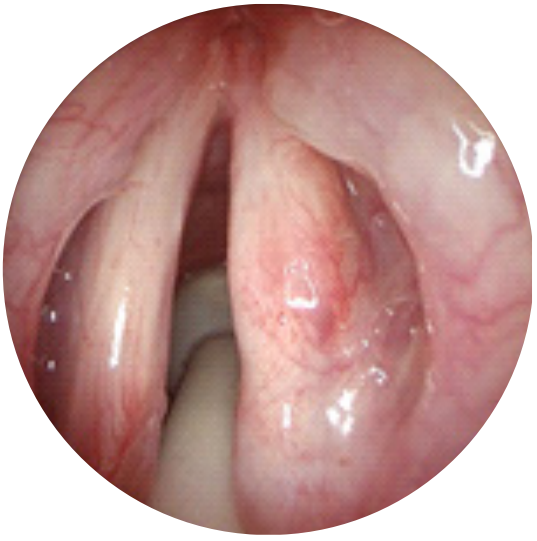


**Figure 3**
Narrow band imaging (NBI) right after the third bevacizumab injection shows no papillomas.



by HPV and can obstruct the airway, leading to dysphonia, dyspnea, and stridor. Because of its recurrent nature, RRP often requires continuous treatment and follow-up to control the symptoms and prevent respiratory complications. Treatment usually involves multiple surgeries. Due to its high recurrence rate, adjuvant therapies are being investigated to improve the treatment effectiveness and patients' quality of life. Adjuvant therapeutic

**Figure 4**
Laryngeal endoscopy after the third bevacizumab injection shows vocal folds with an intact and normal epithelium.



options for patients with severe RRP have significantly expanded over the past decade.

Avastin® is a medication approved by the Portuguese Medicines and Health Products Authority (Infarmed) for the treatment of colorectal cancer, and it is not approved for laryngeal use[15]. Considering that vascularization is a critical factor in determining the rate of papilloma recurrence, we hypothesized that Avastin® could be used for the treatment of RRP. In medicine, the off-label use of medications is legal and often necessary in clinical practice, provided that the physicians are well informed about the product and base this use on solid scientific and medical evidence.

The use of intralaryngeal bevacizumab for RRP was first reported in 2009[17]. Subsequently, Zeitels et al.[17–18] published a pilot study of ten patients undergoing a 5-injection protocol with bevacizumab that demonstrated decreased recurrence rate and improved vocal function. These findings led to the prospective analysis of 20 adult patients in whom the contralateral vocal fold was used as a control[19] and the protocol consisted of three bevacizumab injections given at an interval of six weeks. The results showed reduced disease burden on the side treated with bevacizumab.

A systemic review published in 2022[12] reported that the intralesional administration of bevacizumab prolonged the time between surgeries from 2–6 weeks to 4–12 weeks and decreased the Derkay score from 3–23 to 0–12 points. The review confirmed that intralesional bevacizumab administration is a safe procedure with few side effects, unlike systemic administration, which is associated with proteinuria, epistaxis, hemoptysis, hypertension, headache, thrombocytopenia, hyperthyroidism, dysgeusia, and early menopause. It concluded that both forms of administration are effective therapeutic options for patients with severe RRP, highlighting the need for additional prospective studies and clinical trials.

Interferon, antiviral agents (acyclovir, cidofovir), retinoids, and HPV vaccination[7] are additional therapeutic options for patients with severe RRP. Currently, the most used antiviral drug is cidofovir, a cytosine analog[7]. This medication can be administered intravenously, nebulized, or injected intralesionally. A recent prospective study linked its intralesional administration with partial or complete regression of papillomas and reduced number of surgical procedures per year[19]. It has the advantage of maintaining plasma levels below those associated with toxicity, without causing local side effects[7,19]. The long-term risks associated with intralesional cidofovir are not well known, but there is theoretical risk of malignant transformation[19].

Another therapeutic option for patients with RRP is the HPV vaccine. The quadrivalent vaccine is indicated for preventing cervical and anogenital cancers and pre-neoplastic lesions associated with HPV subtypes 6, 11, 16, and 18[7]. A 2023 meta-analysis[20] on its effectiveness in patients with RRP concluded that vaccination can be considered a beneficial adjuvant therapy in patients with severe RRP.

The development of a protocol for intralesional bevacizumab injections in patients with severe RRP has several important limitations. One of the key issues is the lack of large-scale studies, as the absence of randomized controlled clinical trials limits the generalization of outcomes and formulation of definitive conclusions. Additionally, the long-term safety of intralesional bevacizumab, particularly in the pediatric population, remains uncertain due to the potential for extended exposure to the medication. Furthermore, the limited understanding of its etiology and factors influencing disease progression hinder predictions regarding the effectiveness of new therapeutic interventions.

The development of clinical protocols is crucial for standardizing the clinical and therapeutic approach to severe RRP and enabling the comparison of outcomes across different centers.

## Conclusion

The proposed protocol, based on numerous international studies and trials, establishes a standardized approach for the intralesional administration of bevacizumab in patients with severe RRP. This protocol aims to improve the organization and standardization of clinical and therapeutic strategies for managing severe RRP, a chronic condition that, although rare in developed countries, poses a significant economic burden on the healthcare system.

### Acknowledgments

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We also thank Dr. Craig Derkay for promptly providing the system used for patients with RRP and for authorizing its translation into European Portuguese.

## Appendixes

### INFORMED CONSENT FOR INTRALESIONAL INJECTION OF AVASTIN® (BEVACIZUMAB)

**Indications**

Recurrent respiratory papillomatosis (RRP): this condition primarily affects the larynx, being characterized by the growth of recurrent, exophytic papilloma-like lesions caused by the human papillomavirus (HPV). Various surgical techniques and adjuvant therapies have been described to reduce recurrence and manage potential sequelae.

**Possible benefits and off-label use**

Currently, RRP has no curative treatment. Standard treatment consists of removing exophytic lesions with cold steel excision, microdebridement, or laser vaporization. Laser treatment combines precise excision with effective hemostasis, particularly for friable lesions. The objective is to remove lesions while preserving the normal laryngeal anatomy. Despite surgery, the virus remains latent. Adjuvant therapies, such as bevacizumab, may extend the disease-free period.

Bevacizumab is an antiangiogenic medication that inhibits the action of vascular endothelial growth factor (VEGF), thus preventing the formation of new blood vessels and stimulating the existing vessels to regress.

It has proven benefits as a postoperative adjuvant therapy for RRP in experimental and investigational settings, and is used in Portugal and other countries. Although Avastin® (Bevacizumab) is authorized by the Portuguese Medicines and Health Products Authority (Infarmed) for the treatment of colorectal cancer, it is not approved for laryngeal use. However, due to the crucial role of vascularization in papilloma recurrence, its use in RRP has been considered.

In medicine, the off-label use of medications is legal and often necessary in clinical practice, provided that physicians are well informed about the product and base this use on solid scientific and medical evidence.

**Possible limitations**

The goal of treatment is to prolong the disease-free period. However, the disease can relapse and progress.

**Medication administration**

The procedure will be conducted in the operating room under aseptic conditions typical for laryngeal surgery. First, general anesthesia, orotracheal intubation, and suspension microlaryngoscopy will be performed to remove the papillomas. Then, the medication will be injected intralesionally into the larynx. The injection must be repeated every three weeks for a total of three procedures. The procedure may be performed by another otolaryngologist or trained intern.

**Alternative treatments**

Surgery is the gold standard for RRP. You may choose to refuse treatment, knowing that untreated disease could lead to difficult breathing and need for emergency tracheostomy. Other off-label adjuvant treatments include cidofovir, interferon, indole-3-carbinol, and Gardasil®.

**Systemic complications**

When administered to patients with metastatic colorectal cancer, Avastin® can cause serious adverse events, including gastrointestinal perforation and thromboembolism, which, in exceptional situations, may be life-threatening. The dose for these patients is 40 times higher and administered more frequently and directly into the vein. Additionally, these patients are often weakened by advanced cancer. For intralesional use, no serious adverse events have been reported, although the long-term effects are not well established.

**Laryngeal complications**

The disease may not improve or even worsen. Potential complications may reduce airway patency, and require additional procedures, including tracheostomy. Although allergic reactions are not documented with intralesional use, they can occur, such as

itching, rash, shortness of breath, and death. These reactions may occur in people who already have allergies to other medications, foods, or the environment (dust or pollen). Inform your doctor of any known allergies.

Potential laryngeal complications include:

- Complications related to anesthesia.
- Bleeding.
- Infection.
- Persistence or worsening of functional disorders or the initial pathology.
- Respiratory or swallowing changes.
- Temporary or permanent voice changes.
- Dental injury or loss.
- Death.

**Patient responsibilities**

- Seek emergency care if you experience any of the following symptoms: increasing pain which is unresponsive to medication, fever, new-onset hoarseness, or difficulty in breathing.
- Attend all scheduled outpatient appointments and tests.
- Although serious complications affecting other organs are rare and may be related to the underlying condition rather than the injection, contact your physician or seek emergency care if you experience abdominal pain with vomiting or bleeding, chest pain, severe headache, difficulty speaking, or inability to move one side of your body or limbs. Notify your otolaryngologist as soon as possible.
- Inform your otolaryngologist if you need to undergo any other type of surgery.

**Informed consent**

Name: _____

Medical record number: _____

I declare that I have read or been read and understood the explanation about my condition and the risks, benefits, alternatives, and limitations of the surgical procedure to be performed.

- I understand that Avastin® (bevacizumab) is approved for the treatment of metastatic colorectal cancer and that its use in the larynx is considered off-label. Nevertheless, I consent to be treated with this medication.

- I authorize the administration of intralesional injections of Avastin® (bevacizumab) at regular intervals. This consent remains valid until I decide to withdraw it or if my condition changes to the point of significantly affecting the risks and benefits of the treatment.

Patient's signature

_____

Physician's signature

_____

Matosinhos

Date,

____/____/_____

**Clinical and laryngoscopic assessment scale in patients with RRP (laryngeal, adapted)**

## A. Clinical Score

**1. Describe the patient voice today:**

Normal _____ (0), abnormal _____ (1), Aphonic _____ (2)

**2. Describe the patient's stridor today:**

Absent _____ (0), Present with effort _____ (1), Present at rest _____ (2)

**3. Describe the urgency of today's procedure**

Scheduled _____ (0), Elective _____ (1), Urgent _____ (2), Emergent _____ (3)

**4. Describe the patient's level of breathing difficulty:**

None _____ (0), Mild _____ (1), Moderate _____ (2), Severe _____ (3), Extreme _____ (4)

**Total Clinical Score:** _____

## B. Anatomical Score

**For each location, rate: 0=None, 1=Superficial injury, 2=Vegetative injury, 3=Bulky injury**

**1. Larynx**

Epiglottis _____ , Lingual Surface _____ , Laryngeal Surface _____

Aryepiglottic Fold _____ Right _____ , Left _____

Ventricular Band _____ Right _____ , Left _____

Vocal Chords _____ Right _____ , Left _____

Arytenoid _____ Right _____ , Left _____

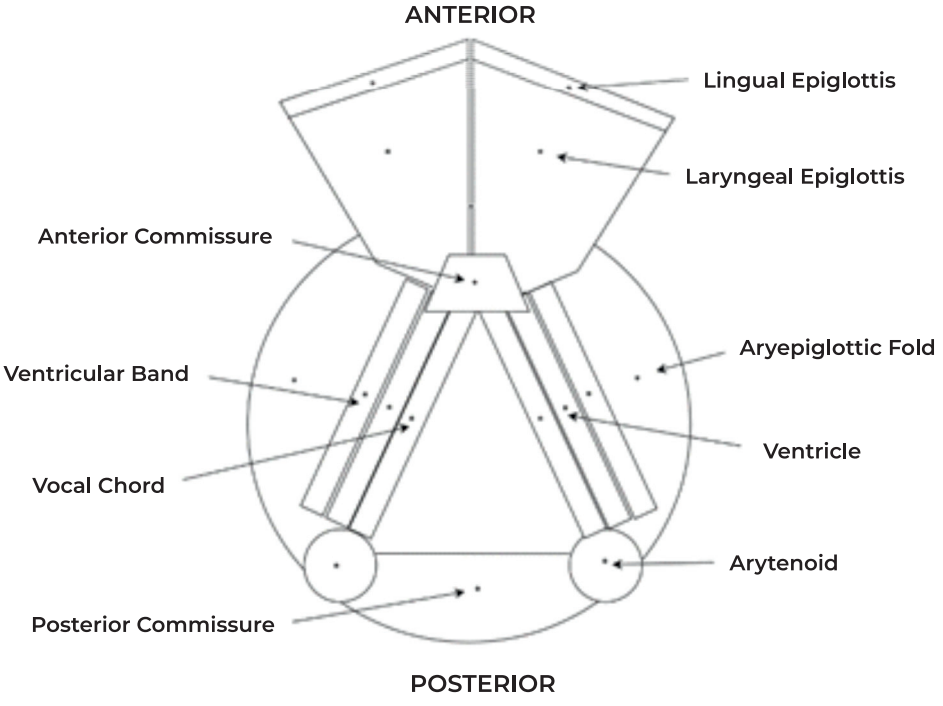
Anterior Commissure _____

Posterior Commissure _____

Subglottis _____

**Total Anatomical Score:** _____

**C. Total Score = Total Clinical Score + Total Anatomical Score =** _____



## Conflict of Interests

The authors declare that they have no conflict of interest regarding this article.

## Data Confidentiality

The authors declare that they followed the protocols of their work in publishing patient data.

## Human and animal protection

The authors declare that the procedures followed are in accordance with the regulations established by the directors of the Commission for Clinical Research and Ethics and in accordance with the Declaration of Helsinki of the World Medical Association.

## Privacy policy, informed consent and Ethics committee authorization

All the processed data were based in published reports that fulfilled privacy policy and ethical considerations.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## Scientific data availability

There are no publicly available datasets related to this work.

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