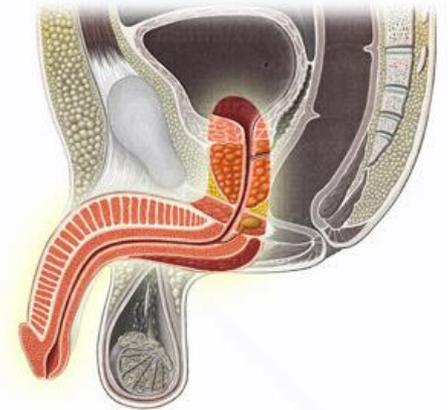
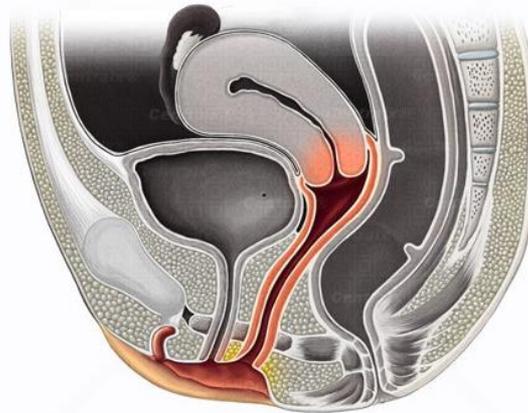
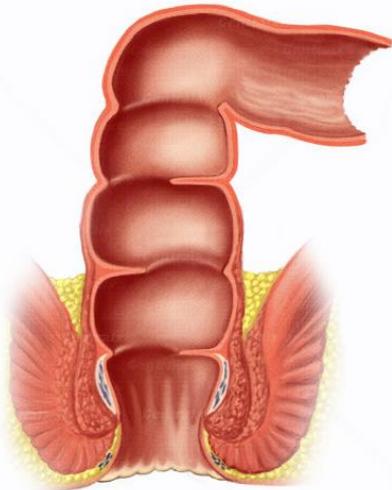
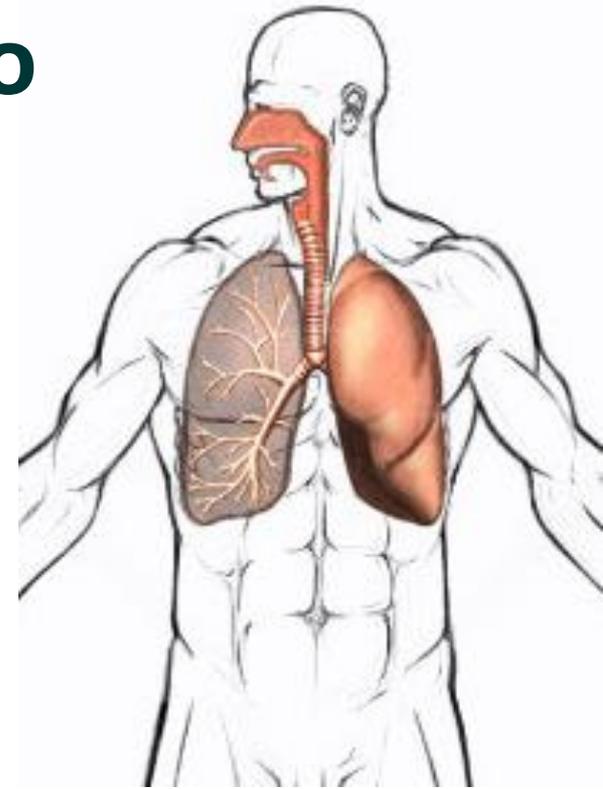
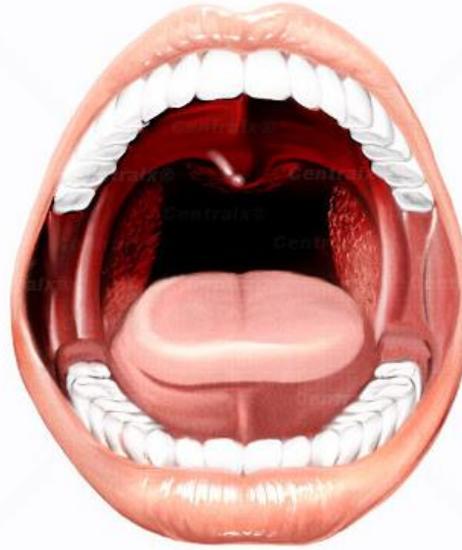


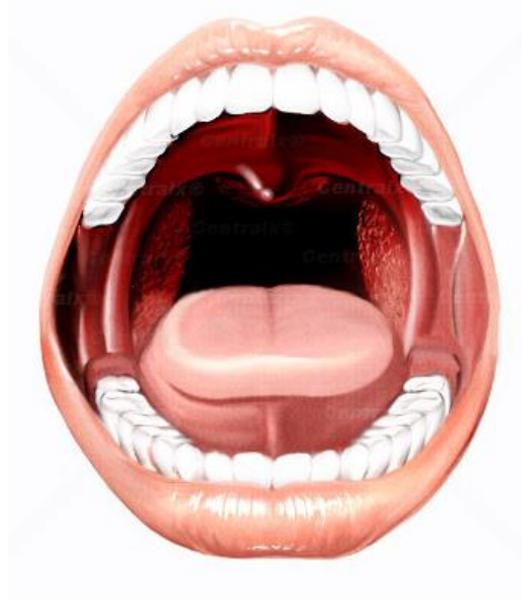
## HPV en epitelio escamoso: cérvix, orofaringe y ano

Eva Musulén

# Epitelio escamoso

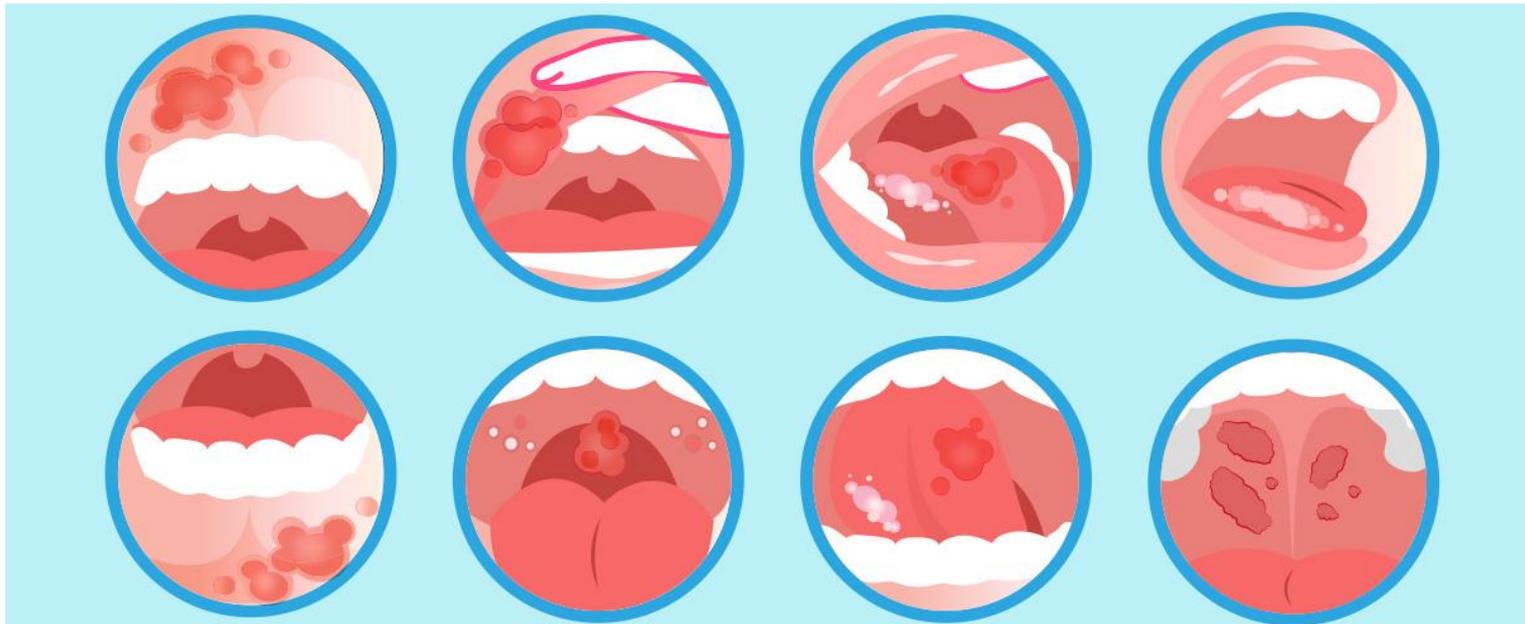


# HPV en orofaringe



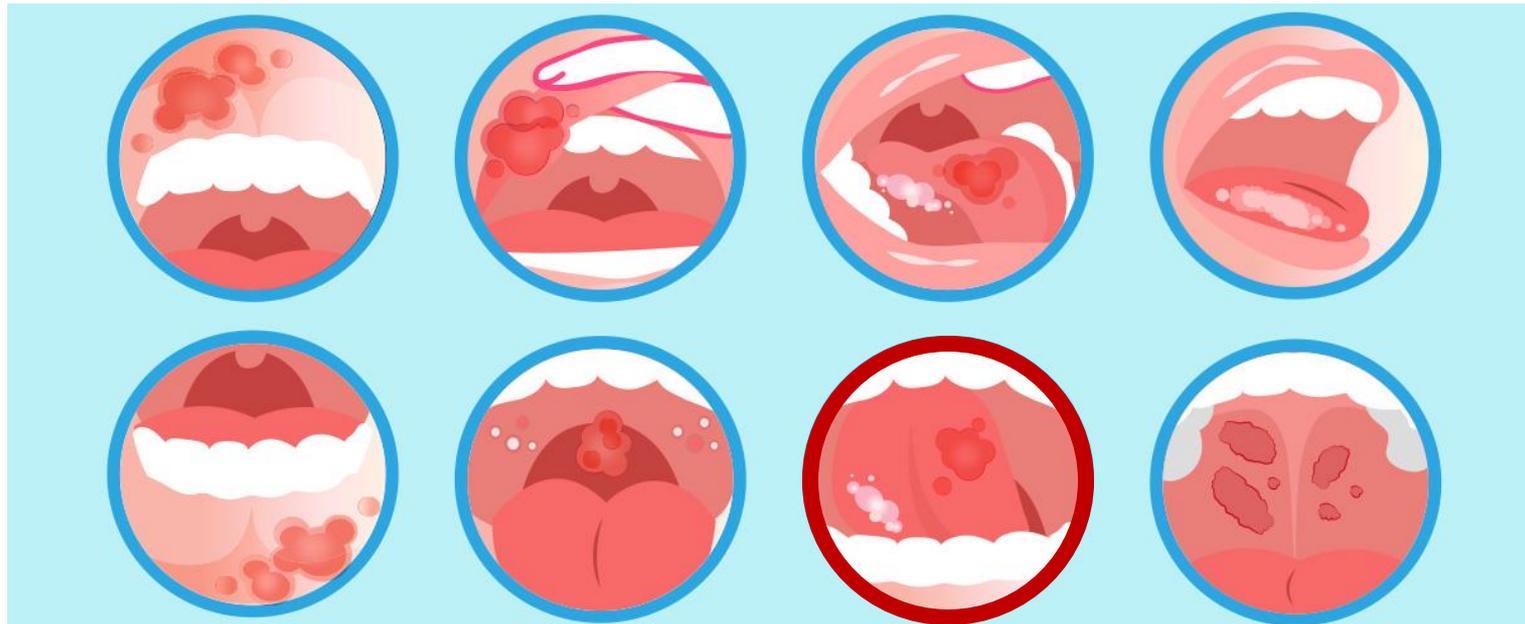
# Carcinoma escamoso de orofaringe

- Base de la lengua
- Amígdalas
- Pared faríngea posterior
- Paladar blando



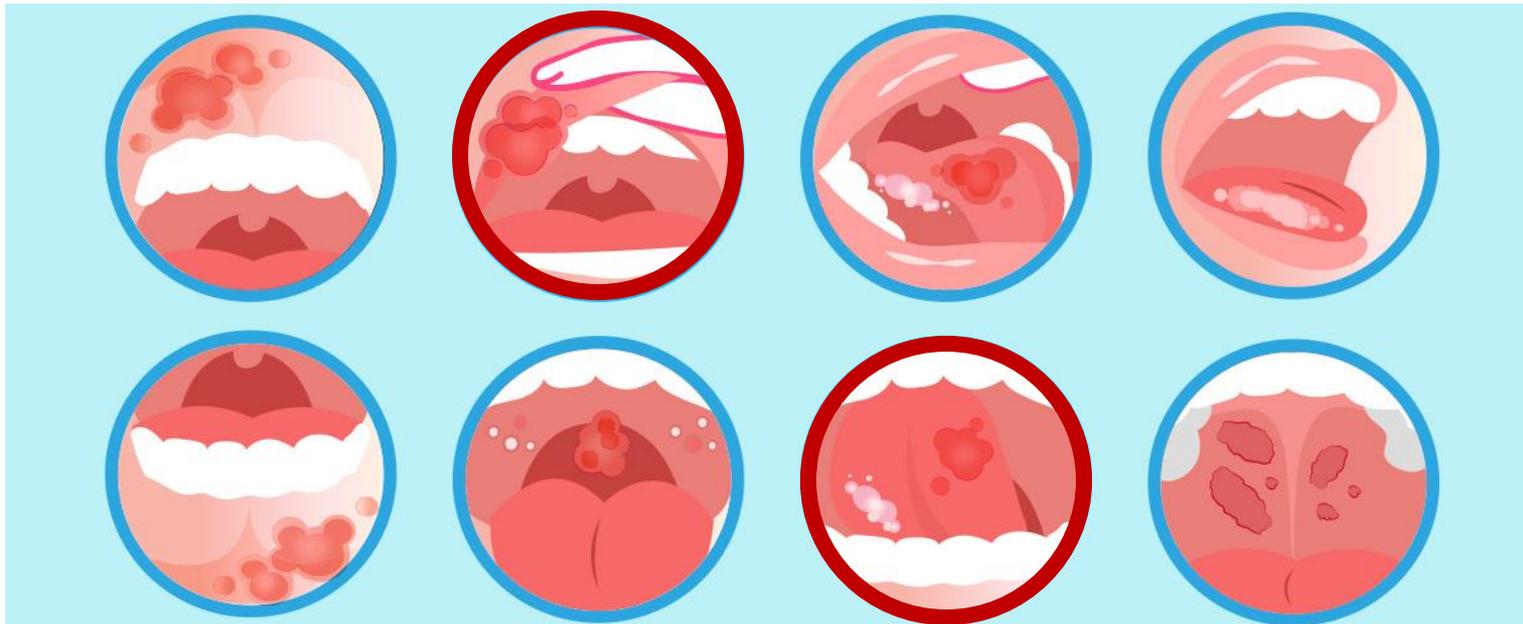
# Carcinoma escamoso de orofaringe

- Base de la lengua
- Amígdalas
- Pared faríngea posterior
- Paladar blando



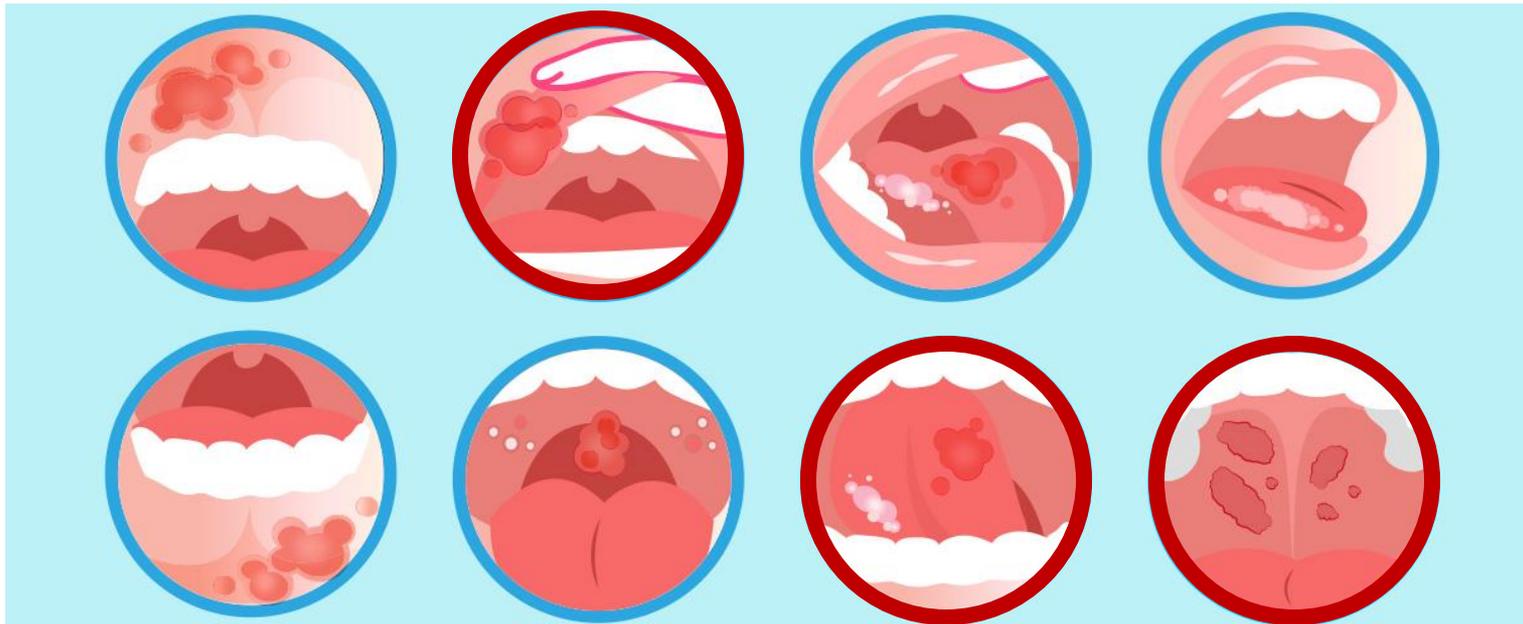
# Carcinoma escamoso de orofaringe

- Base de la lengua
- Amígdalas
- Pared faríngea posterior
- Paladar blando



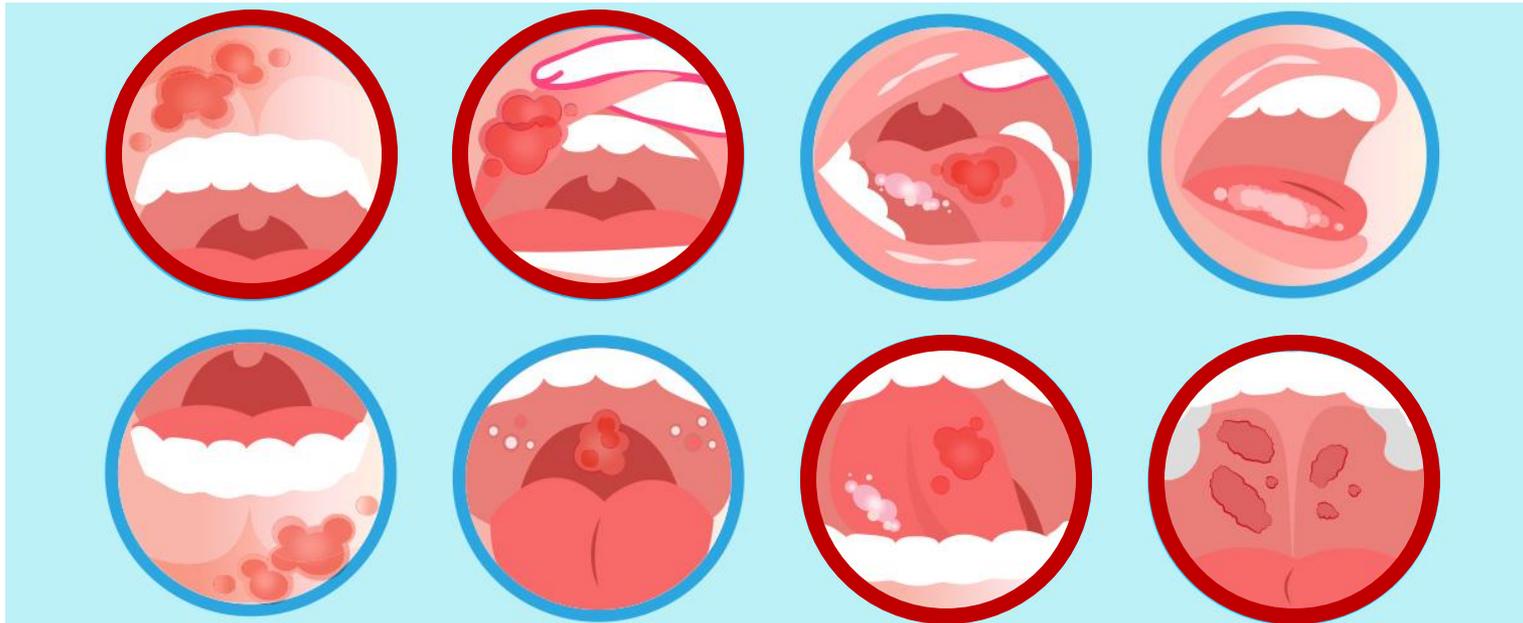
# Carcinoma escamoso de orofaringe

- Base de la lengua
- Amígdalas
- Pared faríngea posterior
- Paladar blando

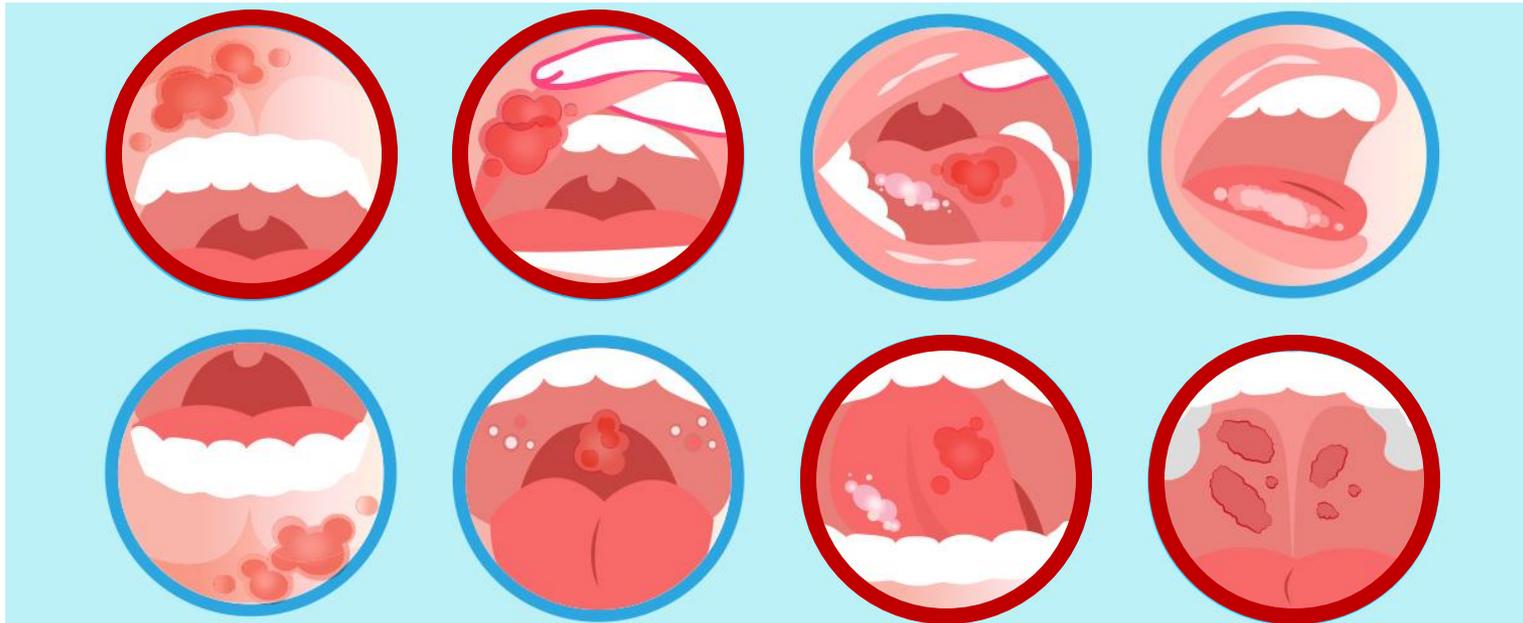


# Carcinoma escamoso de orofaringe

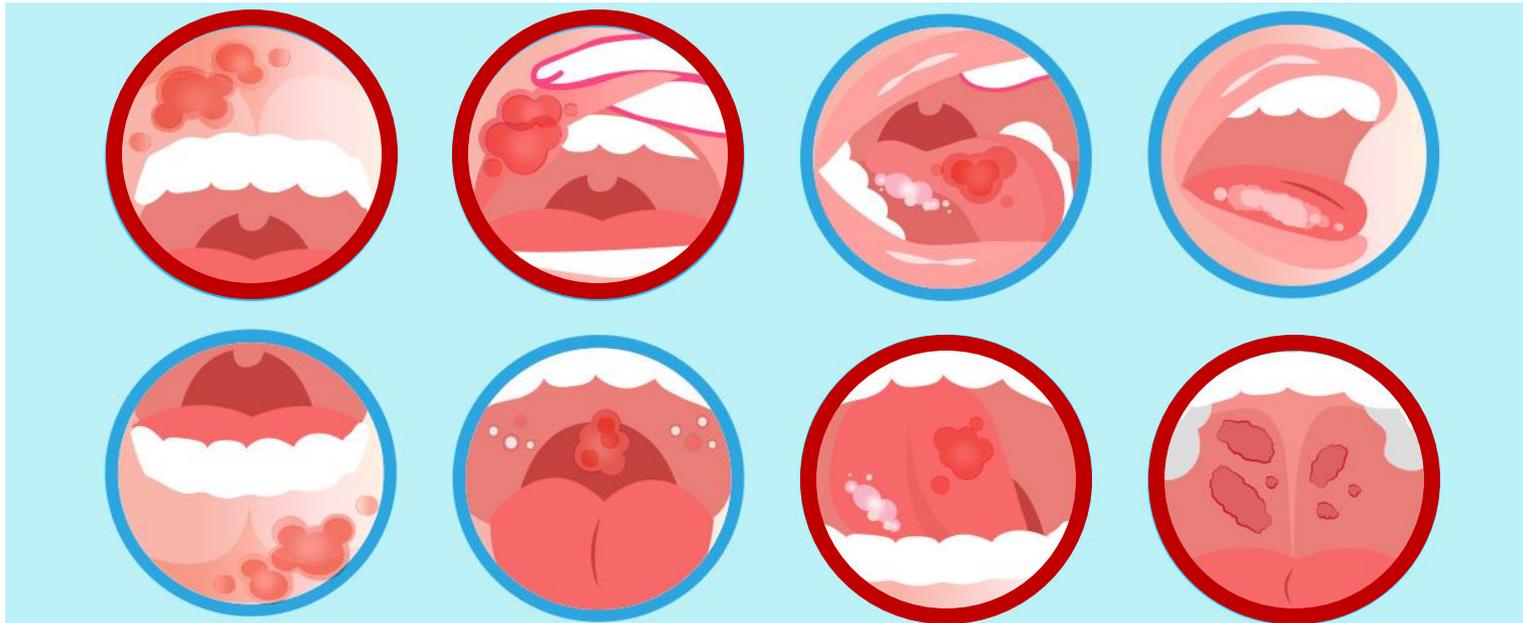
- Base de la lengua
- Amígdalas
- Pared faríngea posterior
- Paladar blando



# Carcinoma escamoso del tracto respiratorio superior



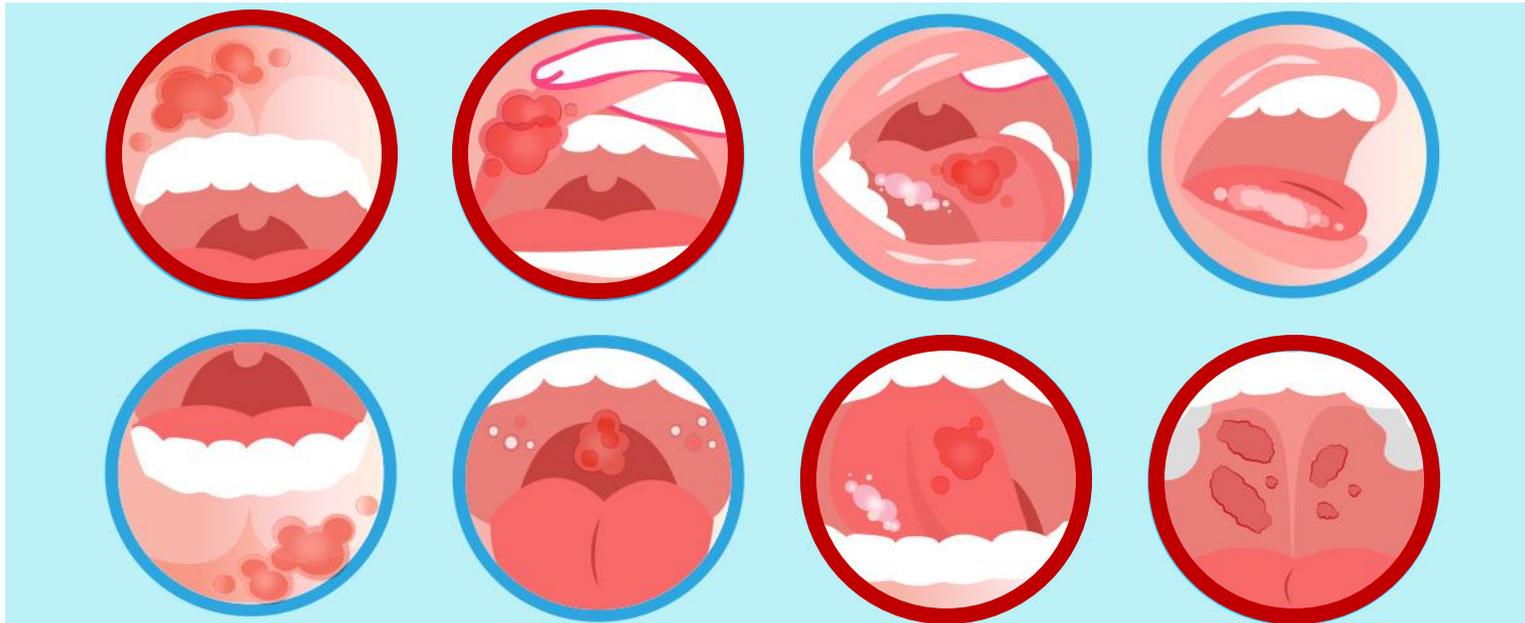
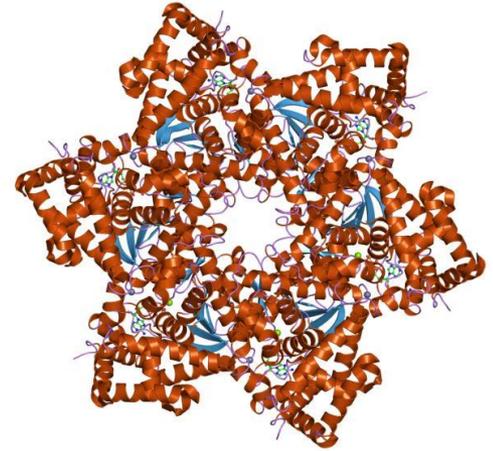
# Carcinoma escamoso del tracto respiratorio superior



# Carcinoma escamoso del tracto respiratorio superior



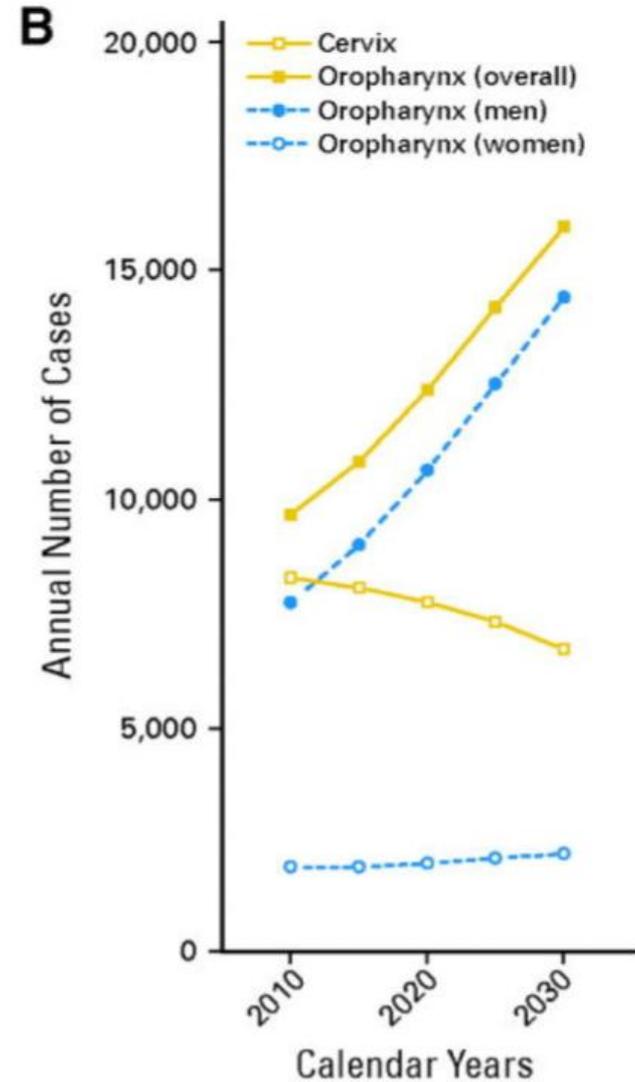
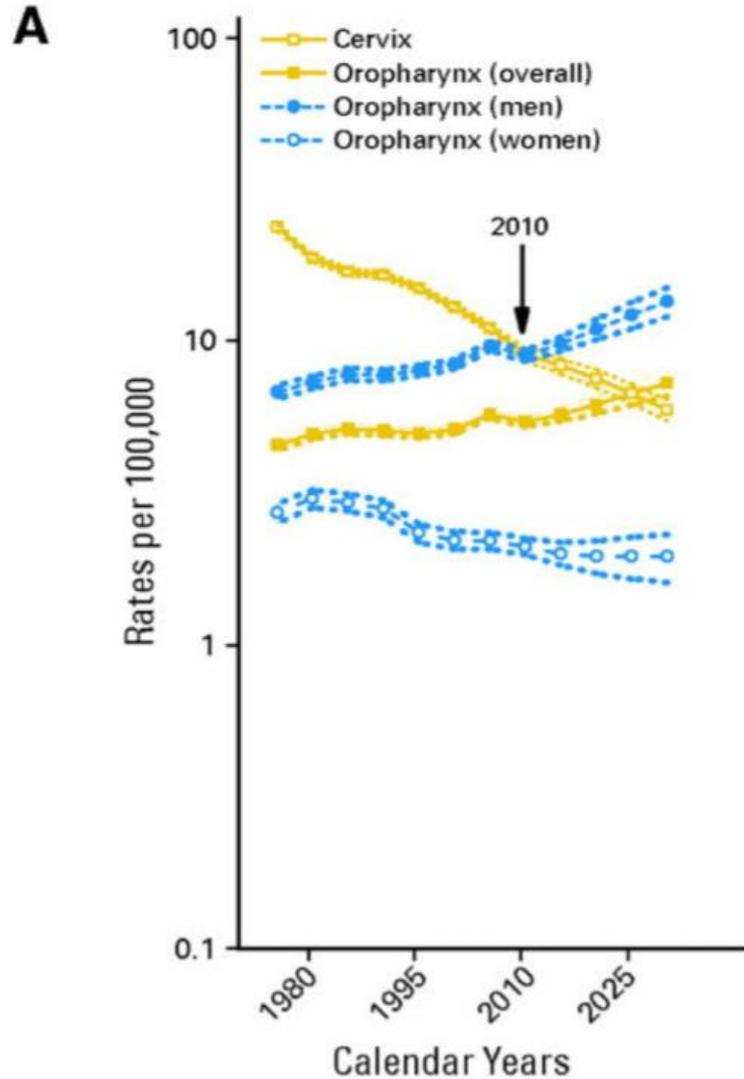
**HPV**



# Epidemiology of HPV-associated oropharyngeal cancer



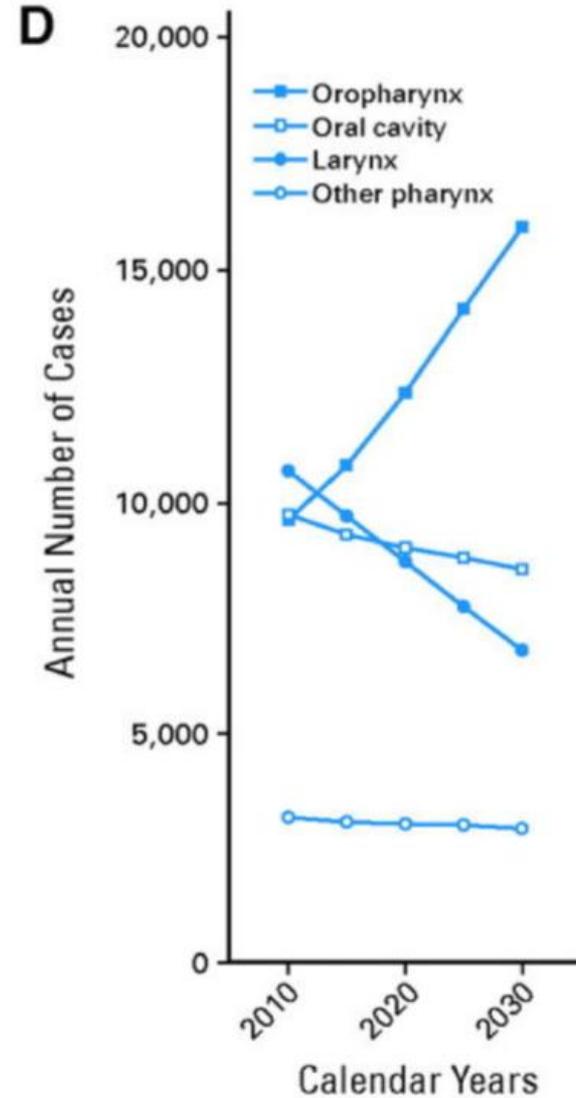
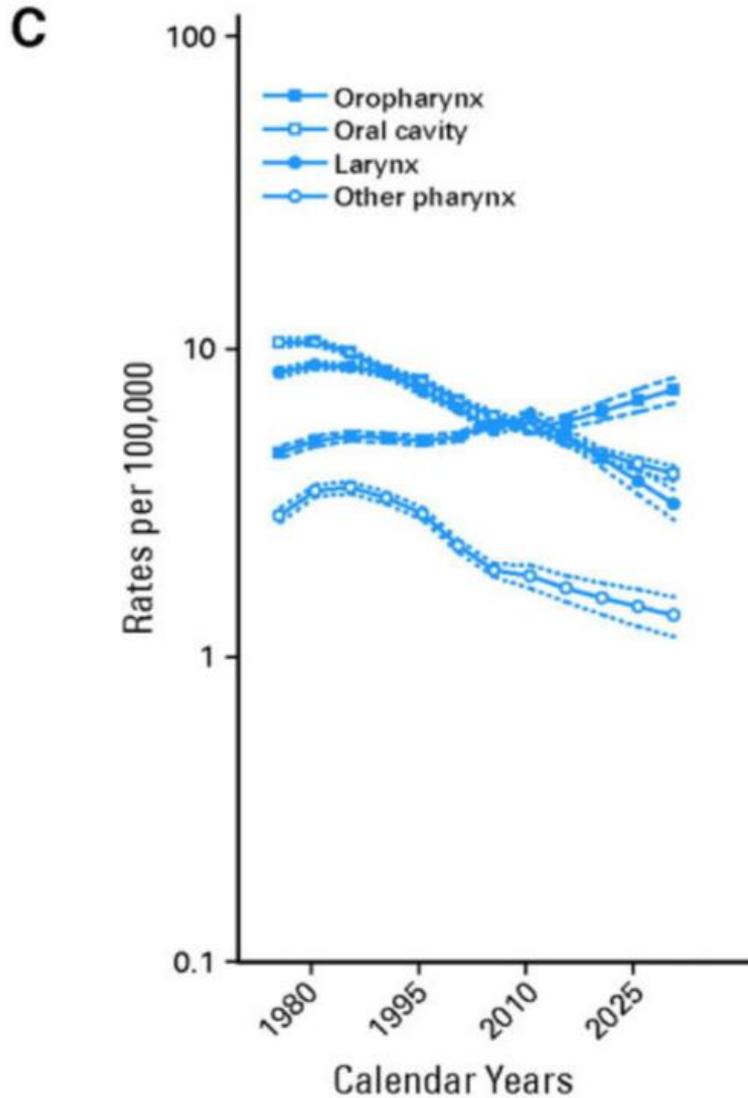
*Oral Oncol.* 2014 May ; 50(5): 380–386.



# Epidemiology of HPV-associated oropharyngeal cancer



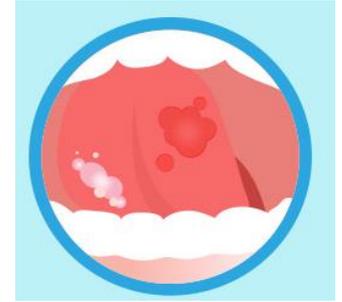
*Oral Oncol.* 2014 May ; 50(5): 380–386.



# Carcinoma escamoso HPV(+) orofaringe

## Incidencia

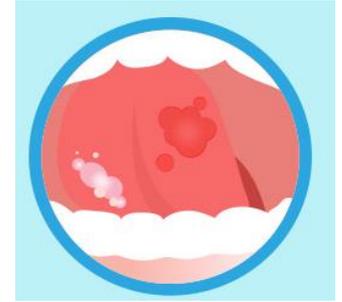
- Hombres jóvenes



# Carcinoma escamoso HPV(+) orofaringe

## Incidencia

- Hombres jóvenes
- Sexo oral



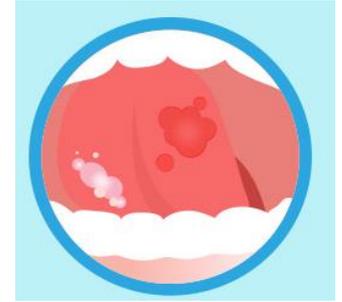
# Carcinoma escamoso HPV(+) orofaríngeo

## Incidencia

- Hombres jóvenes
- Sexo oral

## Etiología

- > 90% HPV 16



# Carcinoma escamoso HPV(+) orofaringe

## Incidencia

- Hombres jóvenes
- Sexo oral

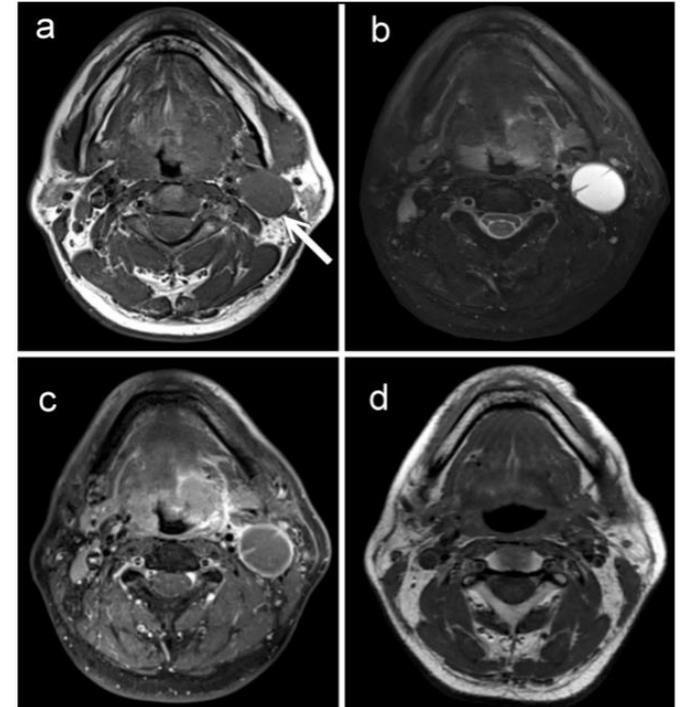
## Etiología

- > 90% HPV 16

## Características neoplasias

- Tumores primarios pequeños
- N1 al diagnóstico

MT ganglionares QUÍSTICAS !

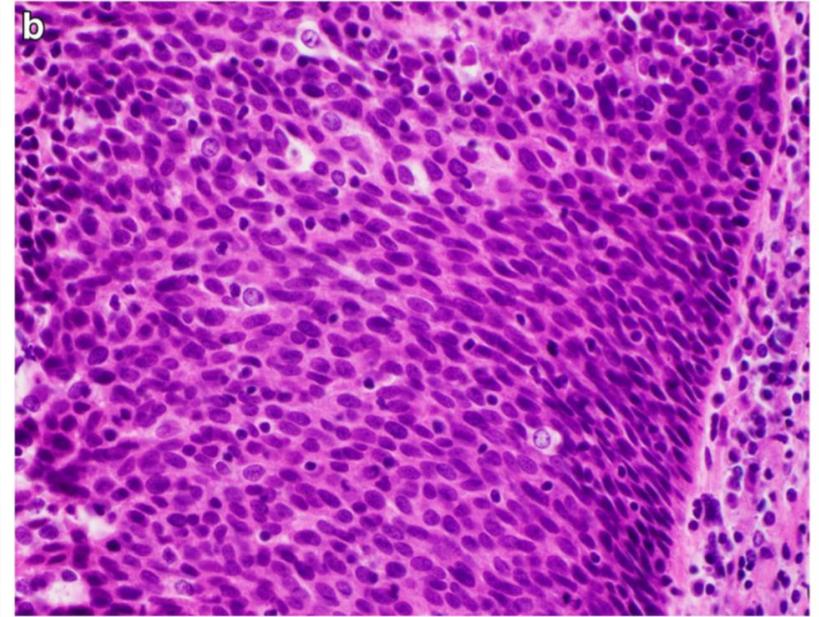
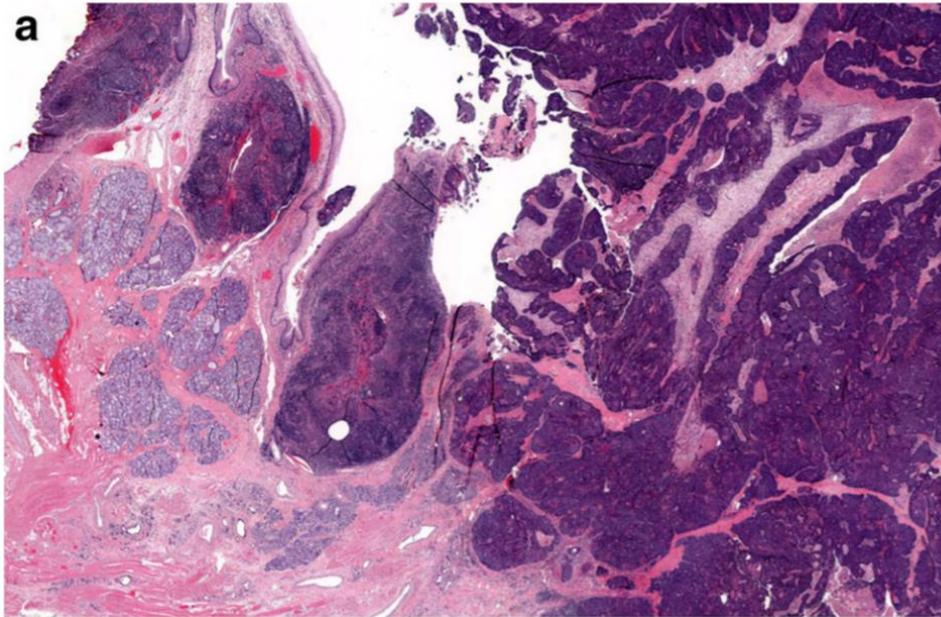


<https://doi.org/10.1371/journal.pone.0180779.g002>

# Carcinoma escamoso HPV(+) orofaringe

## Tipo histológico

- Basaloide

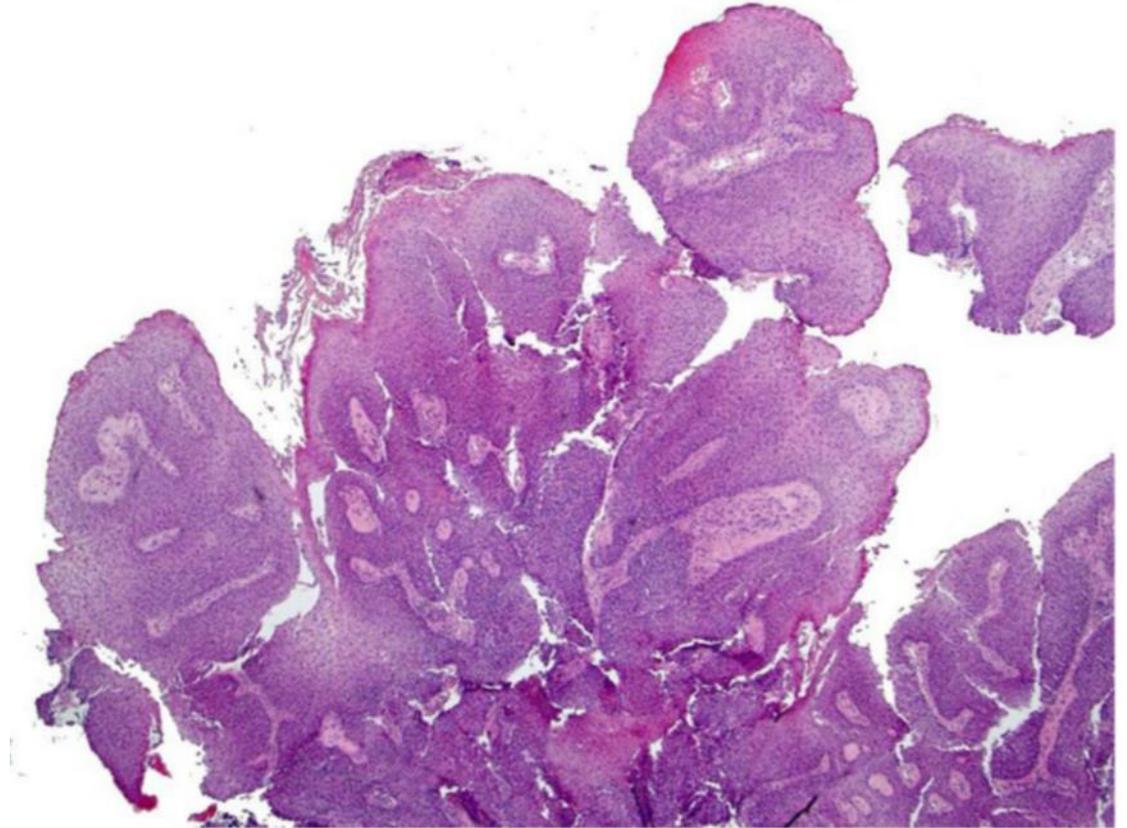


Virchows Arch. 2017 Aug;471(2):295-307

# Carcinoma escamoso HPV(+) orofaringe

## Tipo histológico

- Basaloide
- Papilar

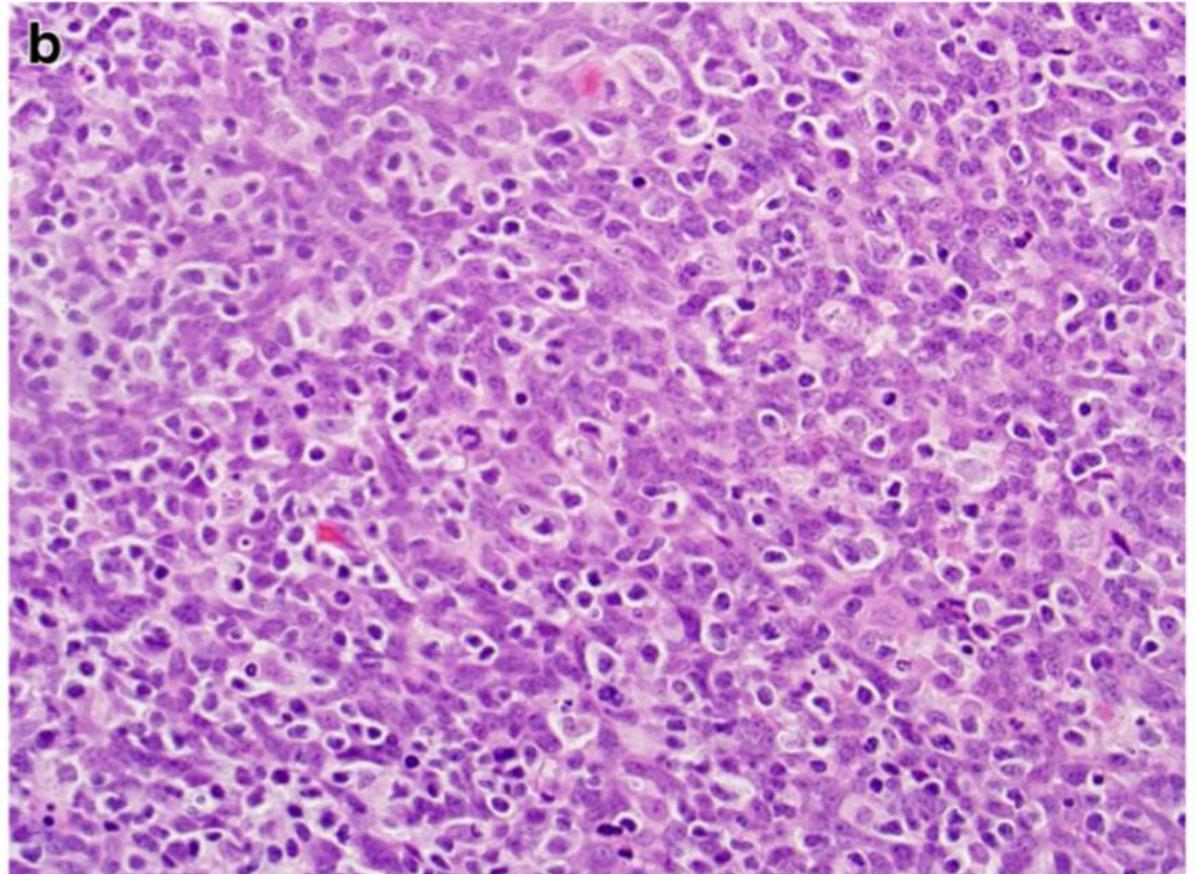


Virchows Arch. 2017 Aug;471(2):295-307

# Carcinoma escamoso HPV(+) orofaringe

## Tipo histológico

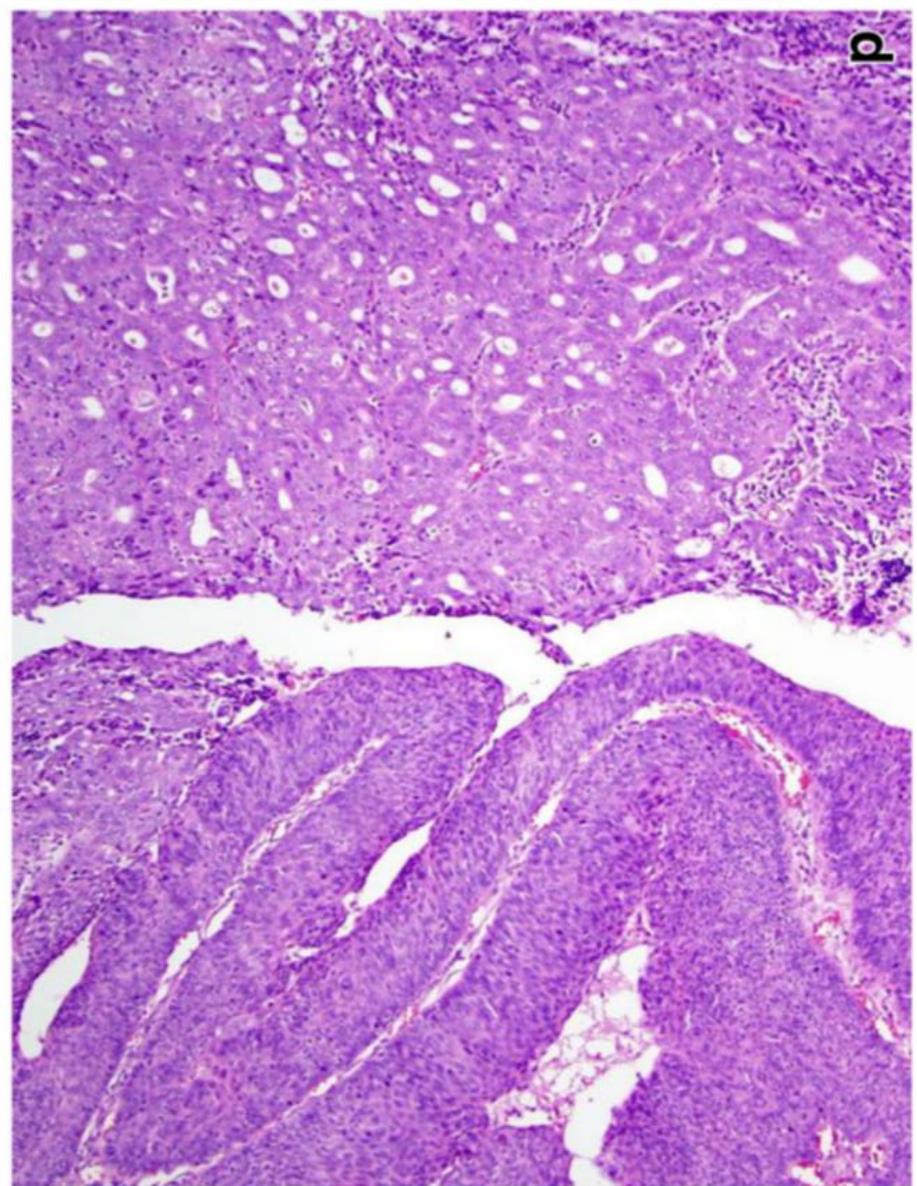
- Basaloide
- Papilar
- Linfoepitelial



# Carcinoma escamoso HPV(+) orofaringe

## Tipo histológico

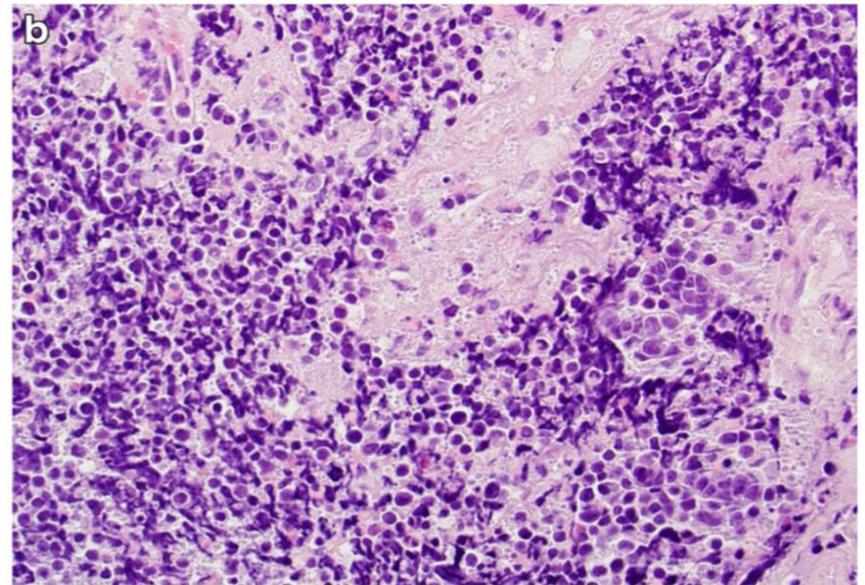
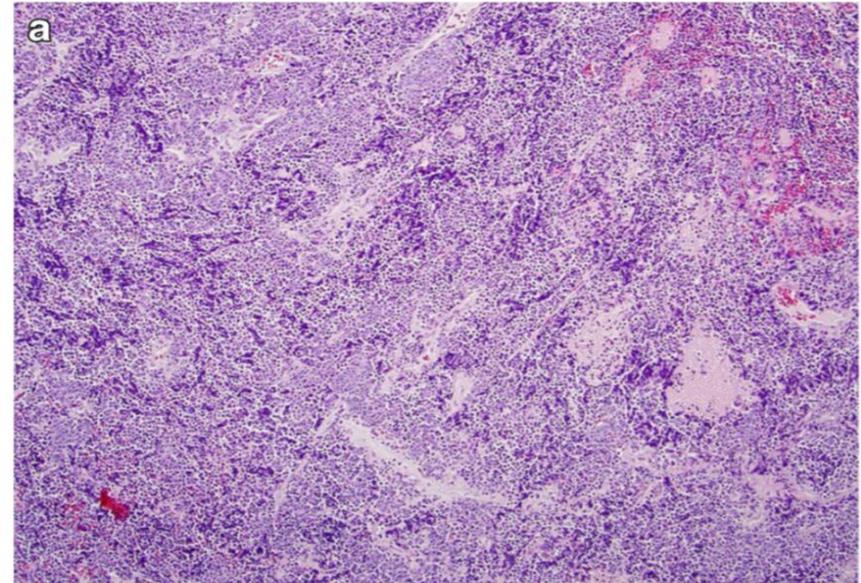
- Basaloide
- Papilar
- Linfoepitelial
- Adenoescamoso



# Carcinoma escamoso HPV(+) orofaringe

## Tipo histológico

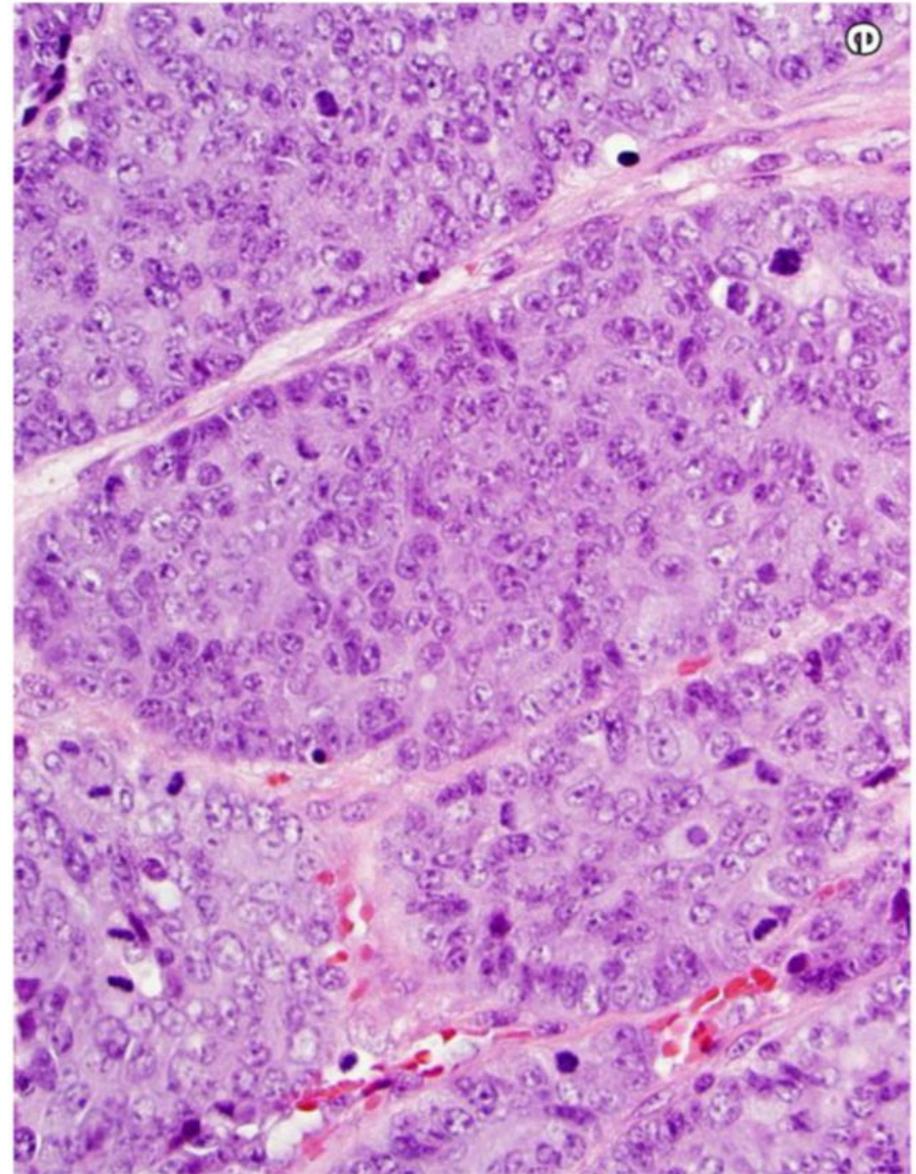
- Basaloide
- Papilar
- Linfoepitelial
- Adenoescamoso
- Neuroendocrino de células pequeñas



# Carcinoma escamoso HPV(+) orofaringe

## Tipo histológico

- Basaloide
- Papilar
- Linfoepitelial
- Adenoescamoso
- Neuroendocrino de células pequeñas
- Neuroendocrino de células grandes



# Carcinoma escamoso HPV(+) orofarínge

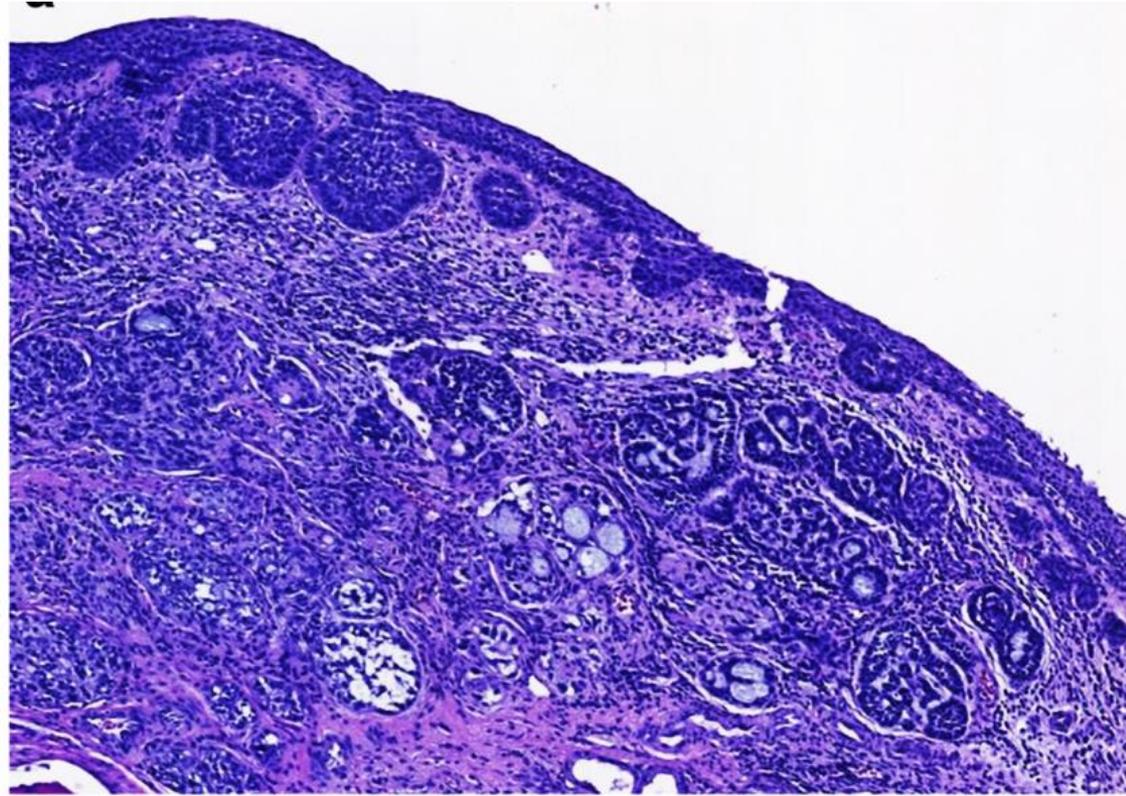
## Tipo histológico

- Basaloide
- Papilar
- Linfoepitelial
- Adenoescamoso
- Neuroendocrino de células pequeñas
- Neuroendocrino de células grandes
- Fusocelular/ sarcomatoide

# Carcinoma escamoso HPV(+) orofaringe

## Tipo histológico

- Basaloide
- Papilar
- Linfoepitelial
- Adenoescamoso
- Neuroendocrino de
- Neuroendocrino de
- Fusocelular/ sarcomatoide
- Tipo quístico adenoide

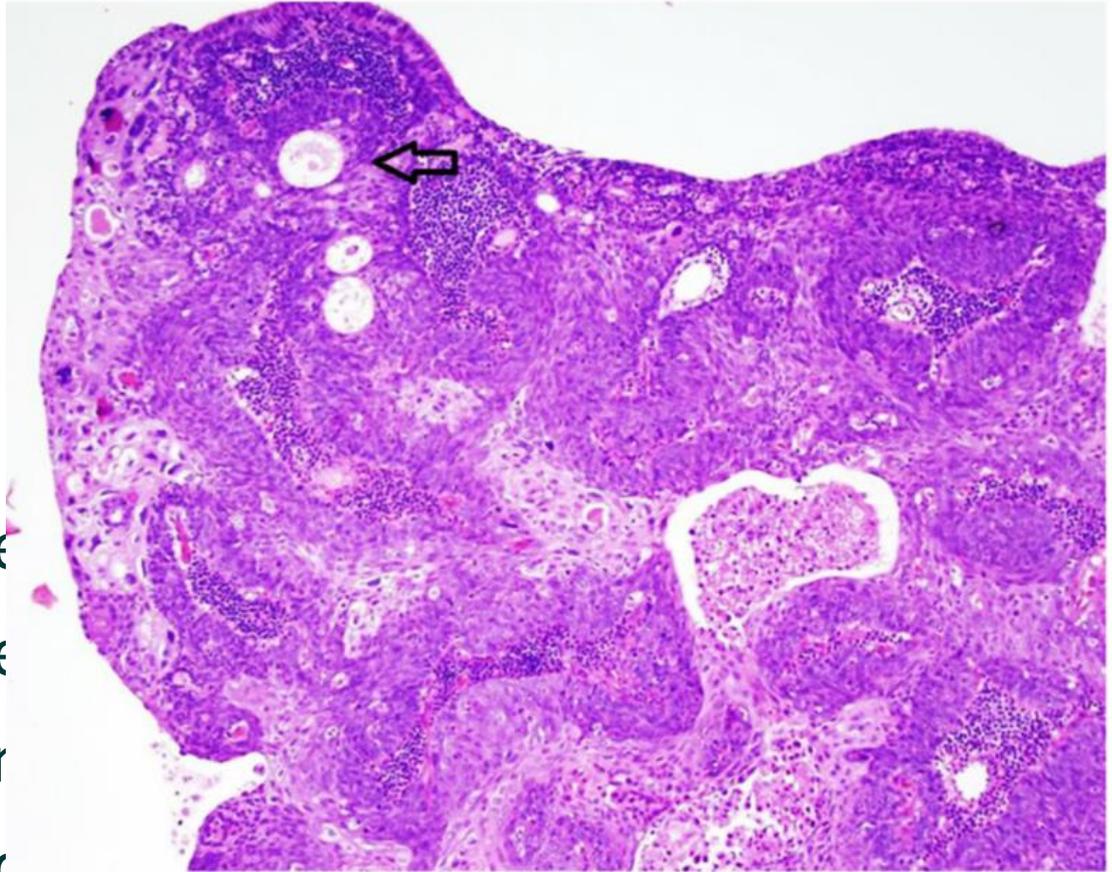


Virchows Arch. 2017 Aug;471(2):295-307

# Carcinoma escamoso HPV(+) orofaringe

## Tipo histológico

- Basaloide
- Papilar
- Linfoepitelial
- Adenoescamoso
- Neuroendocrino de
- Neuroendocrino de
- Fusocelular/ sarcor
- Tipo quístico adenc
- Ciliado HPV-asociado



Virchows Arch. 2017 Aug;471(2):295-307

# Carcinoma escamoso HPV(+) orofarínge

## Tipo histológico

- Basaloide
- Papilar
- Linfoepitelial
- Adenoescamoso
- Neuroendocrino de células pequeñas
- Neuroendocrino de células grandes
- Fusocelular/ sarcomatoide
- Tipo quístico adenoide
- Ciliado HPV-asociado
- Adenocarcinoma de base de lengua HPV-asociado

# Carcinoma escamoso HPV(+) orofarínge

## Características moleculares

- Ca Escamoso HPV(+): p53-wt / p16 (+)
- Ca Escamoso HPV(-): p53-mut / p16 (-)

# Carcinoma escamoso HPV(+) orofarínge

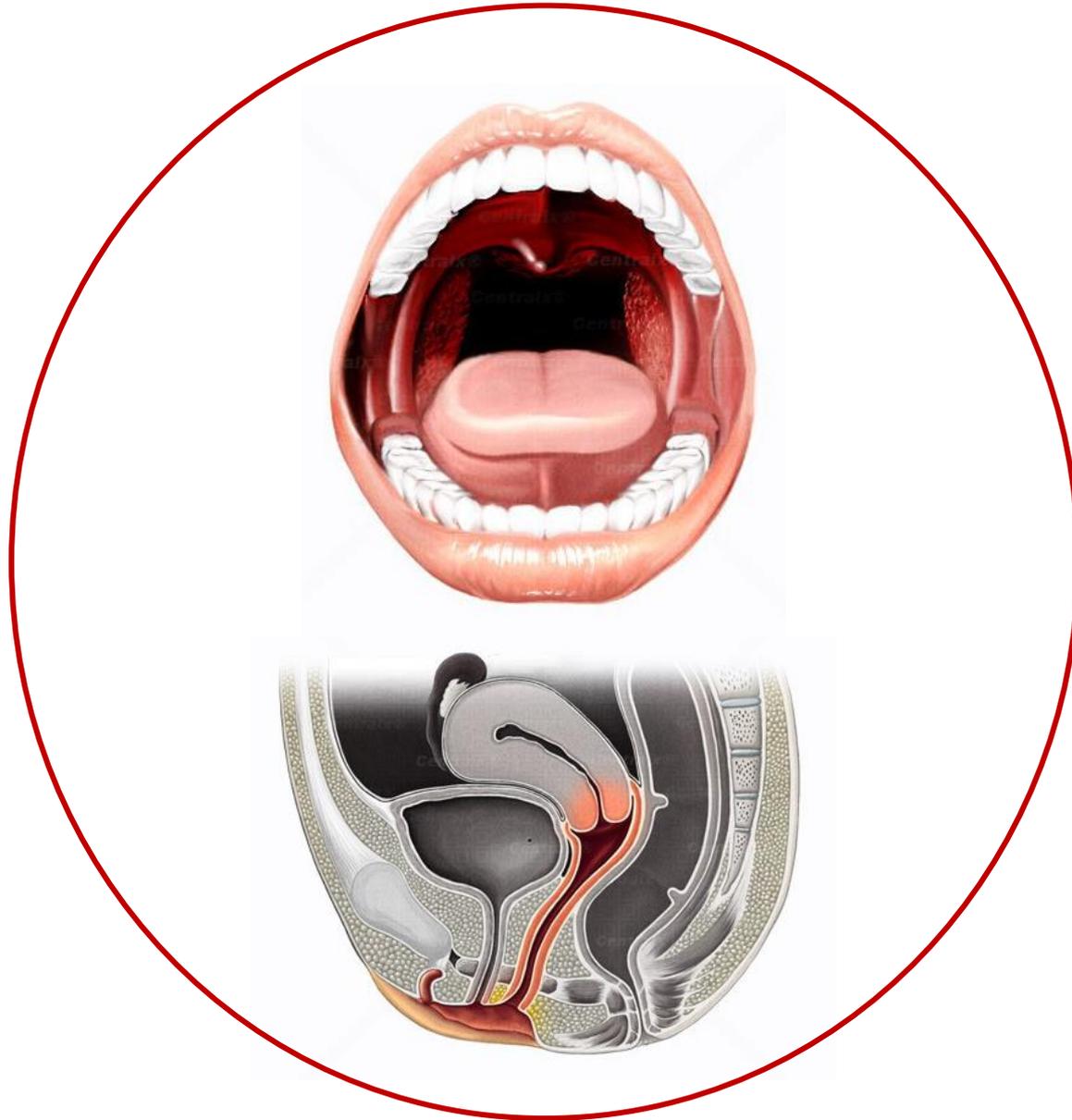
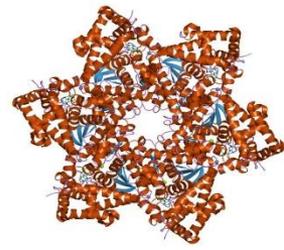
## Características moleculares

- Ca Escamoso HPV(+): p53-wt / p16 (+)
- Ca Escamoso HPV(-): p53-mut / p16 (-)

## Evolución

- ↑ tasa recurrencias a distancia
- MT inusuales ≠ pulmón
- Mejor supervivencia HPV(-)
- Menor tasa de tumores secundarios

# HPV en orofaringe y cérvix



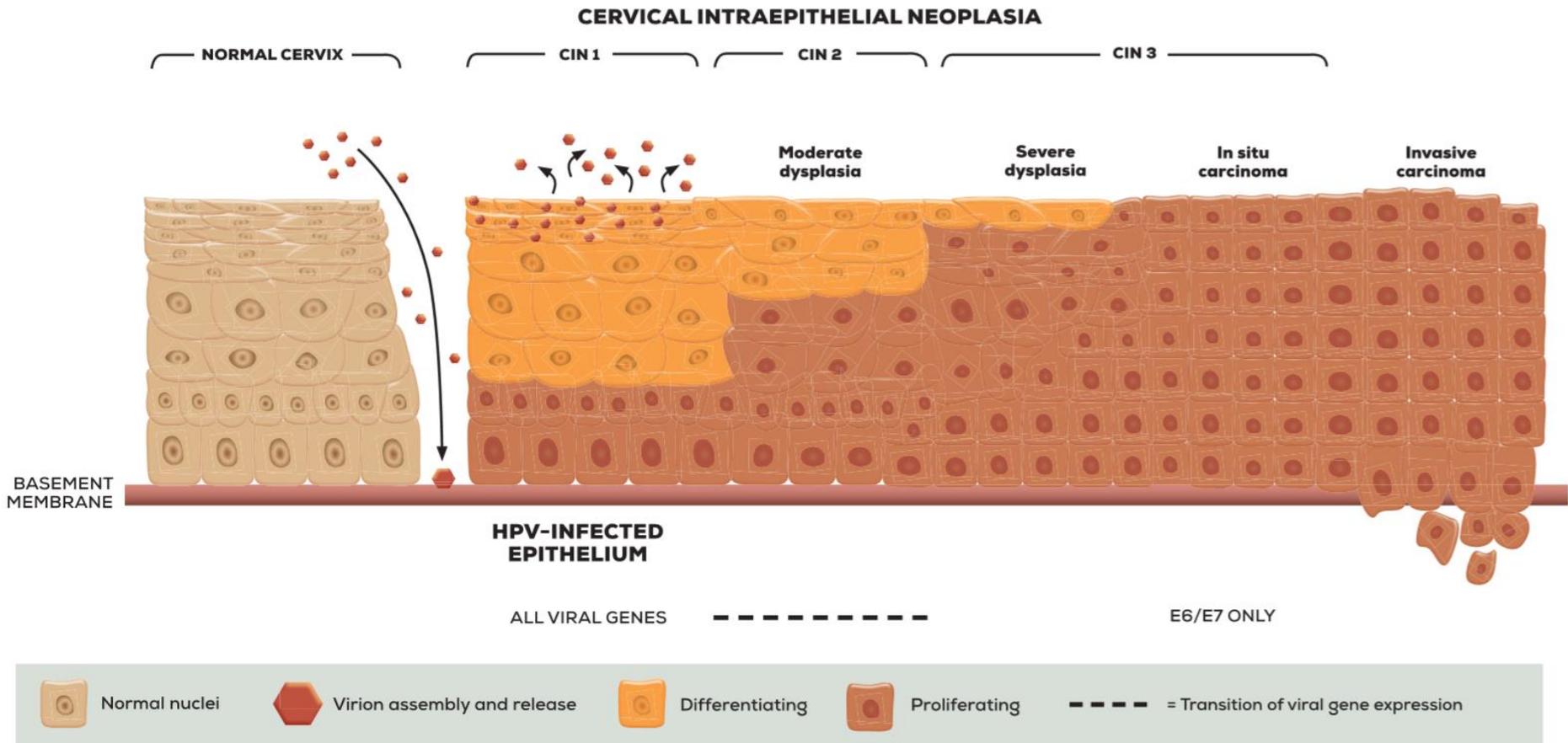
# Human Papillomavirus in Cervical Cancer and Oropharyngeal Cancer: One Cause, Two Diseases

Tara A. Berman, MD, MS<sup>1,2</sup>; and John T. Schiller, PhD<sup>2</sup>

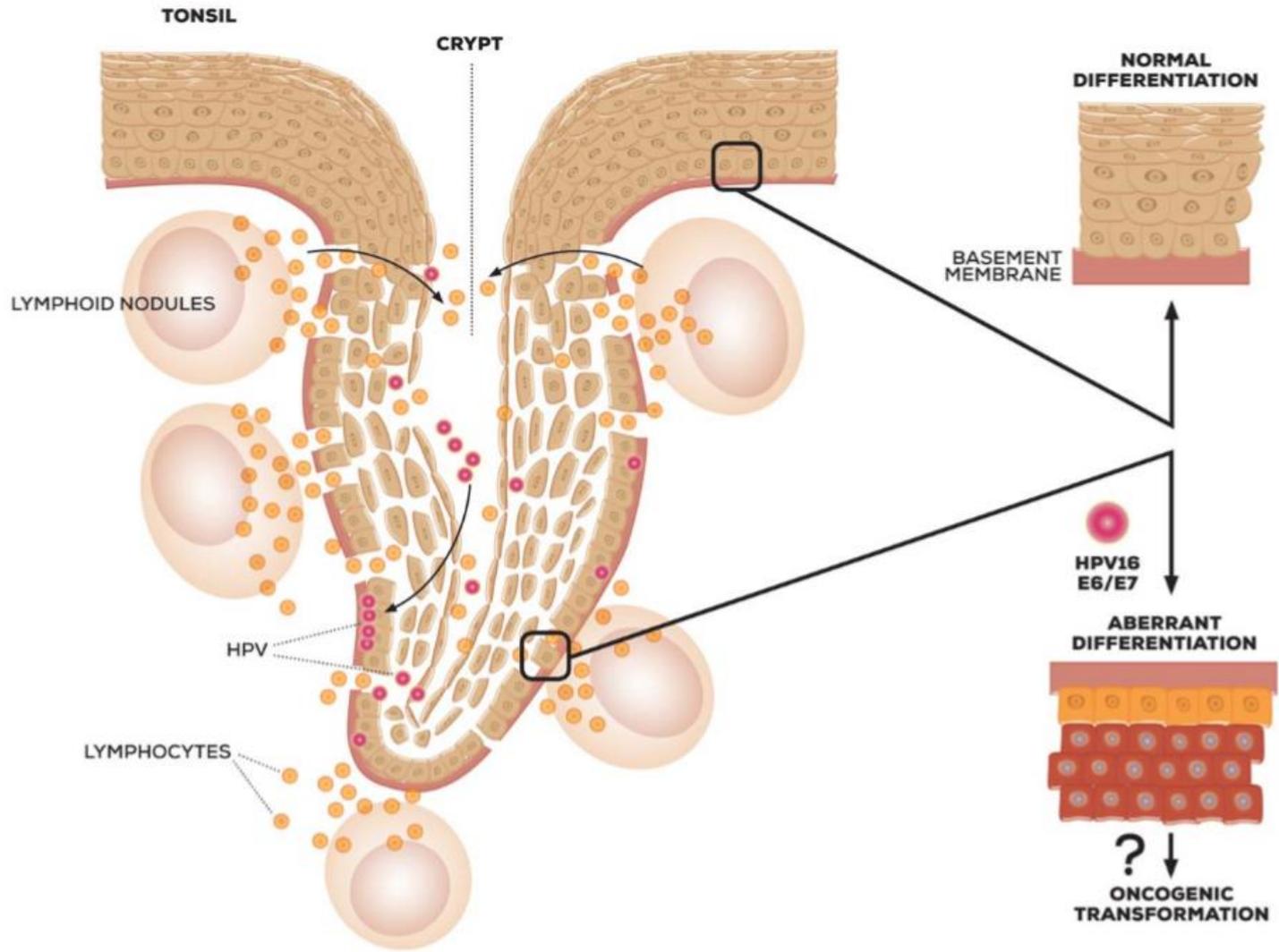
**TABLE 1.** Common Risk Factors and Biologic Features Shared by Human Papillomavirus-Associated Cervical and Oropharyngeal Cancer

Characteristic	HPV-Associated Cervical Cancer <sup>a</sup>	HPV-Associated OPC <sup>a</sup>
HPV16/18 positive	70%	90%
E6/E7 expression	Yes	Yes
p53 and pRb wild type	Yes	Yes
Median age at detection	49 y	54 y
Age at peak virus prevalence	20 y	25-30 y and 55-60 y
Latency period	30 y	10-30 y
Sex ratio	100% Women	70% Men
Premalignant lesions	Well documented	Uncertain
Sexually transmitted	Yes	Yes
Other risk factors	Multiple vaginal-sex partners, partners with many partners, early age of coitarche, cigarette smoking, long-duration oral contraceptive use, multiple live births, immunocompromised status, and low folate levels	High number of lifetime vaginal-sex partners (>25) and ≥6 lifetime oral-sex partners, female partner with anogenital HPV-associated SCC, cigarette smoking, alcohol use, immunocompromised status, male sex
Susceptibility to chemo/Rx	Moderate	High
Screening tests		
Cytology	Yes	No
Virologic	Yes	No
5-Year survival rate	68%	85-90%

**Cancer 2017;123:2219-29**



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Cancer 2017;123:2219-29

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**Cancer 2017;123:2219-29**

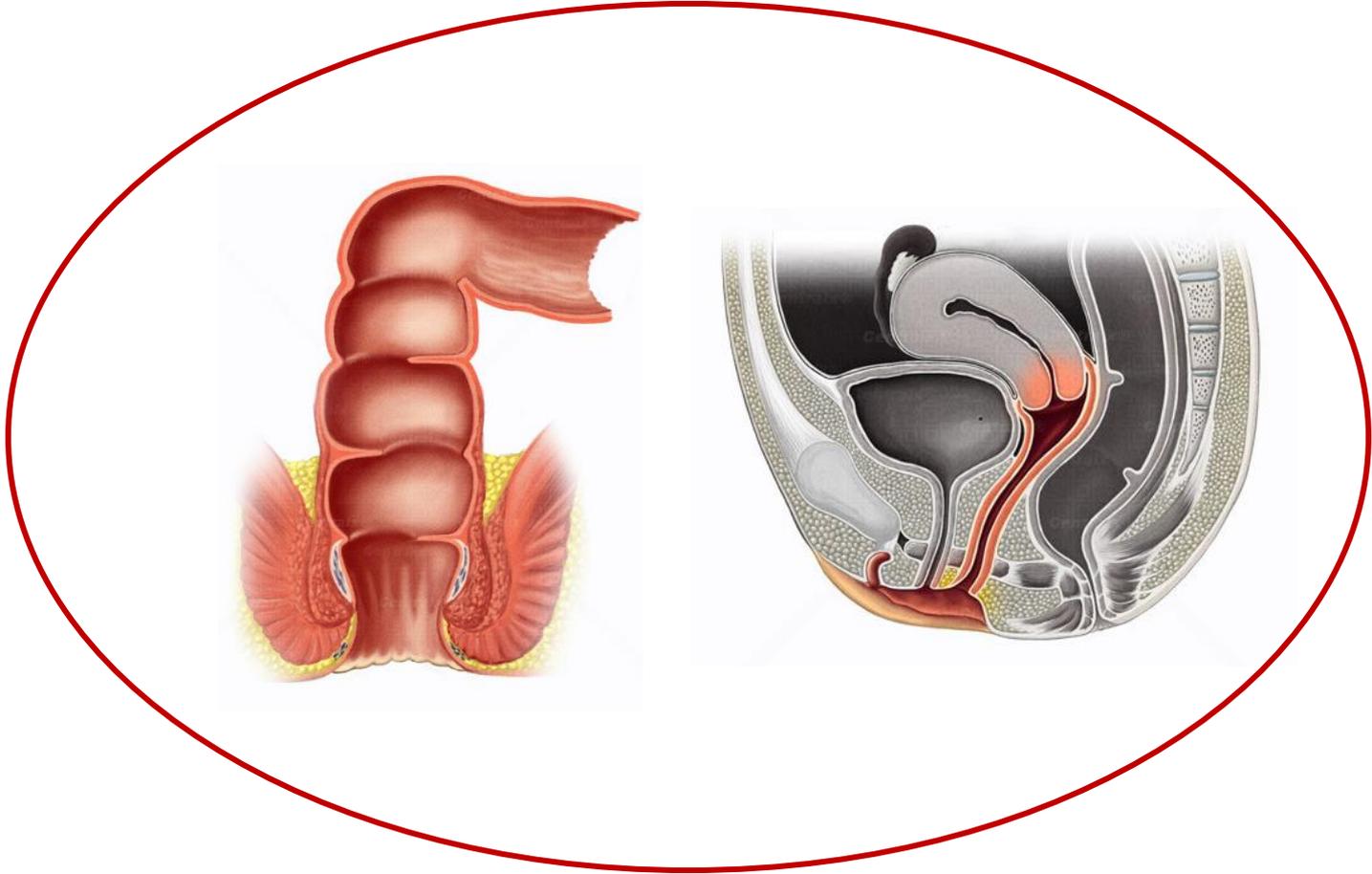
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Virologic	Yes	No
5-Year survival rate	68%	85-90%

# HPV en canal anal y cérvix



# Ca escamoso HPV(+) del canal anal

## Incidencia

- Mujeres (ratio 1.5)
- > 50 años

# Anal and Cervical High-Risk Human Papillomavirus Genotyping in Women With and Without Genital Neoplasia

*Amy J. Bregar, MD,<sup>1</sup> Beth Cronin, MD,<sup>2</sup> Christine Luis, MA,<sup>2,3</sup> Paul DiSilvestro, MD,<sup>2,3</sup> Steven Schechter, MD,<sup>4</sup> Latha Pisharodi, MD,<sup>5</sup> Christina Raker, ScD,<sup>2,6</sup> Melissa Clark, PhD,<sup>2,6,7</sup> and Katina Robison, MD<sup>2,3</sup>*

*(J Low Genit Tract Dis 2018;22: 115–119)*

**Objective:** The aim of the study was to compare the prevalence, genotypes, and rates of concomitant anal and cervical high-risk human papillomavirus (HR-HPV) in women with and without a history of HPV-related genital neoplasia.

**Materials and Methods:** This was a prospective cohort study conducted from December 2012 to February 2014. Women with a history of neoplasia were considered the high-risk group. Women without a history of neoplasia were considered the low-risk group. Cervical and anal cytology and HPV genotyping were performed. All women with abnormal anal cytology were referred for anoscopy.

# Anal and Cervical High-Risk Human Papillomavirus Genotyping in Women With and Without Genital Neoplasia

Amy J. Bregar, MD,<sup>1</sup> Beth Cronin, MD,<sup>2</sup> Christine Luis, MA,<sup>2,3</sup> Paul DiSilvestro, MD,<sup>2,3</sup> Steven Schechter, MD,<sup>4</sup> Latha Pisharodi, MD,<sup>5</sup> Christina Raker, ScD,<sup>2,6</sup> Melissa Clark, PhD,<sup>2,6,7</sup> and Katina Robison, MD<sup>2,3</sup>

(*J Low Genit Tract Dis* 2018;22: 115–119)

**TABLE 2.** Prevalence of HPV Positivity

	History of genital dysplasia or cancer		<i>P</i>
	Yes, high-risk history (n = 118)	No, low-risk history (n = 66)	
HR-HPV cervix			<.0001
Positive	36 (30.5)	5 (7.6)	
Negative	67 (56.8)	57 (86.4)	
Insufficient	15 (12.7)	4 (6.1)	
HR-HPV anus	(n = 115)	(n = 65)	.003
Positive	20 (17.4)	1 (1.5)	
Negative	63 (54.8)	44 (67.7)	
Insufficient	32 (27.8)	20 (30.8)	
Both high-risk cervix and anal HPV	(n = 115)	(n = 65)	.2
Positive	5 (4.4)	0	

The prevalence of HPV positivity in the study population is presented.

HPV indicates human papillomavirus; HR-HPV, high-risk human papillomavirus.

# Anal and Cervical High-Risk Human Papillomavirus Genotyping in Women With and Without Genital Neoplasia

Amy J. Bregar, MD,<sup>1</sup> Beth Cronin, MD,<sup>2</sup> Christine Luis, MA,<sup>2,3</sup> Paul DiSilvestro, MD,<sup>2,3</sup> Steven Schechter, MD,<sup>4</sup> Latha Pisharodi, MD,<sup>5</sup> Christina Raker, ScD,<sup>2,6</sup> Melissa Clark, PhD,<sup>2,6,7</sup> and Katina Robison, MD<sup>2,3</sup>

(*J Low Genit Tract Dis* 2018;22: 115–119)

**Results:** One hundred eighty-four women met inclusion criteria. High-risk HPV was detected in the anal canal of 17.4% of the high-risk group and 1.5% of the low-risk group ( $p = .003$ ). High-risk HPV was detected in the cervix of 30.5% of the high-risk group and 7.6% of the low-risk group ( $p < .001$ ). Concomitant anal and cervical high-risk HPV was detected in 4.4% of the high-risk group and was not detected in the low-risk group ( $p = .2$ ). Among women with anal intraepithelial neoplasia 2 or greater ( $n = 5$ ), 60% had HR-HPV detected in the anal canal while none had HR-HPV detected in the cervix.

**Conclusions:** Women with a history of genital neoplasia are more likely to be positive for anal and cervical HR-HPV compared with women without a history of genital neoplasia. Although there was no significant difference in rates of concomitant HR-HPV between low- and high-risk groups, HR-HPV can be found concomitantly in the anus and the cervix and may be associated with anal intraepithelial neoplasia or carcinoma.

# Ca escamoso HPV(+) del canal anal

## Incidencia

- Mujeres (ratio 1.5)
- > 50 años

## Etiología

- HPV 16 y 18

## Factores de riesgo

- Tabaco
- Transplante órgano
- Terapia inmunosupresora
- Promiscuidad sexual
- Coito anoreceptivo
- Historia de verrugas genitales

# Ca escamoso HPV(+) del canal anal

## Histología

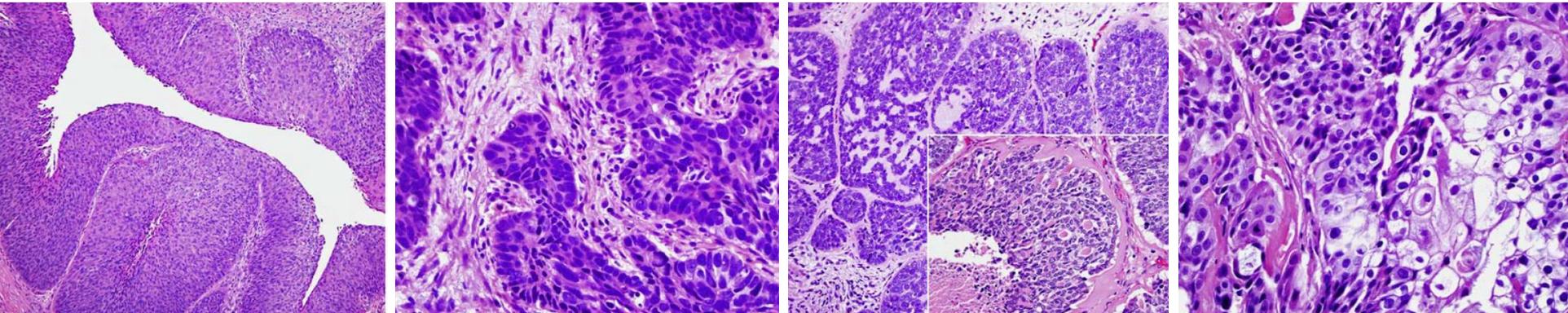
- Carcinoma escamoso 80%
    - Queratinizante
    - No queratinizante (transicional)
    - Basaloide
- Cloacogénico**

# Basaloid Squamous Cell Carcinoma of the Anus Revisited

*Rondell P. Graham, MBBS,\* Christina A. Arnold, MD,†  
Bita V. Naini, MD,‡ and Dora M. Lam-Himlin, MD§*

*Am J Surg Pathol 2016;40:354–360*

- Relacionado con HPV
- Originado en el epitelio de transición
- Cuatro patrones:
  - ✓ Transicional-like
  - ✓ Basaloide con empalizada periférica
  - ✓ Adenoide quístico-like
  - ✓ Mucinoso microquístico

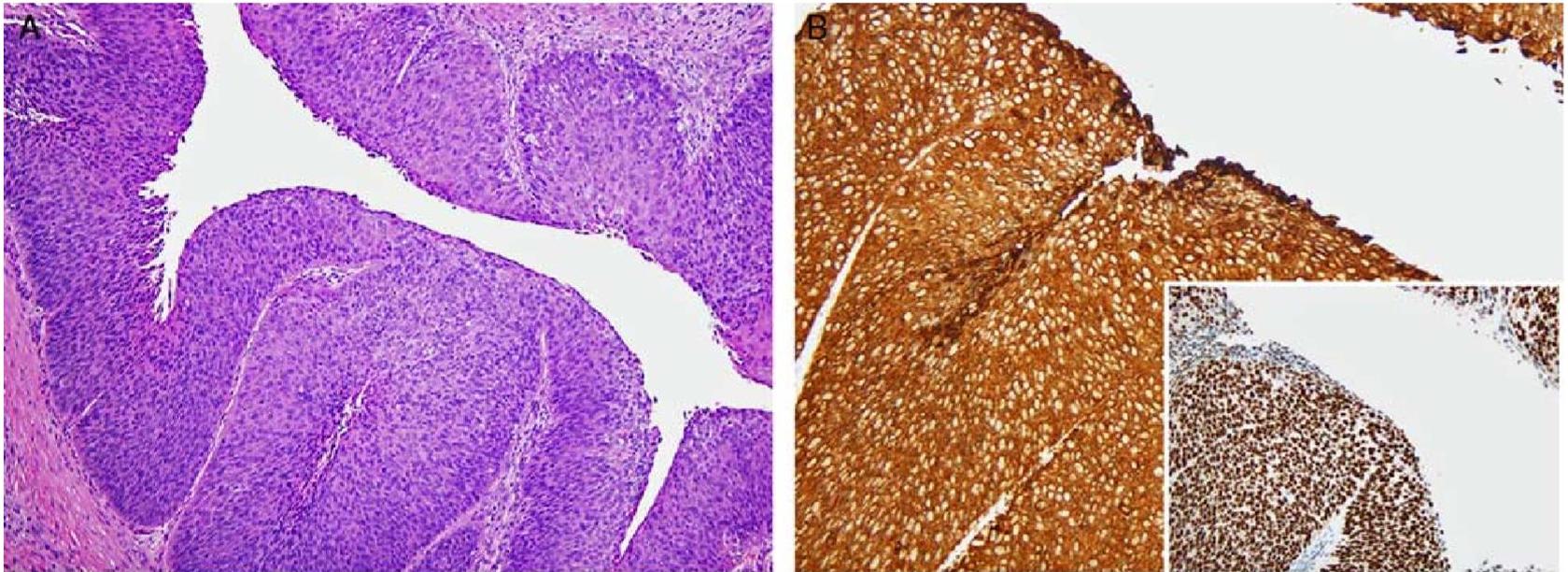


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*Am J Surg Pathol 2016;40:354–360*

**p16**

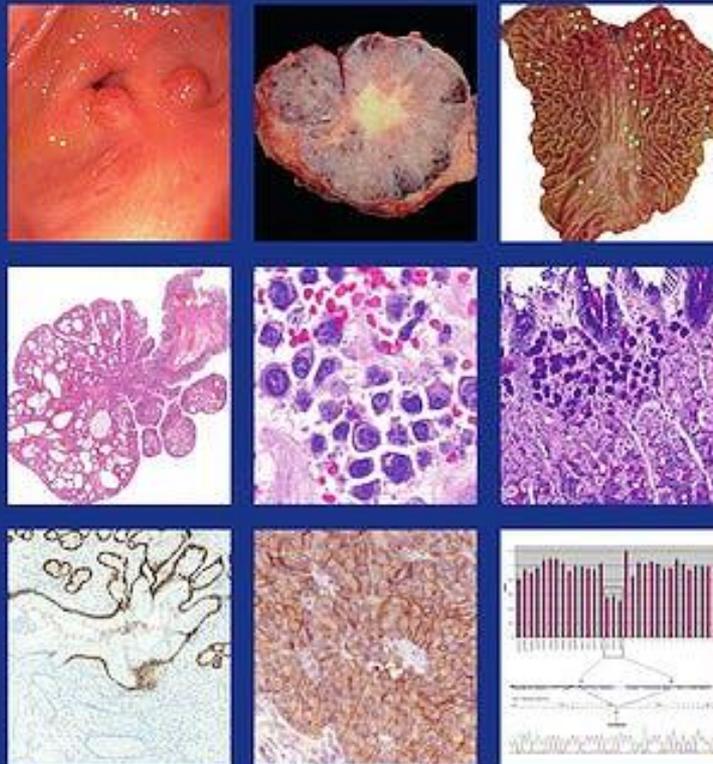


**CK 5/6**

WHO Classification of Tumours • 5th Edition

# Digestive System Tumours

Edited by the WHO Classification of Tumours Editorial Board



# WHO classification of tumours of the anal canal

## Benign epithelial tumours and precursors

- 8077/0 Squamous intraepithelial neoplasia, low grade
- 8077/2 Squamous intraepithelial neoplasia, high grade

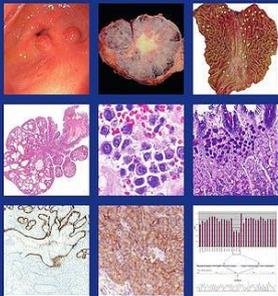
## Malignant epithelial tumours

- 8070/3 Squamous cell carcinoma NOS
- 8051/3 Verrucous squamous cell carcinoma
- 8140/3 Adenocarcinoma NOS
- 8240/3 Neuroendocrine tumour NOS
- 8240/3 Neuroendocrine tumour, grade 1
- 8249/3 Neuroendocrine tumour, grade 2
- 8249/3 Neuroendocrine tumour, grade 3
- 8246/3 Neuroendocrine carcinoma NOS
- 8013/3 Large cell neuroendocrine carcinoma
- 8041/3 Small cell neuroendocrine carcinoma
- 8154/3 Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN)

WHO Classification of Tumours • 5th Edition

## Digestive System Tumours

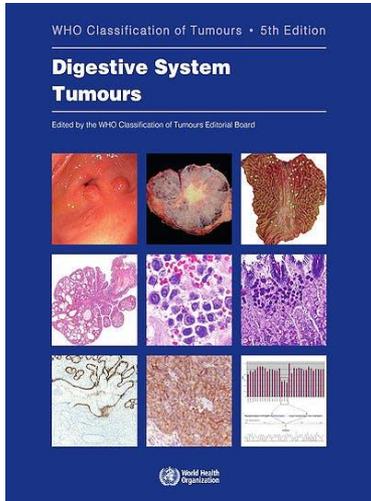
Edited by the WHO Classification of Tumours Editorial Board



# Ca escamoso del canal anal

## Definición

- Tumor epitelial maligno
- Originado en la mucosa anal
- Productor de queratina
- Puentes intercelulares
- Frecuente infección por HPV



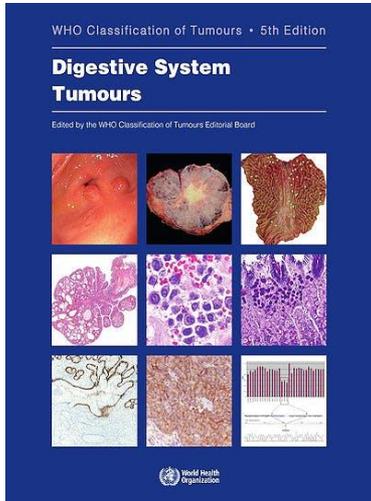
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## Terminología relacionada

- Carcinoma cloacogénico
- Carcinoma transicional



# Ca escamoso del canal anal

## Definición

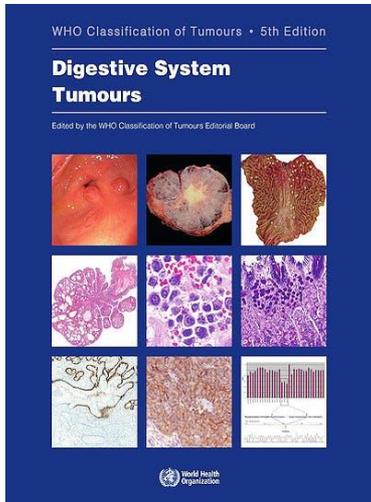
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- Carcinoma cloacogénico
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## Subtipo

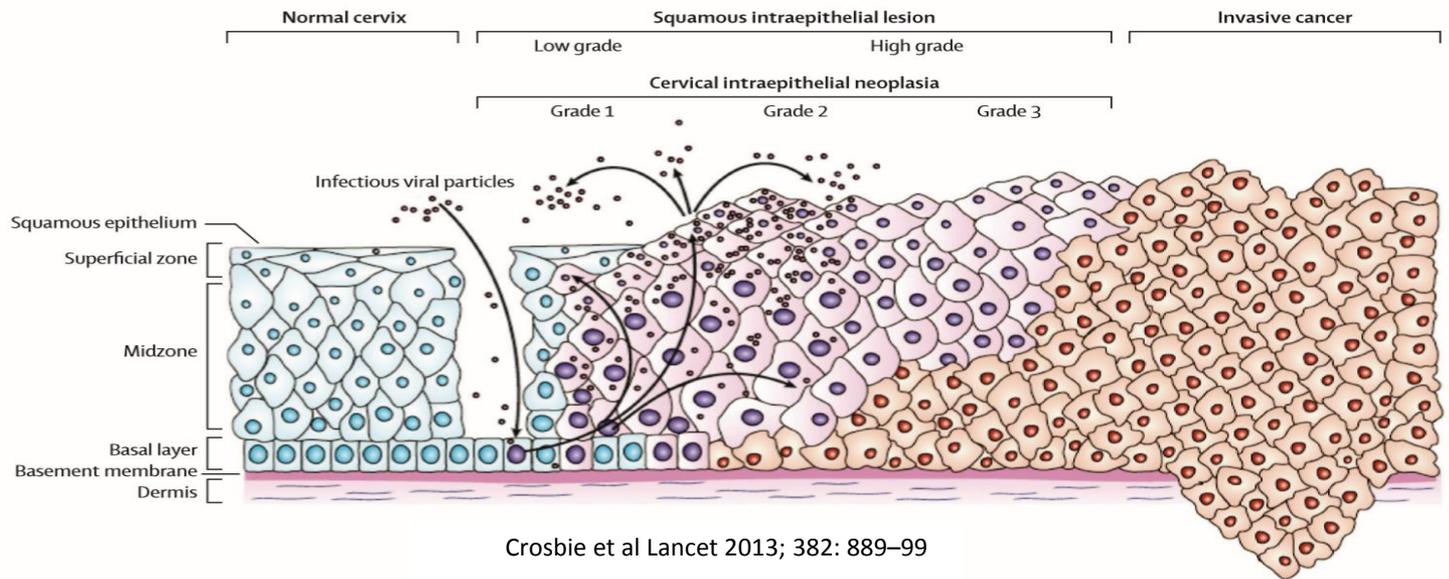
- Carcinoma escamoso verrucoso



# Ca escamoso del canal anal

## Histología

- Carcinoma escamoso
  - Verrucoso
- Lesiones premalignas
  - AIN I = LSIL
  - AIN II-III = HSIL



# Ca escamoso del canal anal

## Diagnóstico

- Tacto rectal

Esencial pero no suficiente

Cualquier paciente con sintomatología

Poco sensible en enfermedad recurrente



# Ca escamoso del canal anal

## Diagnóstico

- Tacto rectal

Esencial pero no suficiente

Cualquier paciente con sintomatología

Poco sensible en enfermedad recurrente

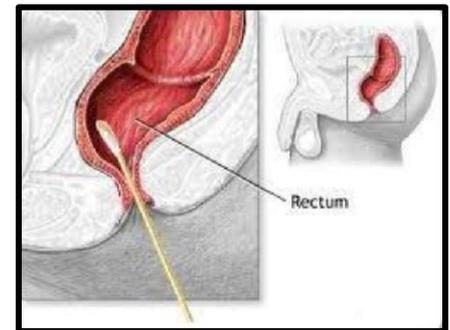
- Citología anal

Desde 1990

Bajo coste y reproducible

Población de riesgo

Si lesión → Rectoscopia rígida y biopsia



# Ca escamoso del canal anal

## Diagnóstico

- Determinación HPV

En estudio

- Anuscopia de alta resolución

Ante cualquier alteración citología

Permite:

Visualizar lesiones sospechosas

Biopsias bajo visión directa

Tratamientos *in situ*



# Ca escamoso del canal anal

## Screening

*World J Gastrointest Surg* 2016 January 27; 8(1): 41-51

**Table 1 Summary characteristics of anal cancer screening modalities**

	<b>DARE</b>	<b>Anal Pap test</b>	<b>HPV testing</b>	<b>High resolution anoscopy</b>
Sensitivity <sup>[56,57,61,62,101]</sup>	Not studied	69%-93%	Alone: 100% Co-testing with Pap <sup>[49]</sup> : 72%-96%	Current diagnostic standard
Specificity <sup>[56,57,61,62,101]</sup>	Not studied	32%-59%	Alone: 16%	Current diagnostic standard
Resource availability	N/A	Ubiquitous	Ubiquitous	Highly selective centers
Provider availability	Universal	Specialty clinics	Specialty clinics	Highly selective centers
Learning curve	Part of usual clinical training	Part of usual clinical training	Part of usual clinical training	> 200 cases
Current consensus <sup>[52]</sup>	Annually, all HIV-positive patients	Annually in highest-risk groups	Alone: No recommendation Co-testing: No recommendation	Second-line screen following positive Pap test

DARE: Digital anorectal exam; HPV: Human papilloma virus; N/A: Not applicable; HIV: Human immunodeficiency virus; Pap: Papanicolaou.

# Ca escamoso del canal anal

## Screening

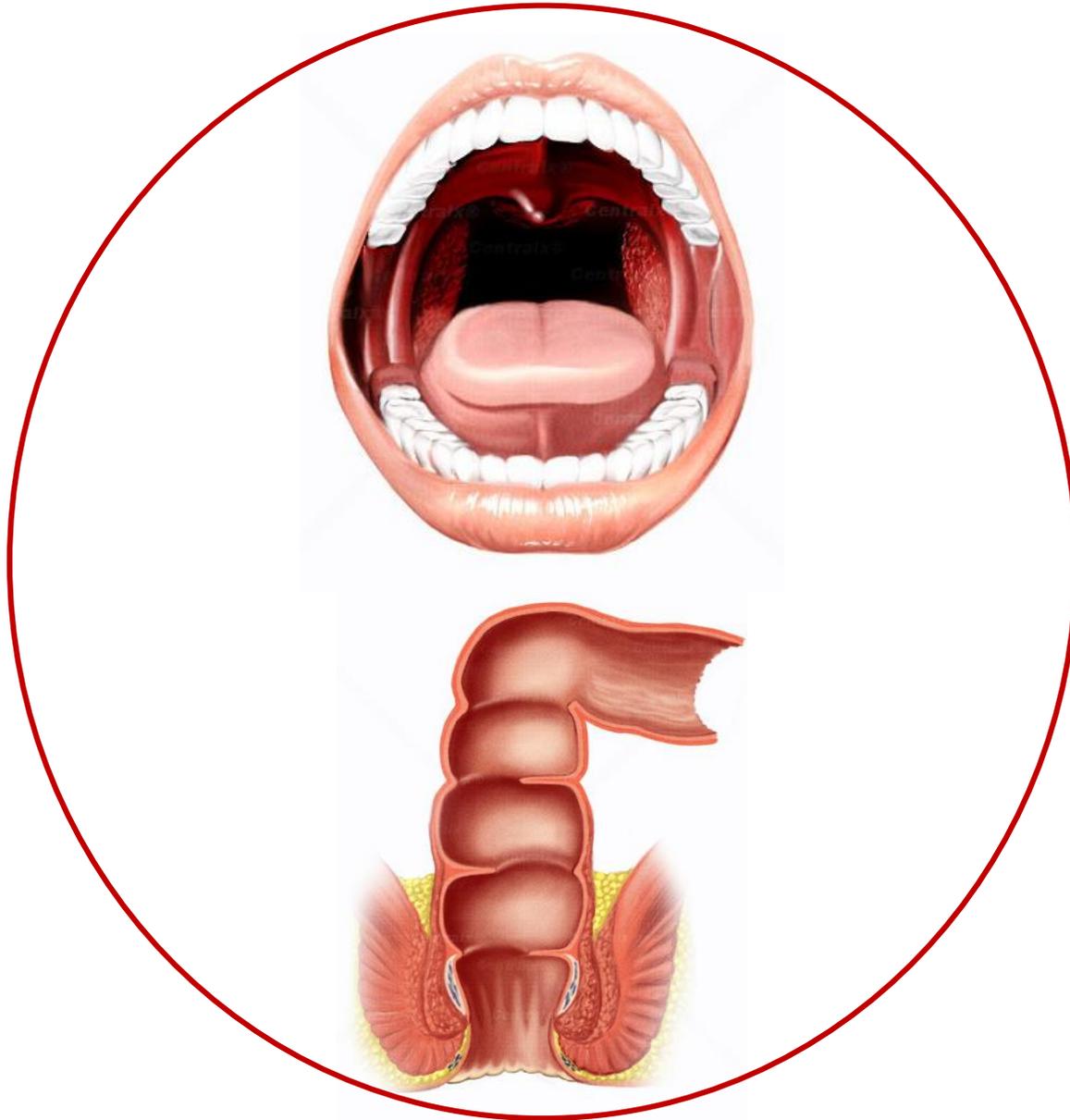
*World J Gastrointest Surg* 2016 January 27; 8(1): 41-51

**Table 2 Professional society recommendations for anal cancer screening**

	<b>Routine screening of general population</b>	<b>Routine screening of high-risk individuals</b>	<b>Assesses modalities for diagnosis</b>	<b>Specific modalities assessed</b>
American Society of Colon and Rectal Surgeons <sup>[54]</sup>	No recommendation	No recommendation	Screening and surveillance	Anal Pap test, high-resolution anoscopy
European Society of Medical Oncology European Society of Surgical Oncology European Society for Therapeutic Radiation and Oncology <sup>[102]</sup>	No recommendation	No recommendation	Surveillance only	Digital anorectal exam, standard anoscopy, computed tomography, magnetic resonance imaging
National Comprehensive Cancer Network <sup>[103]</sup>	No recommendation	No recommendation	Surveillance only	Digital anorectal exam, standard anoscopy
Centers for Disease Control and Prevention <sup>[104]</sup>	No recommendation	No recommendation	Screening and surveillance	Digital anorectal exam, HPV testing
New York State Department of Health <sup>[52]</sup>	No recommendation	All HIV infected adults	Screening only	Digital anorectal exam, anal Pap test, high resolution anoscopy
HIV Medicine Association of the Infectious Diseases Society of America <sup>[20]</sup>	No recommendation	Men who have sex with men, women with a history of abnormal cervical Pap tests, and all HIV-positive persons with genital warts	Screening only	Digital anorectal exam, HPV co-testing, anal Pap test, high resolution anoscopy
British HIV Association <sup>[21]</sup>	No recommendation	No recommendation	Screening and surveillance	Digital anorectal exam, anal Pap test, high resolution anoscopy

HIV: Human immunodeficiency virus; HPV: Human papilloma virus; Pap: Papanicolaou.

# HPV en orofaringe y canal anal



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# Risk of second primary cancer after a first potentially-human papillomavirus-related cancer: A population-based study

Florent Neumann <sup>a,\*</sup>, Jérémie Jégu <sup>b,c,n</sup>, Christiane Mougin <sup>d,e</sup>, Jean-Luc Prétet <sup>d,e</sup>, Anne-Valérie Guizard <sup>f,n</sup>, Bénédicte Lapôtre-Ledoux <sup>g,n</sup>, Simona Bara <sup>h,n</sup>, Véronique Bouvier <sup>i,n</sup>, Marc Colonna <sup>j,n</sup>, Xavier Troussard <sup>k,n</sup>, Brigitte Trétarre <sup>l,n</sup>, Pascale Grosclaude <sup>m,n</sup>, Michel Velten <sup>b,c,n</sup>, Anne-Sophie Woronoff <sup>a,d,n</sup>

## A B S T R A C T

Preventive Medicine 90 (2016) 52–58

Human papillomaviruses (HPV) are involved in the development of anogenital and head and neck cancers. The purpose of this study was to assess the risk of developing a second primary cancer (SPC) after a first potentially-HPV-related cancer, and to analyze the sites where SPCs most frequently occurred in these patients. All patients with a first cancer diagnosed between 1989 and 2004, as recorded by 10 French cancer registries, were followed up until December 31, 2007. Only invasive potentially-HPV-related cancers (namely, cervical, vagina, vulva, anal canal, penile, oropharynx, tongue and tonsil) were included. Standardized Incidence Ratios (SIRs) were calculated to assess the risk of SPC. A multivariate Poisson regression model was used to model SIRs separately by gender, adjusted for the characteristics of the first cancer. 10,127 patients presented a first potentially-HPV-related cancer. The overall SIR was 2.48 (95% CI, 2.34–2.63). The SIR was 3.59 (95% CI, 3.33–3.86) and 1.61 (95% CI, 1.46–1.78) in men and women respectively. The relative risk of potentially-HPV-related SPC was high among these patients (SIR = 13.74; 95% CI, 8.80–20.45 and 6.78; 95% CI, 4.61–9.63 for men and women, respectively). Women diagnosed in the most recent period (2000–2004) showed a 40% increase of their relative risk of SPC as compared with women diagnosed between 1989 and 1994 (ratio of SIRs = 1.40; 95% CI, 1.06–1.85). HPV cancer survivors face an increased risk of SPC, especially second cancer. Clinicians may consider this increased risk of developing HPV-related SPC during follow-up to improve subsequent cancer prevention in these patients.

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## Human papillomavirus-related squamous cell carcinoma of the anal canal with papillary features

Marino E Leon, Rania Shamekh, Domenico Coppola

**Core tip:** Human papillomavirus (HPV)-related squamous cell carcinoma with papillary morphology has previously been reported in the oropharynx. Here, we describe the occurrence of such a tumor in the anal canal. The association with high risk HPV is demonstrated and poses the question of whether the HPV infection is responsible for this tumor phenotype.

## Human papillomavirus-related squamous cell carcinoma of the anal canal with papillary features

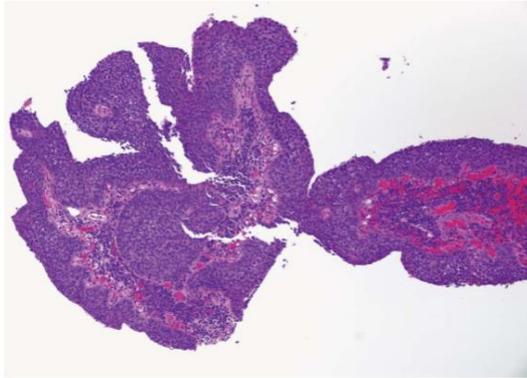


Figure 1 Biopsy of anal mass showing a squamous cell carcinoma with prominent papillary features (HE,  $\times 100$ ).

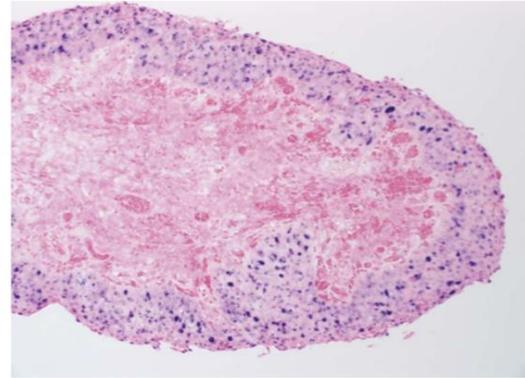


Figure 4 *In-situ* hybridization for high risk types of human papillomavirus showing a strong and diffuse reaction of the epithelial tumor cells ( $\times 200$ ).

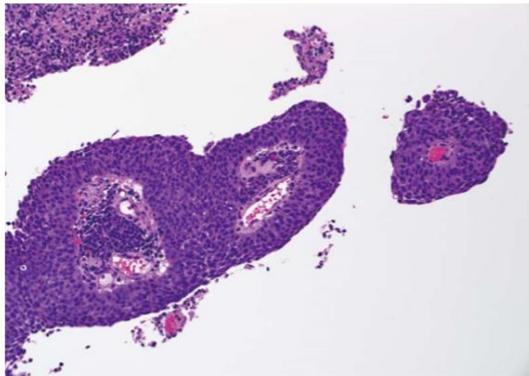


Figure 2 Higher power view of the papillary structures and associated anal intraepithelial neoplasia 3 (carcinoma-situ) (HE,  $\times 200$ ).



Figure 3 p-16 immunohistochemical stain showing strong and diffuse positive reaction of the tumor cells ( $\times 100$ ).

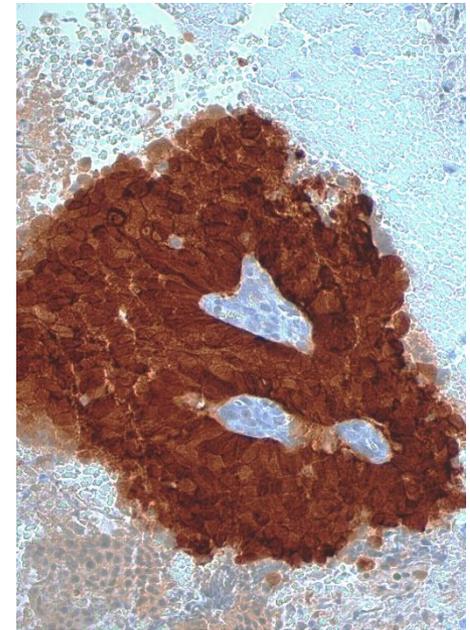
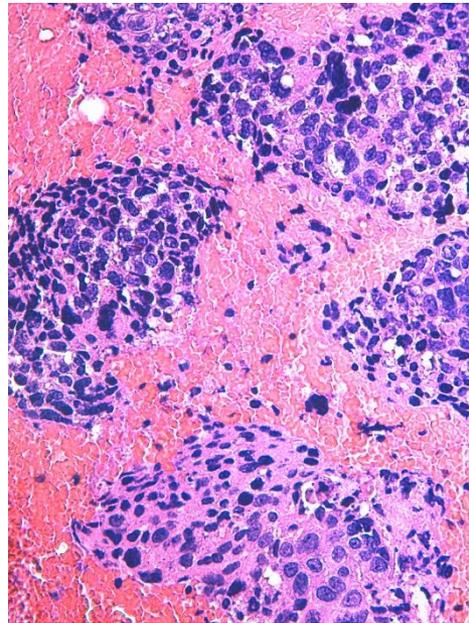
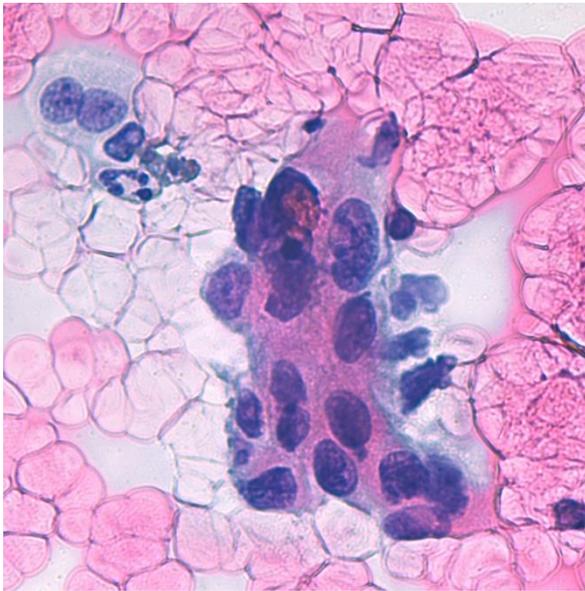
# Mujer de 50 años con adenopatía submandibular

PAAF del ganglio linfático:

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PAAF del ganglio linfático:

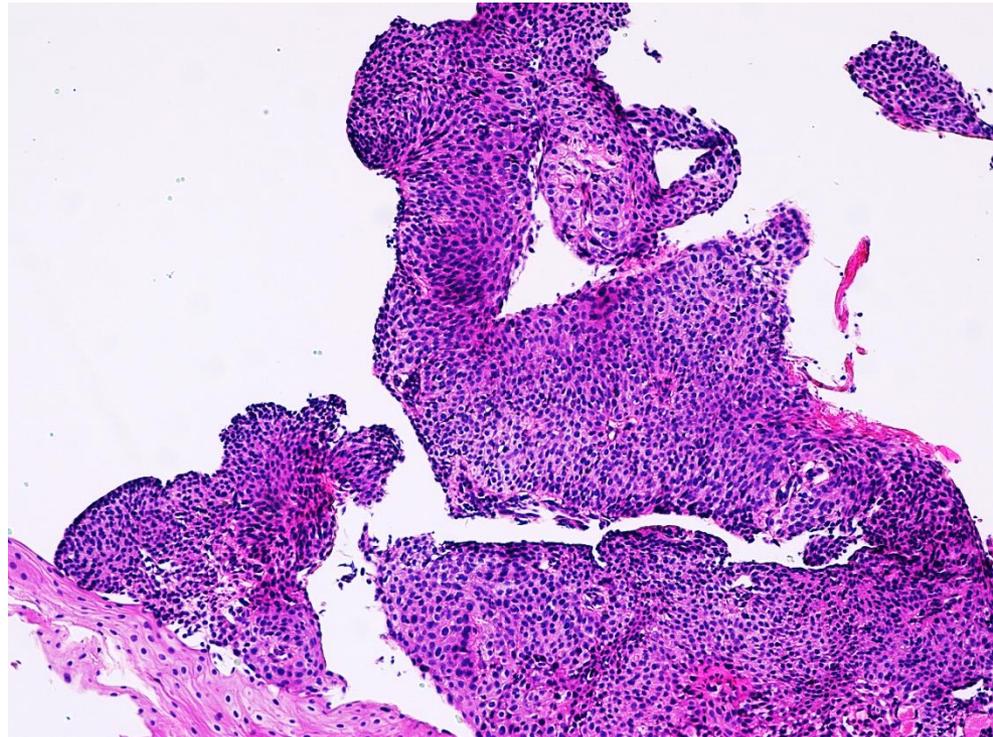
Metástasis de carcinoma escamoso pobremente diferenciado no queratinizante, p16 (+).



La exploración clínica exhaustiva, no identificó lesiones macroscópicas en la cavidad oral, orofaríngea o laríngea.

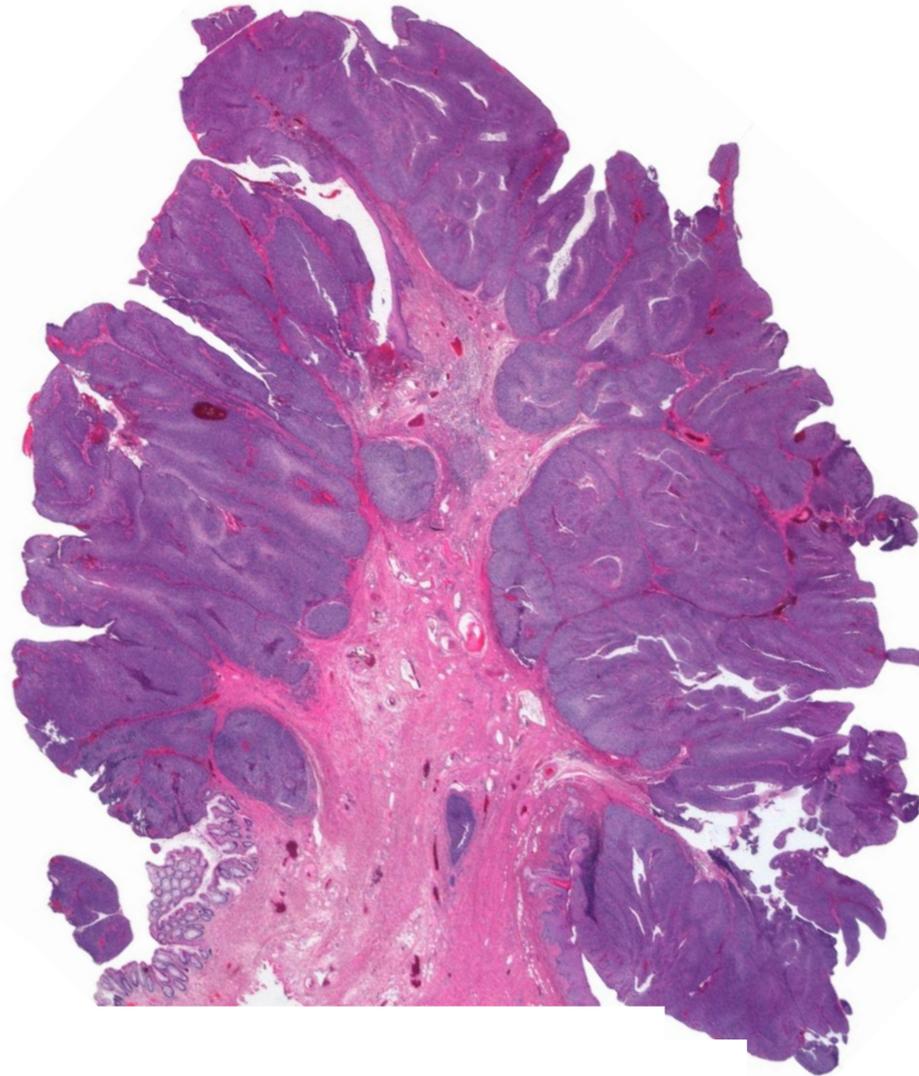
La exploración clínica exhaustiva, no identificó lesiones macroscópicas en la cavidad oral, orofaringe o laringe.

Biopsias randomizadas mostraron displasia epitelial de alto grado p16 (+) en la amígdala.



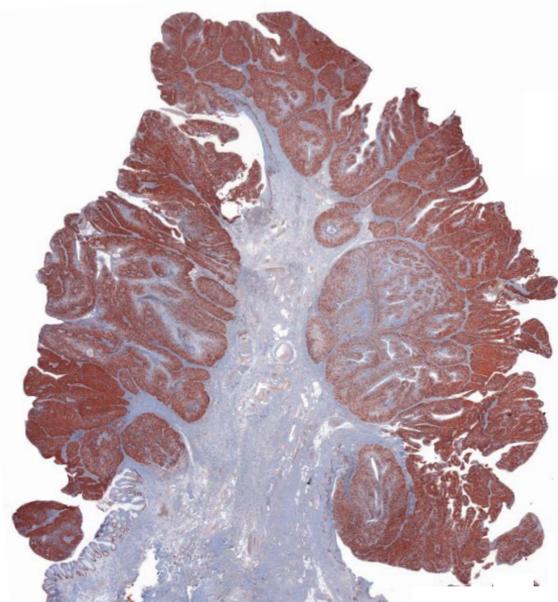
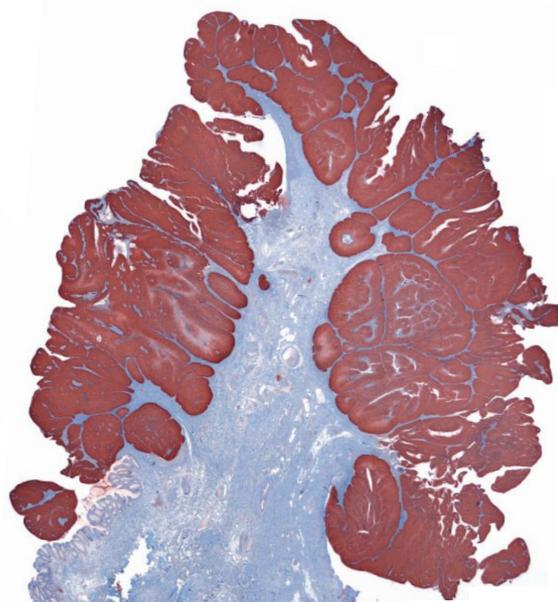
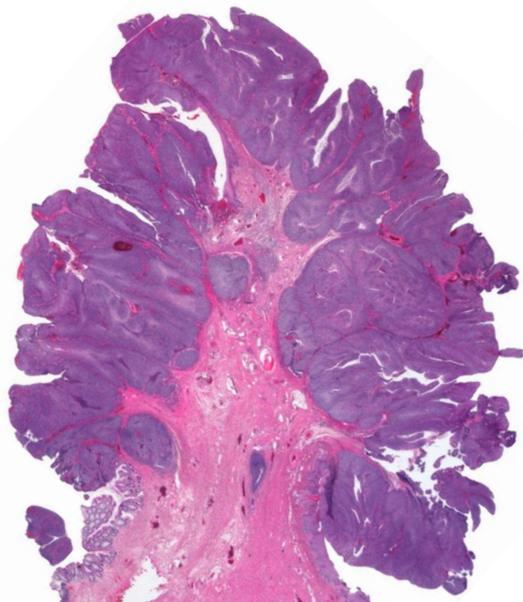
Simultáneamente se resecó una lesión polipoide del canal anal.

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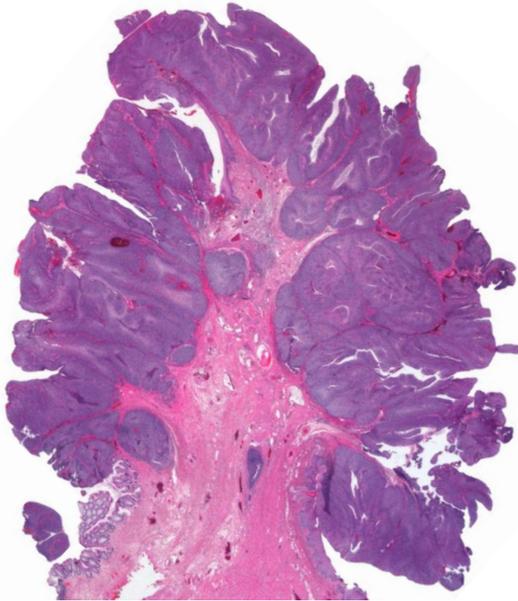
**p16**

**Ki-67**

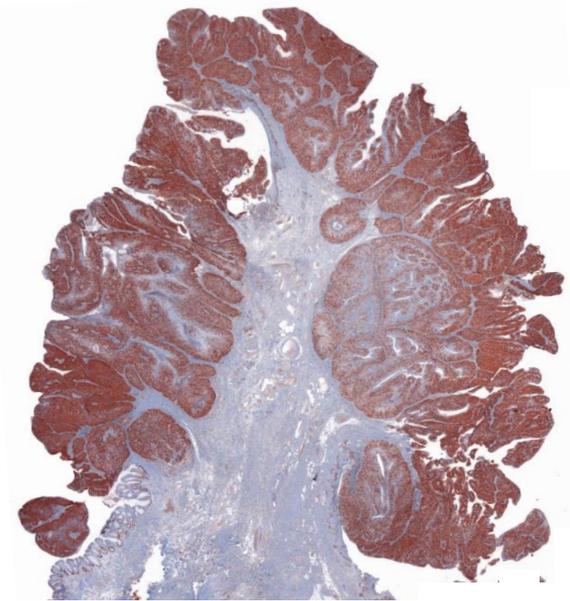
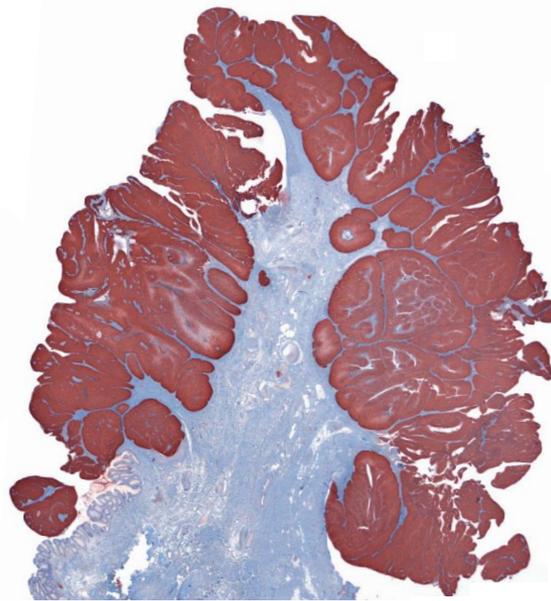


# Carcinoma escamoso anal asociado a HPV

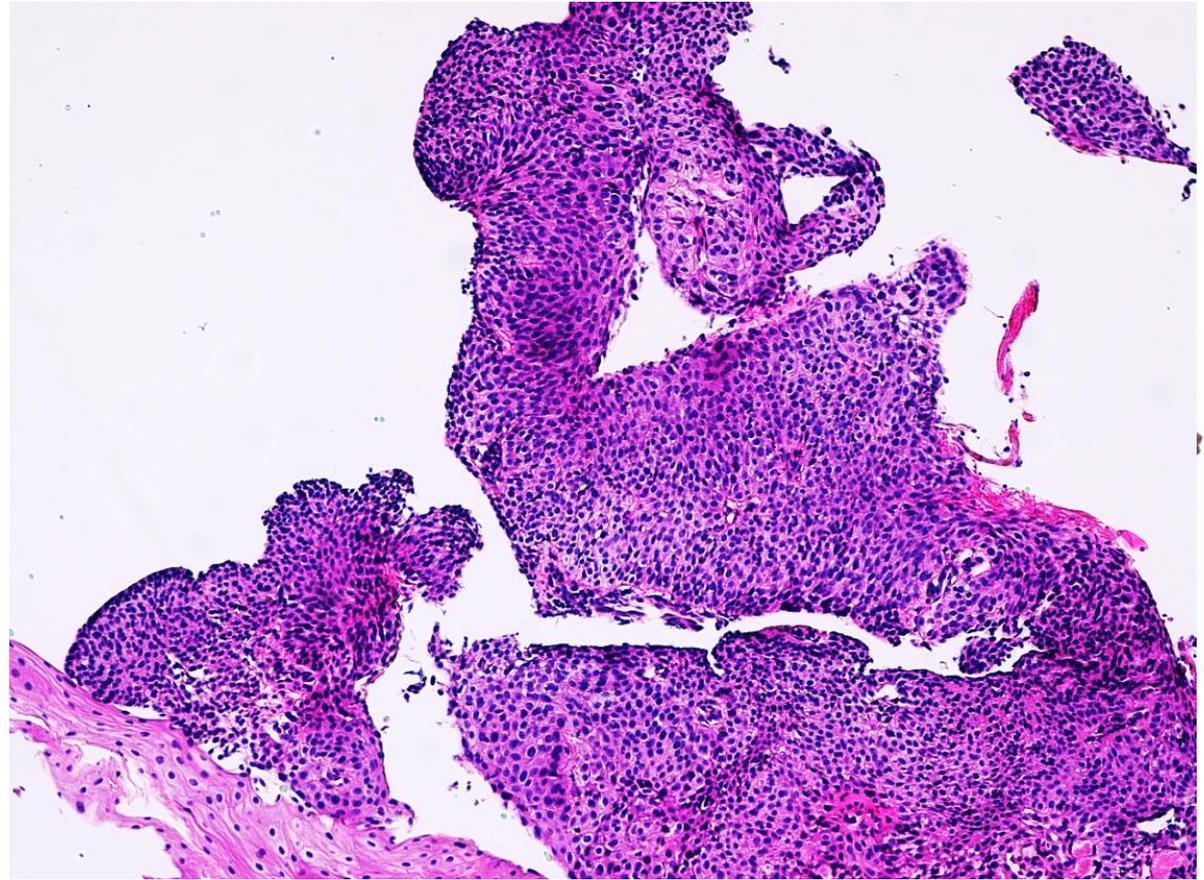
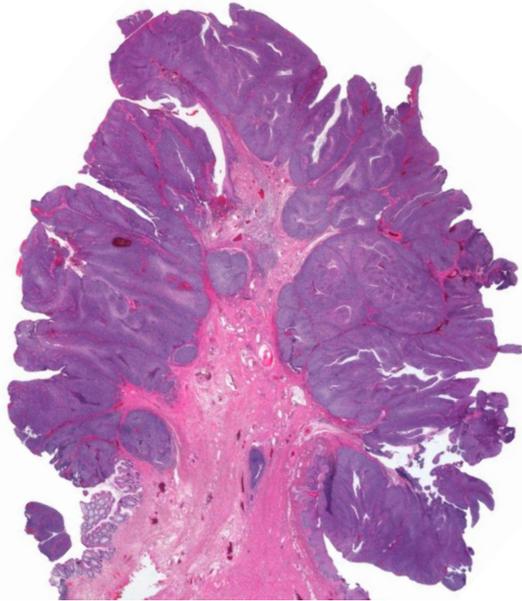
**p16**



**Ki-67**



# Carcinoma escamoso anal asociado a HPV sincrónico con carcinoma escamoso orofaríngeo



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