Otolaryngology journal reading

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The Laryngoscope

ORIGINAL REPORT

Dysplasia and Carcinoma in Recurrent Respiratory Papillomatosis Patients Older Than 45 Years

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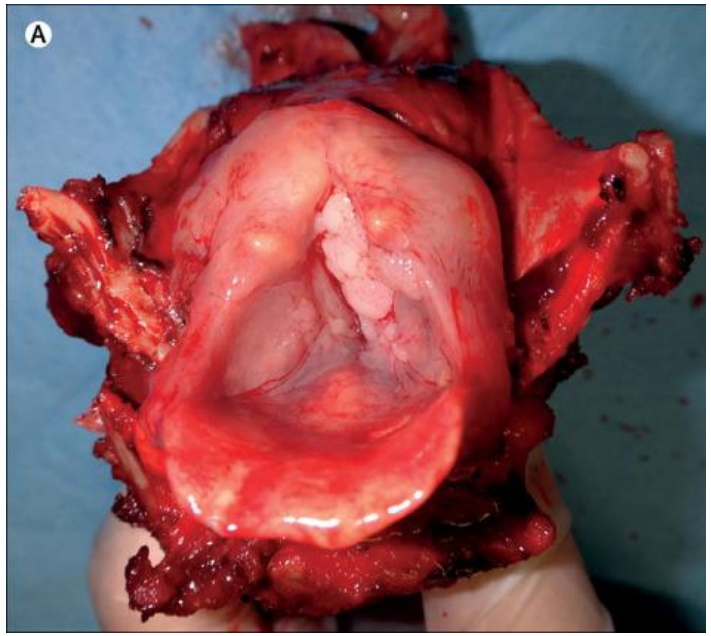
Recurrent respiratory papillomatosis (RRP)

Most common benign epithelial tumor of the larynx

Most common location Laryngoscope, 128:138-143, 2018.

- 1st : **true vocal folds and ventricles**
- 2nd : false vocal cords
- rarely extend to extra-laryngeal locations



Dysphonia, dyspnea as main symptoms

- more severe in children, rapid growth leads to airway obstruction

Etiology and Epidemiology

HPV mediated

- > 90% with low-risk HPV
- HPV-6 (64%), HPV-11 (19%)

Bimodal age distribution of disease onset

- Juvenile-onset (JoRRP): onset < 18 y/o, median : 3-4 y/o
- Adult-onset (AoRRP): onset > 18 y/o, median: 34-38 y/o, M:F ≈ 3:2

Disease nature

Dysplasia reported in 10%–50%

- WHO 2017: low-grade/high-grade(moderate to carcinoma in situ)

Risk factors for potential SCC malignant transformation

- HPV-11: in some studies
- **HPV-negative** PLoS One 2014;9:e99114

Rates of malignant transformation

- Pediatric < 1%
- Adult 3%–7%

Disease nature

Recurrent nature

- multiple surgical procedure
- decreased quality of life
- high health care cost

Aim

Risk factor for dysplasia and malignant transformation

- **varies over studies**
- previous study with small sample size
- age, gender, tobacco, OP frequency, smoking, advanced age of onset

Goal

- identify **risk factors for dysplasia and malignant transformation**
- **> 45- year- old AORRP** population

Study design

Retrospective study

Inclusion criteria

- Newly diagnosed RRP
- > 45 y/o at diagnosis
- 2008/1/1 - 2022/12/31

▸total of 49 patients

▸average follow-up time of 100.1±47.3 months

Study design

Diagnostic process for RRP

- **laryngoscopy** initially
- **tracheobronchoscopy** routinely, office-based procedure or surgery
- **CXR/LDCT** for extra-laryngeal disease suspicious in bronchoscopy

Treatment of RRP

- **Gardasil vaccine at diagnosis**, 9 valent after 2014, at least 2 dose
- **Cidofovir, intralesional**

- dose of 30 mg (maximum: 3 mg/kg), injected after surgical excision

Outcomes

- Patient demographics
- Comorbid conditions
- Treatment history

Malignant transformation

- from 1st dysplasia to 1st invasive carcinoma report time

Statistical analyses

Continuous variables

- Two-tailed t-test with heteroscedastic distribution in Microsoft Excel
- Patient characteristics: mean, median, maximum, minimum

Categorical variables

- Chi- squared analysis and Fisher exact test

Software: Microsoft Excel

TABLE 1 | Demographics and risk factors.

Total $n=49$	Dysplasia ($n=28$)	No dysplasia ($n=21$)	p-value	Malignant transformation ($n=7$)	No malignancy ($n=42$)	p-value
Degree of dysplasia[a]						
High	9 (32%)	0	n/a	5 (71%)	4 (10%)	**0.012**
Low	19 (68%)	0		2 (29%)	17 (40%)	
None	0	21	n/a	0 (0%)	21 (50%)	**<0.0001**
Malignancy	7 (25%)	0	**<0.05**	7 (100%)	0	n/a
HPV subtype						
Low-risk	4 (14%)	2 (9%)		1 (14%)	5 (12%)	
High-risk	1 (4%)	1 (5%)		1 (14%)	0	
No testing	23 (82%)	18 (86%)		5 (71%)	37 (88%)	
Age (mean) [range]	58.2 [45, 79]	59.3 [46, 80]	0.69	53.9 [45, 79]	59.5 [46, 80]	0.28
Gender						
Male	24 (86%)	16 (76%)	0.39	6 (86%)	34 (81%)	0.76
Female	4 (14%)	5 (24%)		1 (14%)	8 (19%)	
Nonbinary/other	0	0		0	0	
Smoking						
Current/former	20 (71%)	9 (43%)	**0.044**	5 (71%)	24 (57%)	0.48
Never	8 (29%)	12 (57%)		2 (29%)	18 (43%)	
Pack-years (mean)	19.23	6.52	**0.018**	20.43	12.78	0.40

Dysplasia ▲
- Smoking hx
- Mean pack-years

No difference
- Age
- Gender
- Alcohol use
- Laryngoesophageal reflux
- Diabetes
- Immunosuppression
- Vaccination rates
- Surgery times/frequency

TABLE 1 | Demographics and risk factors.

Total $n=49$	Dysplasia ($n=28$)	No dysplasia ($n=21$)	p-value	Malignant transformation ($n=7$)	No malignancy ($n=42$)	p-value
None	13 (46%)	12 (57%)		3 (43%)	22 (52%)	
Vaccination status						
Gardasil	9 (32%)	6 (29%)	0.79	0	15 (36%)	0.08
Unvaccinated	19 (68%)	15 (71%)		7 (100%)[b]	27 (64%)	
Non-gardasil						
Adjuvant therapy						
Cidofovir	7 (25%)	10 (48%)	0.13	0	18 (43%)	**0.04**
Bevacizumab	2 (7%)	0	0.50	0	2 (5%)	1.0
Both	6 (21%)	0	**0.031**	2 (29%)	4 (9%)	0.20
None	13 (46%)	11 (52%)	0.78	5 (71%)	18 (43%)	0.23
Laryngopharyngeal reflux	19 (67.8%)	16 (76%)	0.55	6 (86%)	29 (69%)	0.37
Diabetes	6 (21%)	5 (24%)	0.84	0 (0%)	11 (26%)	0.32
Immunosuppression	4 (14.2%)	1 (5%)	0.28	1 (14%)	4 (10%)	0.70
Average total surgeries	7.29	5.10	0.09	5.71	6.59	0.52
Average surgeries per year	2.40	1.76	0.14	1.88	2.16	0.66

[a]Indicates WHO path grade prior to 2017 revision that removed moderate dysplasia as a diagnosis.
[b]One patient was vaccinated after laryngeal cancer developed status post hemilaryngectomy, then continued to develop RRP.

Trend towards unvaccinated group

Malignant transformation

- Cidofovir usage

No difference

- Age
- Gender
- Alcohol use
- Laryngoesophageal reflux
- Diabetes
- Immunosuppression
- Vaccination rates
- Surgery times/frequency
- Smoking hx
- Mean pack-years

TABLE 2 | Dysplasia to carcinoma.

	Dysplasia to carcinoma (days)	Age (years)	Grade of dysplasia	Smoking history	Gender	Gardasil vaccination status
Subject 1	1190	79	High	Former	Male	Unvaccinated
Subject 2	779	60	High	Never	Male	Unvaccinated
Subject 3	1136	49	High	Former	Male	Unvaccinated
Subject 4	1379	45	Low	Former	Female	Unvaccinated
Subject 5	733	48	High	Current	Male	Unvaccinated
Subject 6	2370	50	High	Former	Male	Unvaccinated
Subject 7	310	46	Low	Never	Male	Unvaccinated
Mean (all)	1128.1	53.9				
Median	1136.0					
Mean (low-grade only, $n = 2$)	844.5	2.3 years				
Mean (high-grade only, $n = 5$)	1241.6	3.4 years				

High-grade more likely than low-grade dysplasia **to progress to carcinoma** (p = 0.012)

Average time from initial dysplasia to carcinoma diagnosis: **1128.1 days** (3.1 years)

Risk Factors

for dysplasia and malignant transformation in RRP

Median age of dysplasia in AORRP: 46 - 58.5 y/o

Older age: higher rates of dysplasia/malignancy

- 57% of dysplasia, 14% of malignancy in this study(> 45y/o onset)
- all malignancy with preceding dysplasia(7/28 = 25%)

This study vs. **previous RRP** cohorts vs. **non RRP(**laryngeal dysplasia**)**

- **Higher progression** rate: **25%** vs. 3% - 7% vs. **14%**
- **Higher dysplasia** rate: **57%** vs. 10% - 55% vs. **2% - 74%**
- **Lower mean time to malignant transformation**: 3.1 yrs vs. 5.8 yrs

Risk Factors

for dysplasia and malignant transformation in RRP

Dysplasia: smoking history, mean pack-years

Malignancy: not identified except high-grade dysplasia

- **No direct transformation** from normal cell noted
- **Underpowered** due to small sample size

Risk factors in previous studies, but not in this study

- advanced age at papilloma onset
- infection with high-risk HPV subtypes
- tobacco use
- laryngoesophageal reflux

Protective factors

Malignant transformation

- **Cidofovir** with significance
- **Gardasil vaccination** with trend, no significance

▸slow recurrence, diminish current papilloma burden in previous study

Study limitations

- **Small sample size**, especially malignancy
- **Retrospective** design
- **Incomplete EMR** of laryngoscopy(-2017)
  - Derkay scores
  - Extra-laryngeal disease
- **Limited HPV subtype** reporting

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:
   normal__(0), abnormal__(1), aphonic__(2)
4. Describe the patient's stridor today:
   absent__(0), present with activity__(1), present at rest__(2)
5. Describe the urgency of today's intervention:
   scheduled__(0),elective__(1),urgent__(2),emergent(3)
6. Describe today's level of respiratory distress:
   none__(0), mild__(1), Mod__(2), severe__(3), extreme__(4)

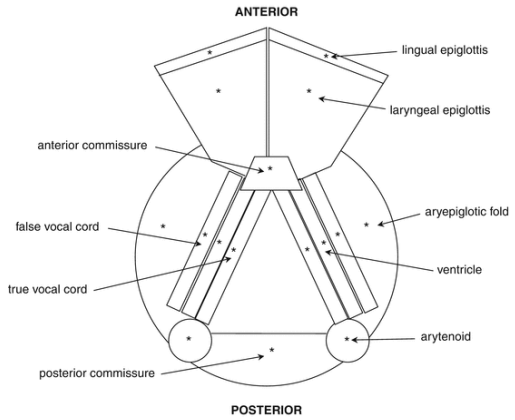
Total score for questions 3-6=_____

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

LARYNX:
- Epiglottis
  - Lingual surface____ Laryngeal surface_____
- Aryepiglottic folds: Right___ Left____
- False vocal cords: Right___ Left____
- True vocal cords: Right___ Left____
- Arytenoids: Right____ Left____
- Anterior commissure_____
- Posterior commissure_____
- Subglottis _____

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:_____

Conclusion

In AORRP >45 y/o

- higher dysplasia and malignancy than >18 y/o AORRP
- **All malignancy had previous dysplasia**
- 25% with dysplasia later developed malignancy
- **Close surveillance for dysplasia and malignancy**

Risk factors of dysplasia

- Smoking hx, mean pack-years

Further investigation

- **Gardasil vaccination protection** against malignancy in RRP

THE Laryngoscope
FOUNDED IN 1896

Original Report

Update on Gardasil Vaccination in Recurrent Respiratory Papillomatosis Patients Aged 45 or Older

Molly O. Meeker ✉, Ryan Ivancic, Brad deSilva, Laura A. Matrka

First published: 18 March 2025 | https://doi.org/10.1002/lary.32123 | Citations: 1

Adjuvant Gardasil **increases intersurgical interval** in RRP patients > 45 y/o

- ISI remain significant but effect wane with time
- timing of booster dose of Gardasil?

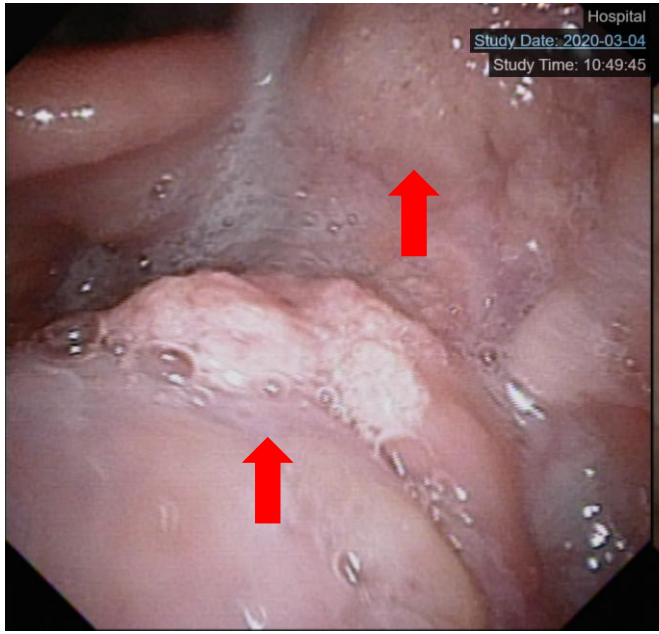
Case presentation

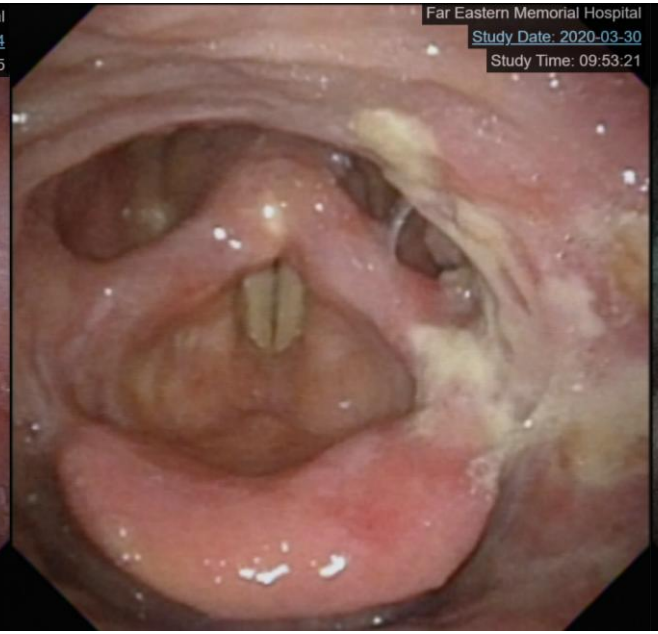
Brief report of a case of AORRP in FEMH

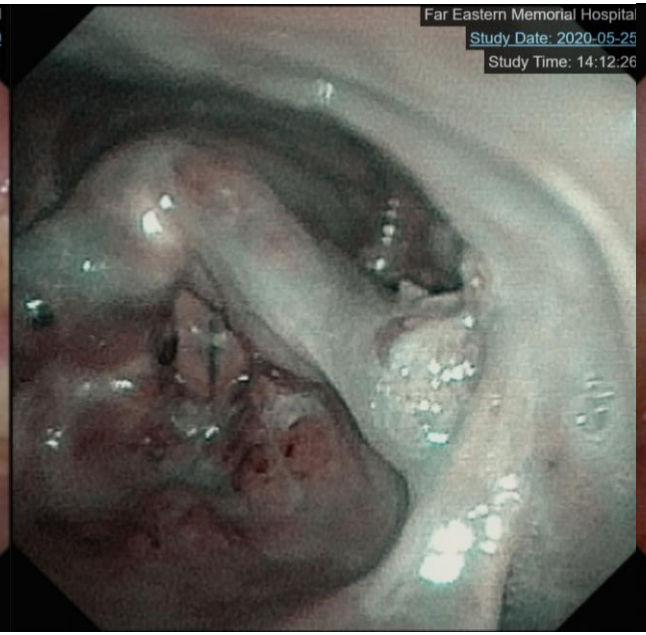
Patient profile

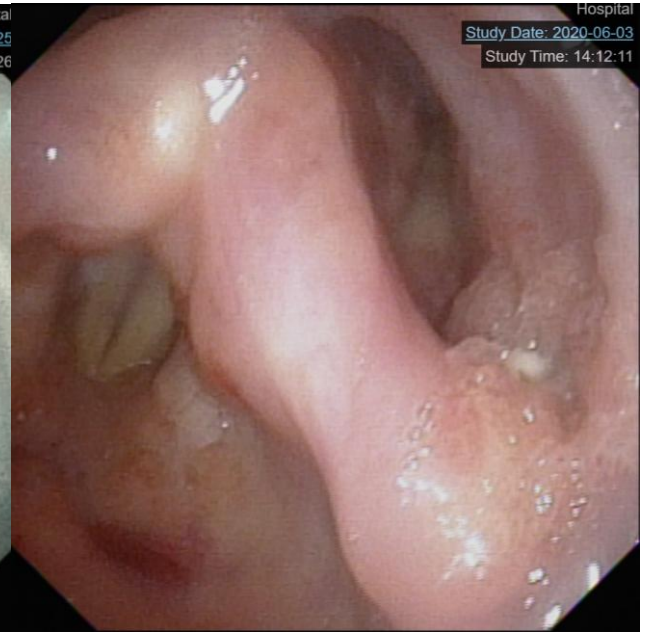
- 林O微 030612
- 68y/o female
- Initial presentation(2020/03): lumping sensation in throat for weeks
- Underlying dz: HTN, RA under sulfasalazine, plaquenil, QW MTX
- Initial diagnosis: **squamous papilloma with high-grade dysplasia**

Fiberscope



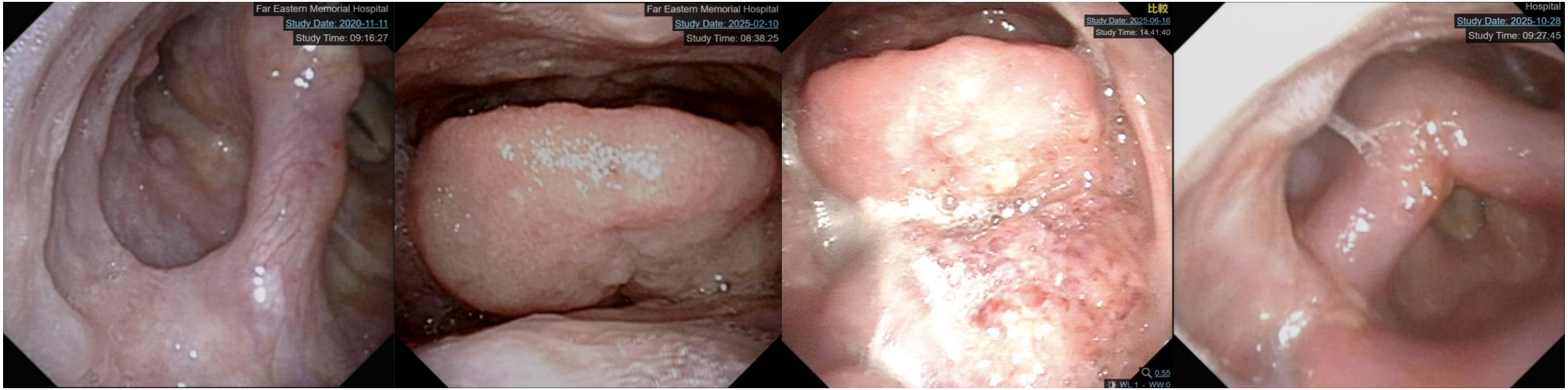






2020/03/04 → 2020/03/20 **Post-OP** → 2020/05/25 **recurrence** → 2020/06/03 **Pre- 2nd OP**

Fiberscope



2020/11/11 **recurrence** → 2025/02/10 **Pre-3rd OP** → 2025/06/16 **Pre-4th OP** → 2025/10/28 **Post-CCRT**

Pathology report

2020/03/18 Tongue base and hypopharynx, left, LMS

- squamous papilloma with **low-grade to high-grade dysplasia**

2020/06/04, 2025/02/18 Hypopharynx

- squamous papilloma with **mild to moderate dysplasia**

2025/06/17 Epiglottis, vallecula and tongue base, frozen biopsy

- **carcinoma in situ** at least, p16(-)

Patient profile

Course:

- **Surgery for symptoms relief and biopsy**
- s/p Gardasil 9(2024/1,4,8)
- **Close F/U with fiberscope** 1-3 times/yr per symptoms
- Probably malignant transformation to invasive carcinoma in 2025/06

Current diagnosis:

- Left tongue base SCC, p16(-), cT3N0 or laryngeal cancer, cT2N0(MRI)

- s/p CCRT with weekly cisplatin(7), 7000cGy/35Fx due on 2025/9/5