

A photograph of a female doctor with glasses and a white lab coat, holding a stethoscope to the chest of a baby. The baby is being held by a woman and is looking directly at the camera with a surprised expression. The background is a blurred clinical setting.

Pediatric Special Case

13 y/o female with hoarseness for 7 years

Presenter R1 吳仲升
Supervisor VS 溫明勳

Patient's profile

- Name: 賴o廷
- Chart num:
- Age: 13y/o
- Gender: female
- BH:148cm BW:39kg BMI: 17.8 kg/m²
- A(-)B(-)C(-)

Personal history

- Important medical history
- Systemic disease: HTN(-), DM(-), CAD(-),asthma(-),HBV(-),HCV(-), other: nil
- Drug allergy: NKA
- Long-term medications: nil
- Operation history: nil

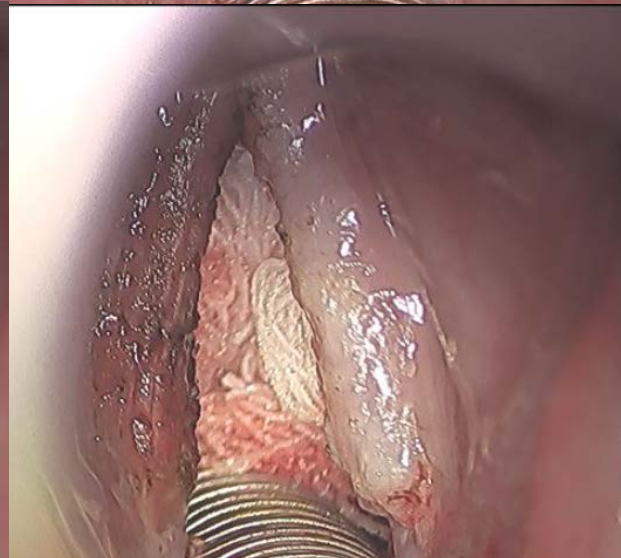
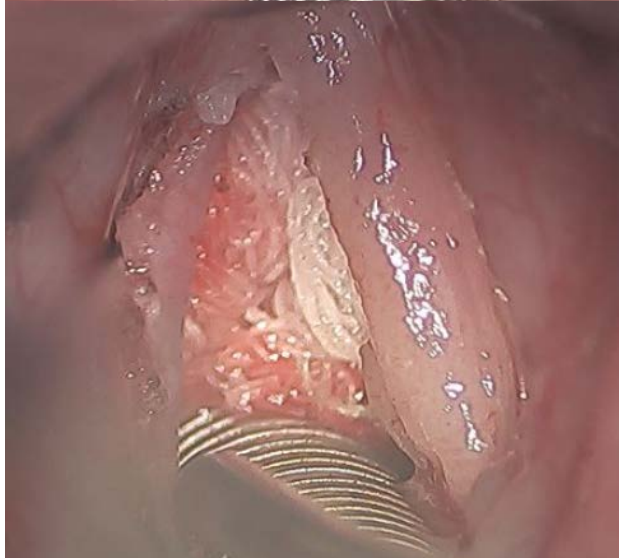
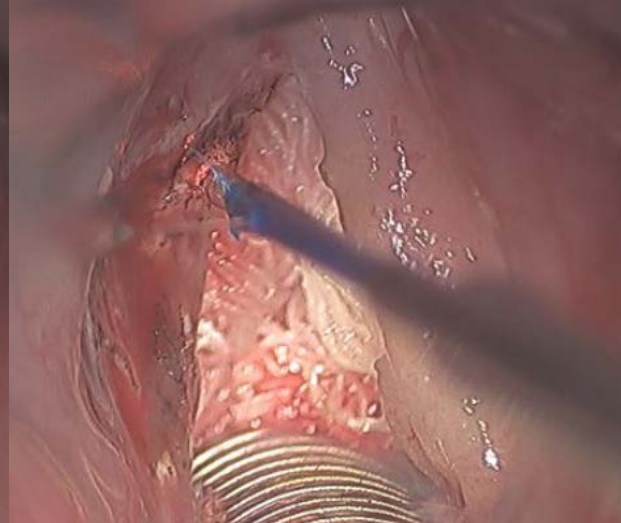
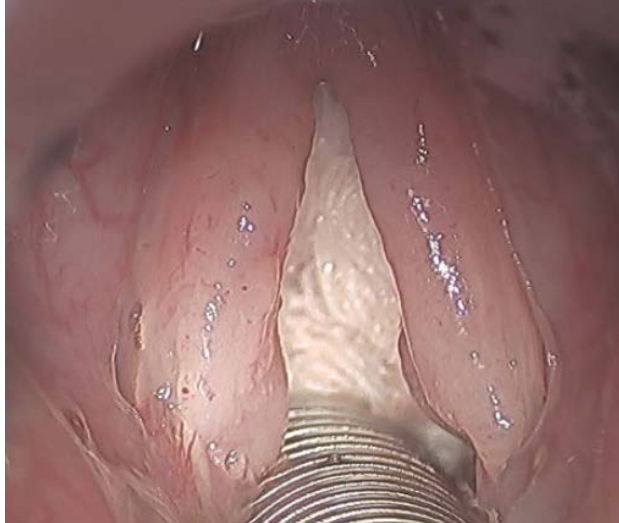
Present Illness

- 2024-07-22 OPD
 - from Chia-Yi
 - hoarseness for 7 years
 - ever visit 成大hospital, biopsy: papilloma
 - lumping sensation(-), dry throat(+)
- scope: bil. VF papillomatous change, right vocal process granuloma/papilloma
- Encourage HPV vaccine (at school)
- Inform LMS + KTP (one VF only), inform uncertain voice recovery



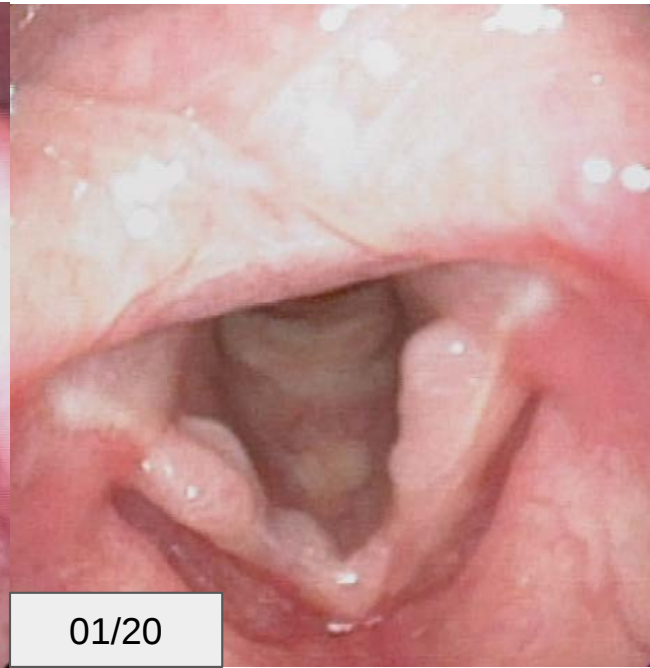
Present Illness

- LMS+KTP on 2024-07-30
- photocoagulation and removal of left VF papilloma, right vocal process granuloma/papilloma was done with KTP laser (7W 35ms 1516P)
- superficial photocoagulation was done at right ant. VF papilloma raw surface
- patho: Larynx, vocal fold, bilateral, laryngomicrosurgery, squamous papillomatosis



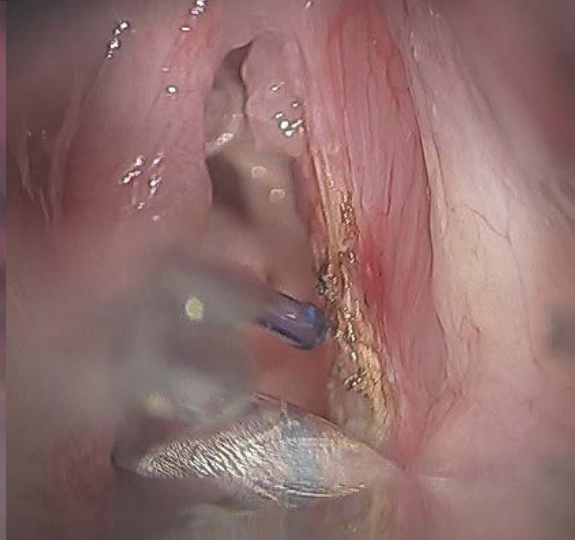
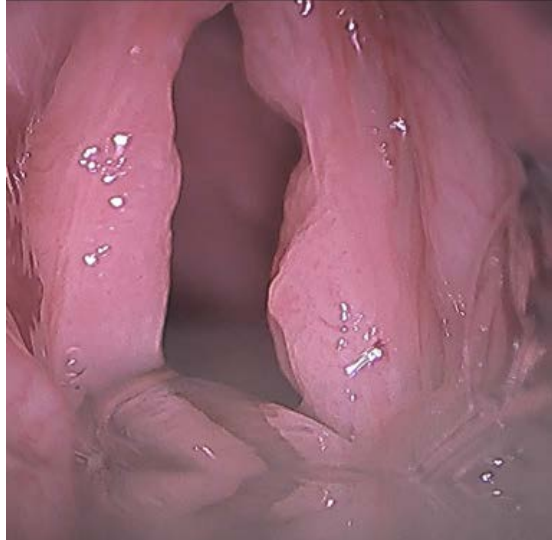
Present Illness

- ENT OPD 2024-08-26
 - explanation 2nd stage OP on R VF during winter vacation
 - pt will receive HPV vaccine at school



Present Illness

- LMS-KTP on 2025-01-21
- photocoagulation and removal of left and right VF (raw surface and residual stump of papilloma) was done with KTP laser (8W 50ms 1335P)
- superficial photocoagulation was done at anterior commissure papilloma raw surface





Diagnosis

- Juvenile Onset Recurrent Respiratory Papillomatosis, s/p LMS+KTP on 2024-07-30, 2025-01-21

Discussion

- RRP(Recurrent Respiratory Papillomatosis)
- Jo-RRP vs. Ao-RRP
- Treatment for RRP

HEAD AND NECK SECTION

Recurrent laryngeal papillomatosis: multimodal therapeutic strategies. Literature review and multicentre retrospective study

*La papillomatosi laringea ricorrente: strategie terapeutiche multimodali.
Revisione della letteratura e analisi retrospettiva multicentrica*

Giulia Bertino¹, Fabio Pedretti¹, Simone Mauramati¹, Marta Filauro², Alberto Vallin^{2,3}, Francesco Mora^{2,3}, Erika Crosetti⁴, Giovanni Succo^{5,6}, Giorgio Peretti^{2,3}, Marco Benazzo¹

¹ Department of Otolaryngology Head and Neck Surgery, University of Pavia, IRCCS Policlinico San Matteo Foundation, Pavia, Italy;

² Unit of Otolaryngology Head and Neck Surgery, IRCCS Policlinico San Martino Hospital, Genoa, Italy; ³ DISC, University of Genoa, Italy; ⁴ ENT Unit, Oncology Department, University of Turin, Orbassano (Turin), Italy; ⁵ ENT Department, San Giovanni Bosco Hospital, Turin, Italy; ⁶ Oncology Department, University of Turin, Turin, Italy

IF: 2.1, Q2

Department of Otolaryngology Head and Neck Surgery, University of Pavia

Bertino, G., Pedretti, F., Mauramati, S., Filauro, M., Vallin, A., Mora, F., ... & Benazzo, M. (2023). Recurrent laryngeal papillomatosis: multimodal therapeutic strategies. Literature review and multicentre retrospective study. Acta Otorhinolaryngologica Italica, 43(2 Suppl 1), S111.

RRP Introduction

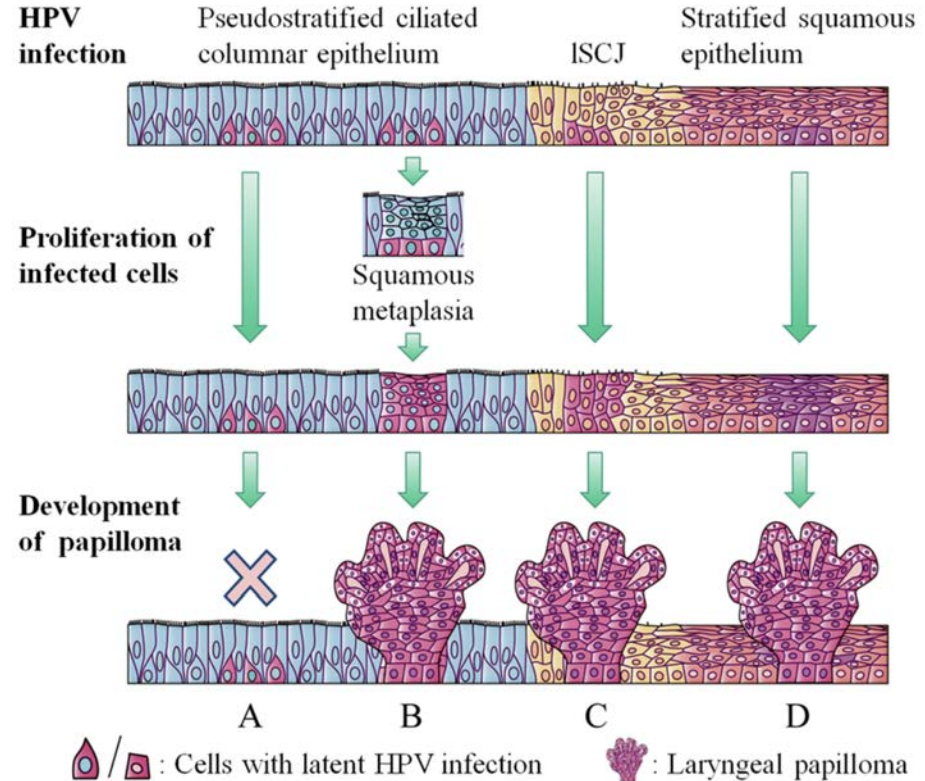
- RRP = HPV-induced papillomatosis of the aerodigestive tract
- 90% caused by HPV types 6 & 11; types 16/18 rarely, more malignant
- Common site: larynx; can affect entire airway
- Bimodal distribution: children (Jo-RRP) and adults (Ao-RRP)
- Jo-RRP: aggressive, recurrent, airway spread risk
- Ao-RRP: localized, mainly glottic, presents with dysphonia

Epidemiology & Risk Factors

- Jo-RRP prevalence: ~4.3/100,000
 - Jo-RRP onset: <12 yrs, 75% <5 yrs, no sex predilection
 - Early onset (<3 yrs) → ↑ recurrence & airway spread
- Ao-RRP: 1.8/100,000
 - onset: 20–40 yrs, more common in males
 - Surgery frequency: ~5.1/year initially, 0.1/year 15 years
 - anterior glottis most frequent site
- HPV-11 linked to more aggressive disease (lower tract spread)

HPV Pathogenesis

- HPV targets **basal epithelial cells**, especially junctions (**squamous-ciliary junction**)
- Laryngeal papillomas grow on stratified epithelium with **fibrovascular core**
- Repeated surgery → **squamous metaplasia** → more infection sites
- Impaired HPV-specific T-cell responses, abnormal IL-10, IFN- γ expression, TAP-1 downregulation—especially **Jo-RRP**→severe clinical course.



Transmission Dynamics

- Reservoir: **anogenital tract**; vertical & sexual transmission
- **Jo-RRP**: vertical transmission during vaginal delivery
 - HPV prevalence: 26.8% (females 14–59), ~45% (ages 20–24)
 - Not all neonates develop disease → host & viral factors critical
 - Risk factors: **primiparity, prolonged labor, maternal HPV warts**
 - Immunity, **local traumas** (intubation, extra-oesophageal reflux)
 - Possible transplacental transmission
- **Ao-RRP**: **sexually transmitted**; linked to ↑ sexual activity

Clinical Features

- Jo-RRP: hoarseness, stridor, misdiagnosed as **asthma/laryngitis**
 - Delayed diagnosis (~**1 year** after symptom onset)
 - Common onset: **2–4 years**; 75% diagnosed before age 5
 - **30%** have **extralaryngeal spread** (oral cavity, trachea, etc.)
- Ao-RRP: **dysphonia** common; dyspnea rare if managed
- Disease severity varies widely among individuals

Feature	Jo-RRP	Ao-RRP
Onset Age	<12 years (often <5 y/o)	>12 years (peak: 20–40 y/o)
Aggressiveness	Higher, multisite, more surgeries	Lower, often glottic, localized
Transmission	Vertical (birth canal)	Sexual, or latent reactivation
Recurrence	Frequent	Less frequent

Clinical Course & Severity

- Some patients require frequent surgeries; others remit spontaneously
- No universal severity grading; **Derkay Score** most used
 - Derkay includes **anatomical** and **clinical sub-scores**
- Persistent dysphonia impacts social, emotional, work life
- Risk of **airway spread** ↑ with **tracheotomy** or **prolonged intubation**
- Most aggressive form = **pulmonary involvement** (rare, **HPV-11** linked)

STAGING ASSESSMENT FOR RECURRENT LARYNGEAL PAPILLOMATOSIS

PATIENT INITIALS: _____ DATE OF SURGERY _____ SURGEON _____

PATIENT ID # _____ INSTITUTION _____

1. How long since the last papilloma surgery? _____ days, ---weeks, --months,

---years, ____ don't know,

---this is the child's first surgery

2. Counting today's surgery, how many papilloma surgeries in the past 12 months? -

3. Describe the patient's voice today:

4. Describe the patient's stridor today:

5. Describe the urgency of today's intervention:

6. Describe today's level of respiratory distress:

Total score for questions 3-6:--

normal--(0), abnormal--(1), aphonic--(2)

absent (0), present with activity--(1), present at rest--(2)

scheduled--(0), elective--(1), urgent (2), emergent(3)

none--(0), mild--(1), Mod--(2), severe--(3), extreme--(4)

..

FOR EACH SITE, SCORE AS: 0= NONE, 1 = SURFACE LESION, 2=RAISED LESION, 3=BULKY LESION

LARYNX:

Epiglottis

Aryepiglottic folds: Right--- Left---

False vocal cords: Right-- Left---

True vocal cords: Right--- Left _____

Arytenoids: Right ____ Left _____

Anterior commissure-----

Posterior commissure-----

Subglottis - _____

Lingual surface _____ Laryngeal surface _____

TRACHEA

Upper one-third _____

Middle one-third _____

Lower one-third _____

Bronchi: Right--- Left ____

Tracheotomy stoma _____

OTHER:

Nose----

Palate----

Pharynx----

Esophagus ____

Lungs-----

Other _____

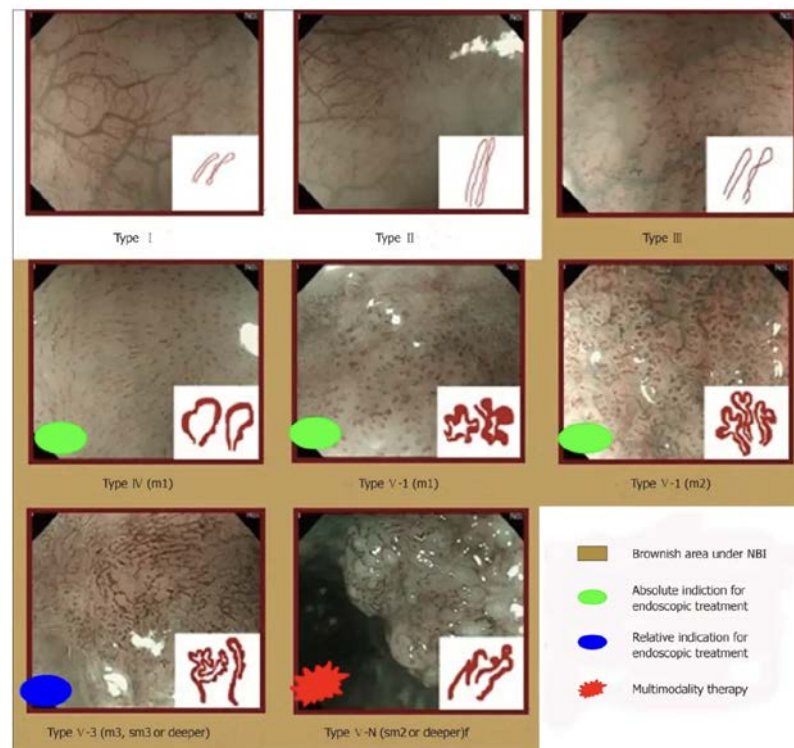
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TOTAL SCORE ALL SITES: _____ TOTAL CLINICAL SCORE:-----

Diagnosis

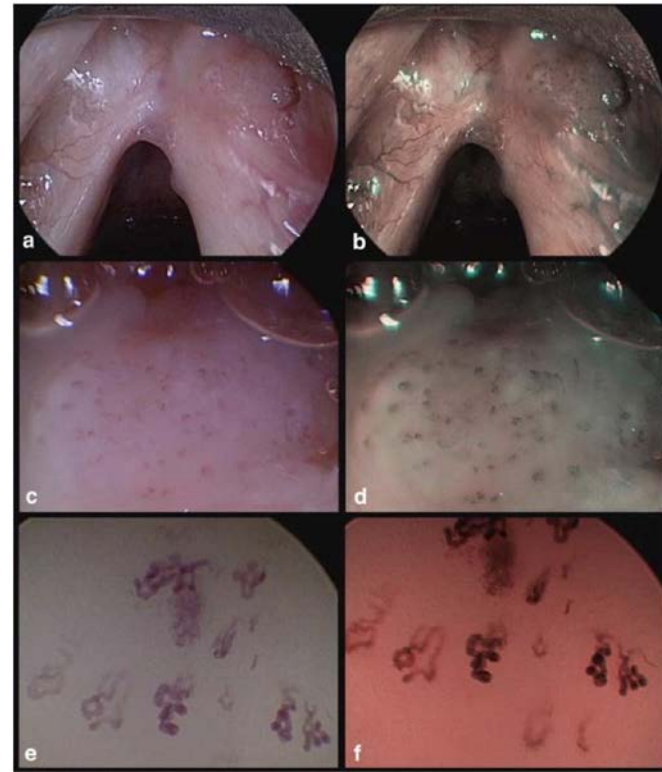
- First-line: **fiberoptic laryngoscopy** under **white light**
- Confirmation: **histology** from biopsy
- New tools: **NBI**, autofluorescence, OCT, contact endoscopy
 - **NBI** helps differentiate benign vs malignant lesions
 - NBI limitations: papillomatosis mimics cancer (IPCL V pattern)
 - Expertise and equipment quality critical for accuracy

NBI Classification

- Ni et al. **IPCL patterns** (I–III benign, IV–V malignant)
- Papillomas may show IPCL-V → mimic carcinoma
 - ELS classification: **longitudinal vessels** = benign
 - IPCL **angle: wide (RRP) vs narrow (cancer)**
- Diagnostic **accuracy of NBI >95%** in expert hands
- Useful in diagnosis, surgery planning, and follow-up
- Enhances detection of **multifocal subclinical lesions**



- ELS classification: longitudinal vessels = benign
- IPCL angle: wide (RRP) vs narrow-angle turning points (cancer)



Treatment Principles

- Mainstay: **surgical resection** (CO₂ laser, cold steel, microdebrider)
- Aim: preserve voice and airway, **avoid scarring or webbing**
- **Avoid aggressive single-stage** resections in commissures
- **Small residual** lesions treated **office-based** after healing
- **Jo-RRP** often requires **staged or repeated surgeries**
- Each surgery risks inducing **more squamous metaplasia**

Airway Management

- Tracheotomy reserved for **severe airway compromise**
- Tracheotomy ↑ risk of **distal viral spread**
- New options: **Tritube with Evone system** → avoids tracheotomy
 - Allows safe intubation in narrowed airway situations
- **Double-stage** resection preferred for **commissural** involvement
- Balance between complete resection and function preservation

Office-Based Laser & Microdebridors

- Office-based laser (**KTP**/PDL): effective, reduces hospitalizations
 - target **haemoglobin**(highly vascularised), less fibrosis, scar formation
 - **True-Blue laser**: newer option for in-office laryngeal use
 - Indicated for **small lesions, compliant adult patients**
 - Not suitable for **children or bulky lesions**
- **Microdebrider**: quick, no thermal damage; often **used with laser**
- Allows **staged treatment**: general anesthesia first, then office procedures
- Enhances **voice-related quality of life** and follow-up adherence

Adjuvant Therapy – Interferon & Cidofovir

- **Consider adjuvant therapy if >4 surgeries/year or lower tract spread**
- **IFN- α** : first immunomodulatory agent (1980s), now rarely used
 - Pegylated IFN: fewer side effects, but still limited by toxicity

Adjuvant Therapy – Interferon & Cidofovir

- **Cidofovir**: antiviral **DNA analog**, used **intralesionally (off-label)**
 - Systemic cidofovir = nephrotoxicity, neutropenia risks
 - Mixed evidence: some studies show benefit, **Cochrane review found no superiority vs placebo**
 - Manufacturer issued safety warning (2011); limited availability outside USA (nephrotoxicity, neutropenia, oncogenicity, fatalities)
 - Large multicenter review(ELS, 11 countries, 16 hospital, 275 Cidofovir: **no clear increased malignancy risk from cidofovir**)

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Bevacizumab in RRP

- **Bevacizumab**: anti-VEGF agent; **reduces papilloma vascularity**
 - VEGF-A overexpressed in RRP → rationale for therapy
- Admin routes:
 - **IV** for deep, non-accessible or bronchopulmonary lesions
 - **Intralesional** for glottic papillomas (7.5–12.5 mg at 25 mg/mL)
- Often combined with KTP laser for synergistic effects
- Safe in both adults and children with proper dosing
- Shows promise in **recurrence control and disease stabilization**

Table II. Summary of bevacizumab in reviewed clinical trials.

Study	Year	Number of patients	Median age (years)	Pre-treat mean Derkay score	Pre-treat surgical rate (surgery per year)	Post-treat mean Derkay score	Post-treat surgical rate (surgery per year)	HPV type	Dose of bevacizumab (mg)	Results and conclusions
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Rogers et al. ⁴⁵	2013	10	8	19	8	13	4	HPV 11	2.5 mg/ml (0.5 ml)	Bevacizumab may indeed limit the number of surgical procedures required per year and increase the duration between procedures in patients with aggressive RRP, while simultaneously improving voice outcomes
		7 Jo 3 Ao						HPV 6		
Best et al. ⁴⁶	2012	43	48							Higher doses of bevacizumab are relatively safe in adult patients
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Zeitels et al. ²⁴	2011	20	Range (18-60)						7.5-12.5 mg	3 complete responses, 16 partial responses with less disease in treated vocal fold, 1 more disease in the treated vocal fold. Treating RRP by coupling the antiangiogenetic agent bevacizumab with KTP laser photoangiolytic is synergistic

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Rogers et al. ⁴⁵	2013	10	8	19	8	13	4	HPV 11	2.5 mg/ml (0.5 ml)	Bevacizumab may indeed limit the number of surgical procedures required per year and increase the duration between procedures in patients with aggressive RRP, while simultaneously improving voice outcomes
		7 Jo 3 Ao						HPV 6		
Best et al. ⁴⁶	2012	43	48							Higher doses of bevacizumab are relatively safe in adult patients
		43 Ao								
Zeitels et al. ²⁴	2011	20	Range (18-60)						7.5-12.5 mg	3 complete responses, 16 partial responses with less disease in treated vocal fold, 1 more disease in the treated vocal fold. Treating RRP by coupling the antiangiogenetic agent bevacizumab with KTP laser photoangiolytic is synergistic

Jo: Juvenile onset; Ao: Adult onset.

Table II. Summary of bevacizumab in reviewed clinical trials.

Study	Year	Number of patients	Median age (years)	Pre-treat mean Derkay score	Pre-treat surgical rate (surgery per year)	Post-treat mean Derkay score	Post-treat surgical rate (surgery per year)	HPV type	Dose of bevacizumab (mg)	Results and conclusions
Albanedo Terrazas et al. ²⁸	2022	6	20	9	1	1.5	0		25 mg/ml	Decrease of Derkay scores but no statistical significance
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Other Adjuvant Options & HPV Vaccine

- Experimental therapies: **celecoxib, indole-3-carbinol, anti-reflux, PD-1 inhibitors, gefitinib**
 - No large trials yet confirm efficacy
- **HPV Vaccine (Gardasil):** protects against HPV 6, 11, 16, 18
 - Used therapeutically in RRP patients to **extend time between surgeries**
 - Improves **anti-HPV antibody titers** in low seropositive patients
 - **Prophylactic vaccination may reduce Jo-RRP via vertical transmission**
- Routine vaccination in both sexes remains key prevention strategy

Therapeutic Use of the Human Papillomavirus Vaccine on Recurrent Respiratory Papillomatosis: A Systematic Review and Meta-Analysis

Tine Rosenberg,^{1,2} Bahareh B. Philipsen,^{1,2} Camilla S. Mehlum,^{1,2} Anne-Kirstine Dyrvig,³ Sonja Wehberg,⁴ Magdalena Chirilă,⁵ and Christian Godballe^{1,2}

- Systematic review and meta-analysis, **n=11, 133 patients**
- Surgeries **per month** significantly decreased **post-vaccination (0.35 > 0.06)**.
- Intersurgical interval : **7.02 > 34.45 months**.

IF 5.0, Q1

Rosenberg, T., Philipsen, B. B., Mehlum, C. S., Dyrvig, A. K., Wehberg, S., Chirilă, M., & Godballe, C. (2019). Therapeutic use of the human papillomavirus vaccine on recurrent respiratory papillomatosis: a systematic review and meta-analysis. *The Journal of Infectious Diseases*, 219(7), 1016-1025.

Take Home Message

- RRP remains **incurable, surgically-managed, immune-modulated**
- Main goals: **airway patency, voice preservation, quality of life**
- Surgical trauma can worsen disease; avoid excessive resections
- **Tracheotomy** ↑ **distal spread risk** → delay or avoid if possible
- Consider **adjuvant therapy** if **>4 surgeries/year** or lower tract spread
- **Office-based treatments** reduce burden, improve follow-up adherence
- Future research: **HPV-immunity interaction, vaccine efficacy, targeted immunotherapies**

Back to out patient

- GA surgery with debrider + KTP laser > further office base KTP laser
- HPV Vaccine
- Consider Bevacizumab intralesional use
- Cidofovir: off-label use

A photograph of a female doctor with glasses and a white lab coat, using a stethoscope to examine a baby. The baby is being held by a woman and is looking directly at the camera with a surprised expression. The background is a soft-focus clinical setting.

Pediatric Special Case

13 y/o female with hoarseness for 7 years

Presenter R1 吳仲升
Supervisor VS 溫明勳