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: 1613996
- 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

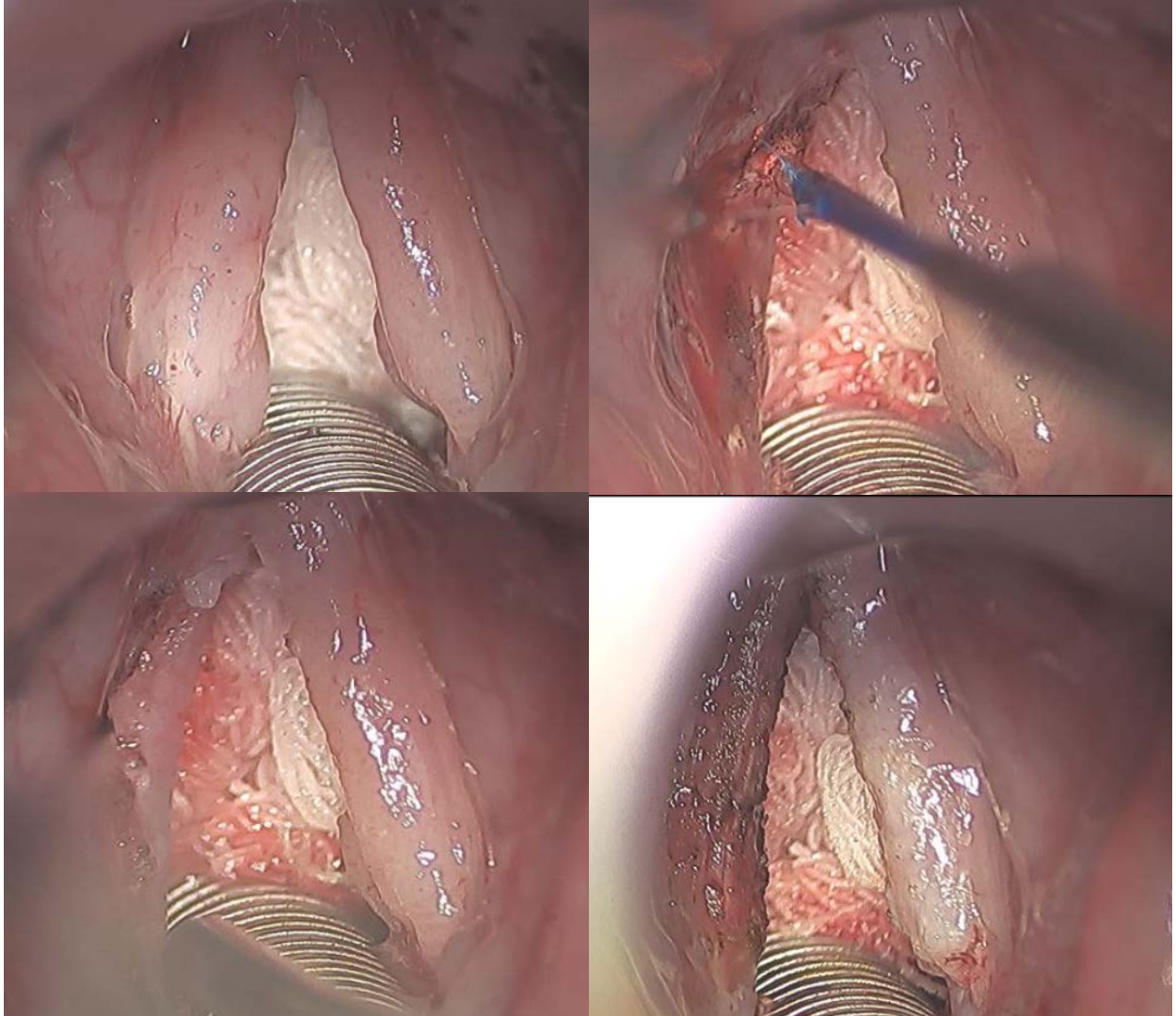
Present Illness

- 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)
- Infrom LMS + KTP (one VF only), inform uncertain voice recovery

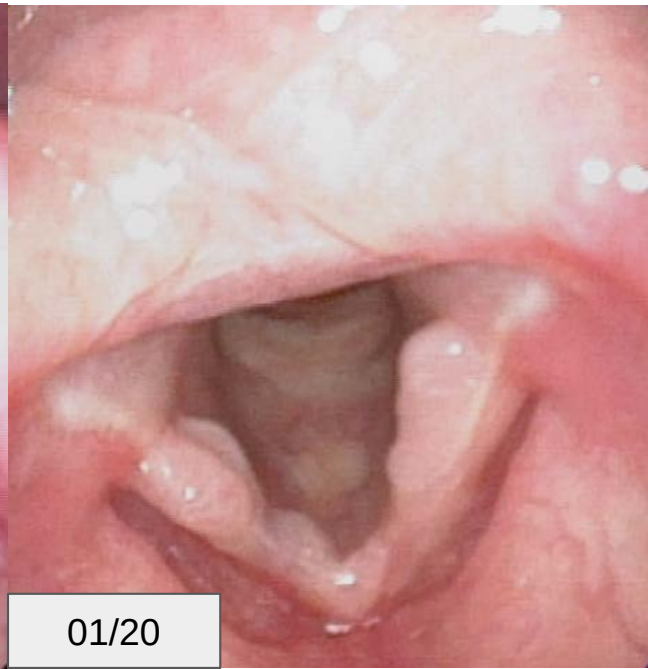
Present Illness

- 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

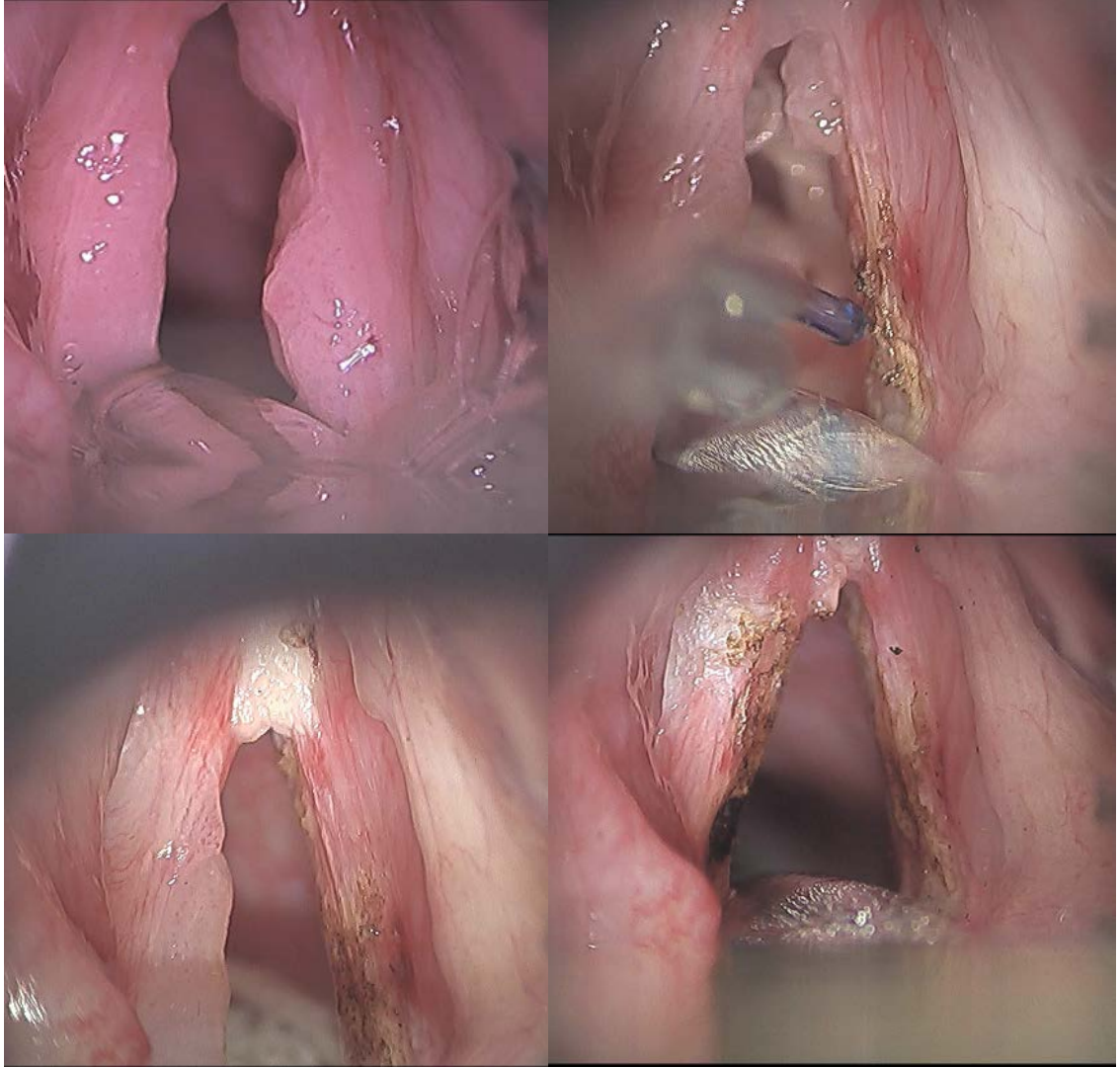


Present Illness

- 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




01/23

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

ACTA OTORHINOLARYNGOLOGICA ITALICA 2023;43(SUPPL.1):S111-S122; doi: 10.14639/0392-100X-suppl.1-43-2023-14

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 Bertino[1], Fabio Pedretti[1], Simone Mauramati[1], Marta Filauro[2], Alberto Vallin[2,3], Francesco Mora[2,3], Erika Crosetti[4], Giovanni Succo[5,6], Giorgio Peretti[2,3], Marco Benazzo[1]

[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

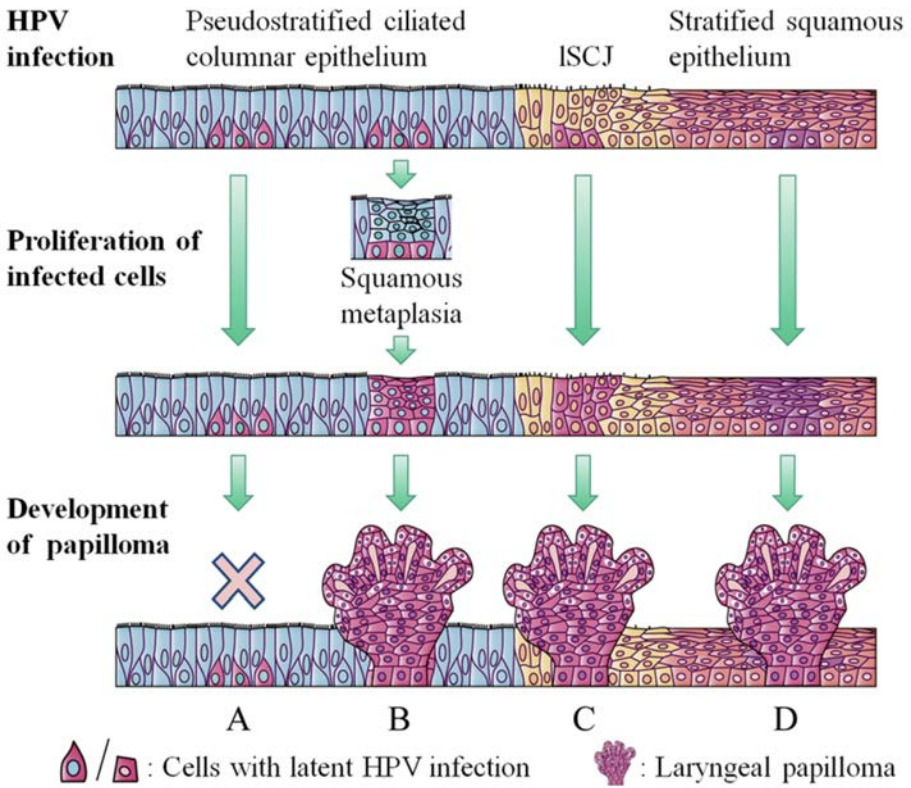
- RRP = HPV-induced papillomatosis of the aerodigestive tract
- 90% caused by HPV types 6 & 11;
  types 16/18 rarely, more malignant
- Common site: **larynx**; can affect entire airway
- Bimodal distribution: children (Jo-RRP) and adults (Ao-RRP)
- Jo-RRP: aggressive, recurrent, airway spread risk
- 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--(O), abnormal--(1), aphonic--(2)
absent (O), present with activity--(1), present at rest-(2)
scheduled-_(O),elective--(1), urgent__(2),emergent(3)
none_-(O), mild_-(l), Mod--(2), severe--(3), extreme--(4)

FOR EACH SITE, SCORE AS: O= 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 _________

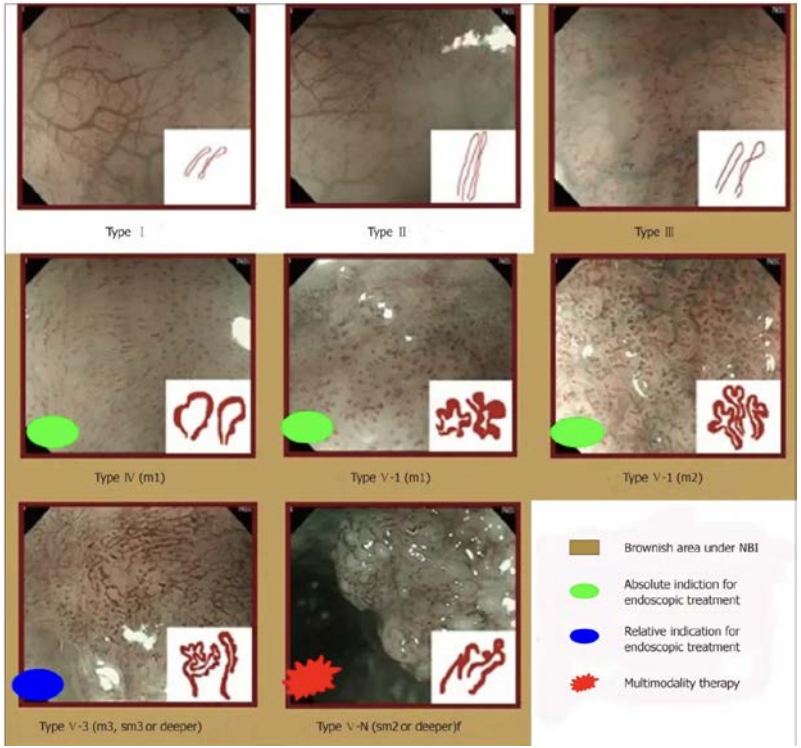
TOTAL SCORE ALL SITES: ________ TOTAL CLINICAL SCORE:-----

Diagnosis

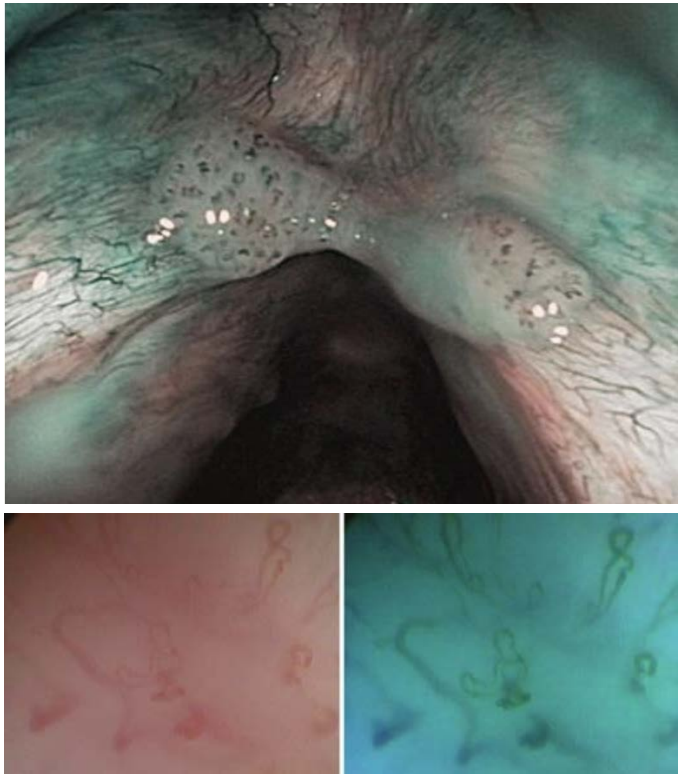
- First-line: **fibreoptic laryngoscopy** under white light
- Confirmation: **histology** from biopsy
- New tools: NBI, autofluorescence, OCT, contact endoscopy
  - **NBI** helps differentiate benign vs malignant lesions
  - NBI limitations: papillomatosis mimics cancer (IPCL V pattern)
  - Expertise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

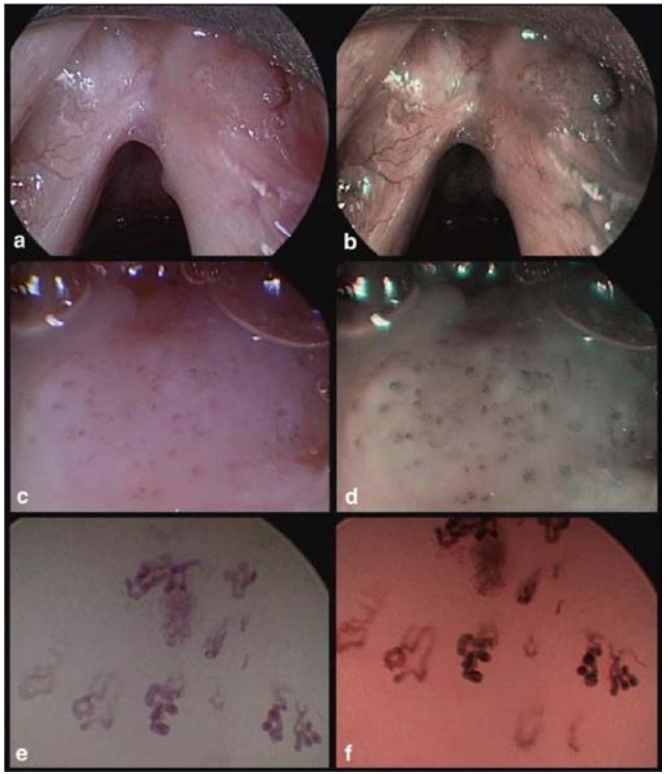
NBI Classification

- 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)





Arens, C., Piazza, C., Andrea, M., Dikkers, F. G., Tjon Pian Gi, R. E., Voigt-Zimmermann, S., & Peretti, G. (2016). Proposal for a descriptive guideline of vascular changes in lesions of the vocal folds by the committee on endoscopic laryngeal imaging of the European Laryngological Society. European Archives of Oto-Rhino-Laryngology, 273, 1207-1214.

Treatment Principles

- Mainstay: **surgical resection** (CO_2 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 & Microdebriders

- 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**

Table I. Summary of cidofovir in reviewed clinical trials.

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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 7 Jo 3 Ao	8	19	8	13	4	HPV 11 HPV 6	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
Best et al. [46]	2012	43 43 Ao	48							Higher doses of bevacizumab are relatively safe in adult patients
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 photoangiolysis is synergistic

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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
		2 Jo								
		4 Ao								
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						HPV 6		
		3 Ao								
Best et al. [46]	2012	43	48							Higher doses of bevacizumab are relatively safe in adult patients
		43 Ao								
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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

The Journal of Infectious Diseases
REVIEW ARTICLE

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

Pediatric Special Case

13 y/o female with hoarseness for 7 years

Presenter R1吳仲升
Supervisor VS 溫明勳