



Implicació dels HPV de Tipus Genital en Tumors Malignes Fora del Cèrvix Uterí

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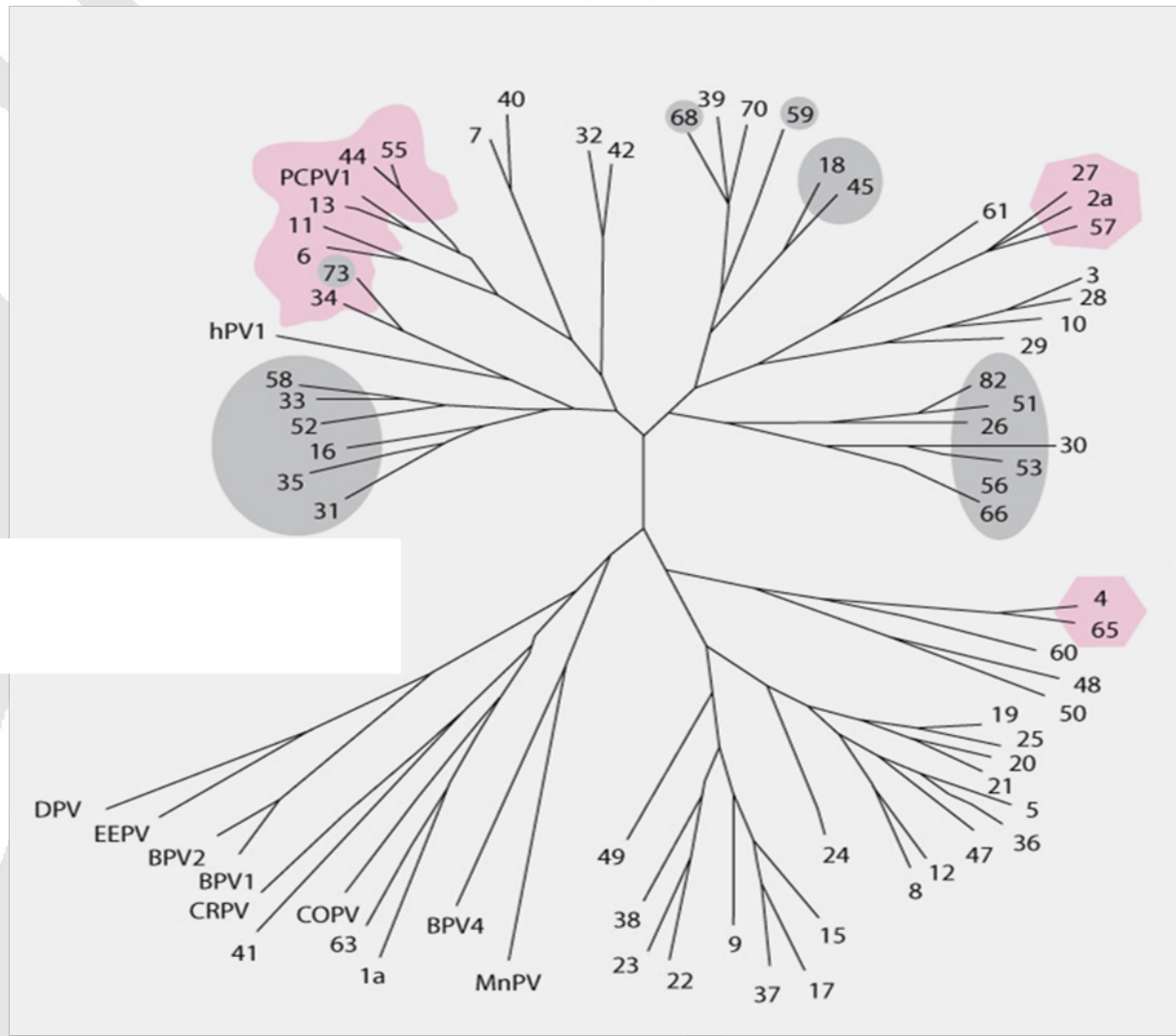


Carcinoma de cérvix y VPH

- International Biological Study on Cervical Cancer:
 - >1000 carcinomas de 22 países utilizando PCR: 93% HPV (Bosch et al, *J Natl Cancer Inst* 1995; 87:796)
 - Reanálisis de casos negativos: 99.7% HPV (Wallboomers et al, *J Pathol* 1999; 189:12)
 - HPV 16 el tipo más prevalente en casi todos los países



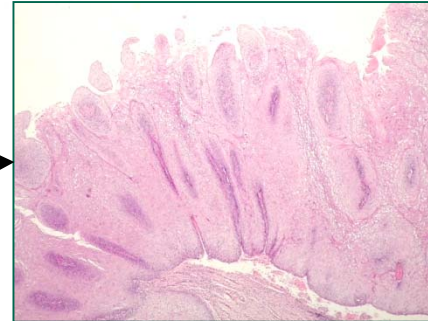
Classificació dels VPH



VPH genitals

Virus baix risc

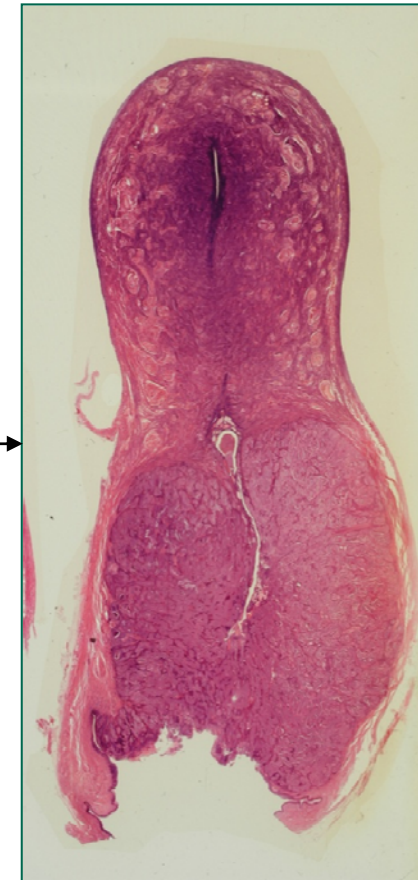
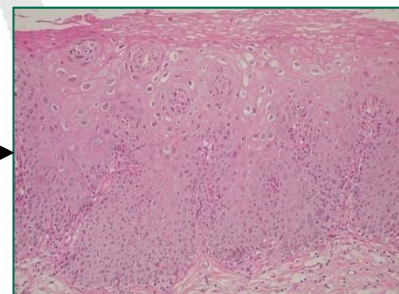
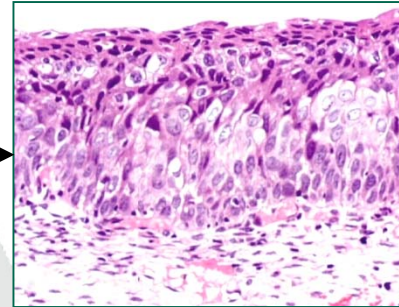
6,11,42,43,44,54,61,70,72,81



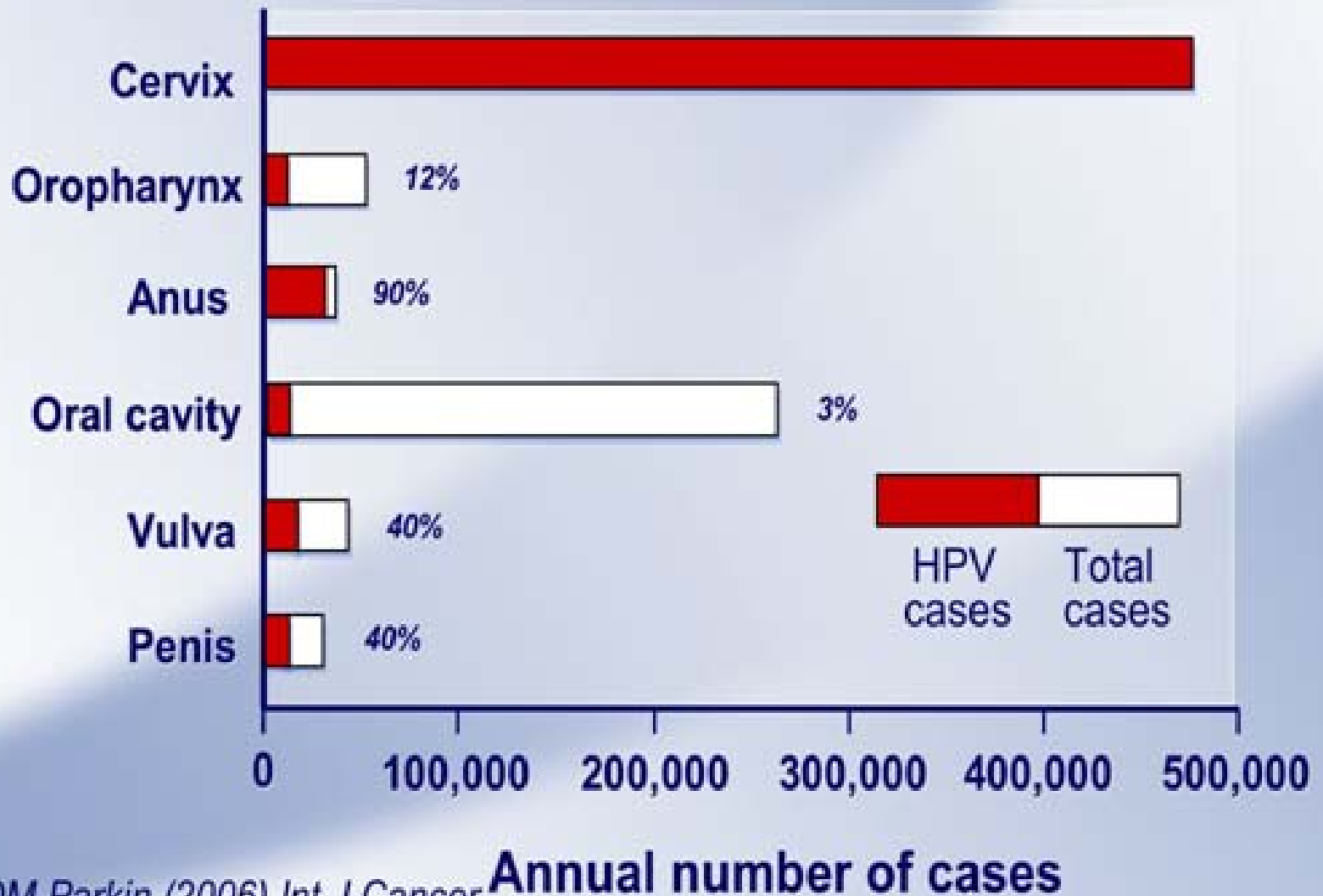
Virus alt risc

16,18,31,33,35,39,45,51,52,56

58,59,68,73,82



HPV and cancer

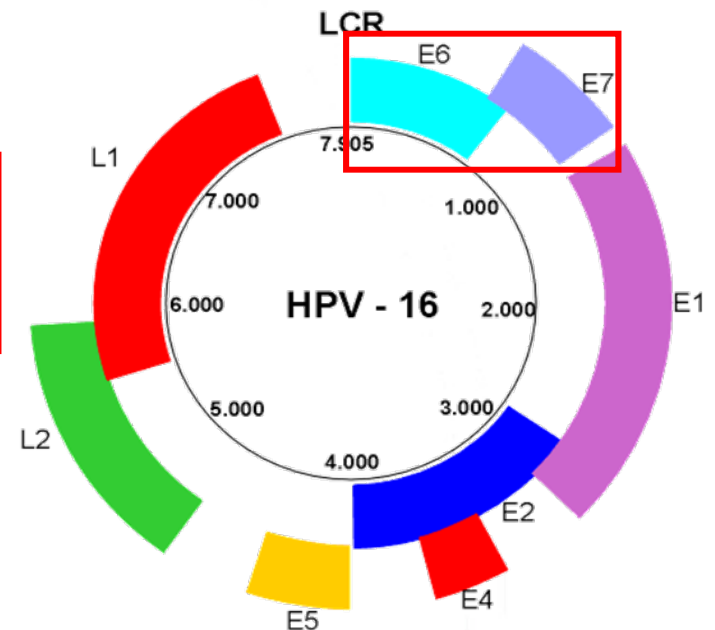


DM Parkin (2006) Int J Cancer

Annual number of cases

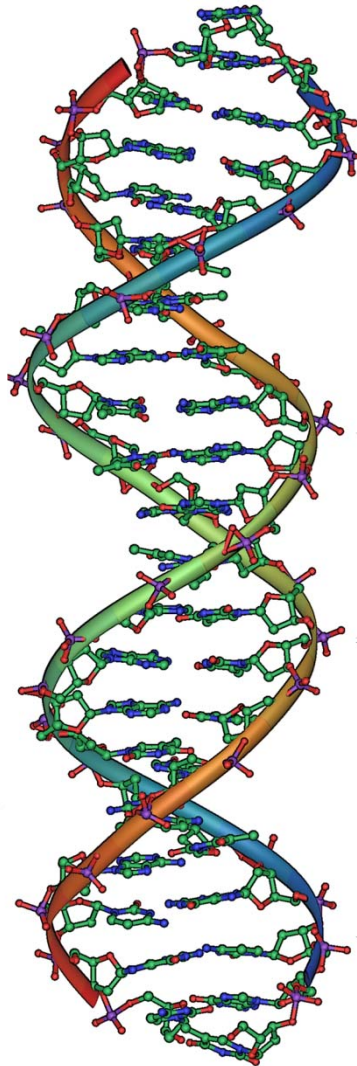
HPV genome

- Double strand DNA (≈ 8.000 base pairs)
- Regulatory region (LCR)
- Early region
 - E1 - E8 genes (DNA replication)
 - **E6 and E7 involved in neoplastic transformation**
- Late region
 - Genes L1 and L2 (Capsid)

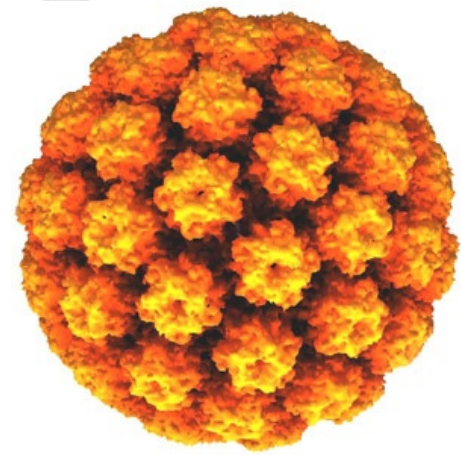




HPV: Mechanisms of transformation

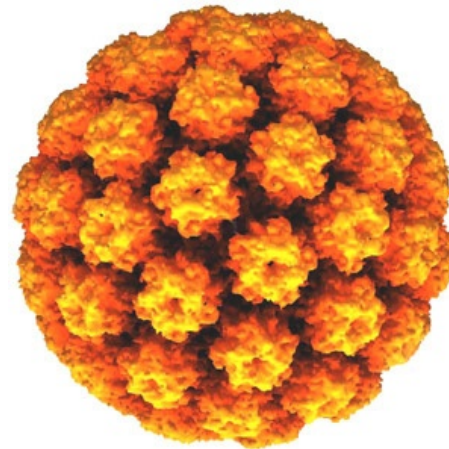
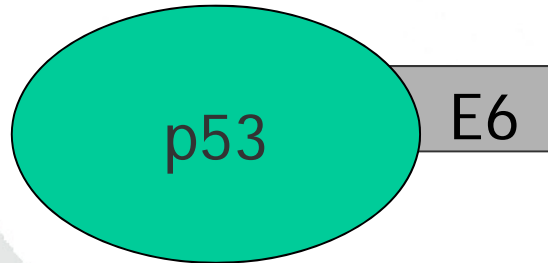
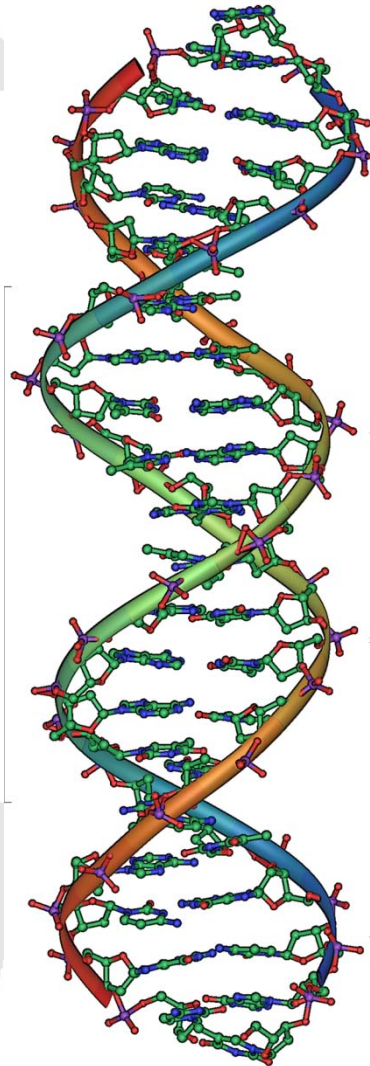


p53

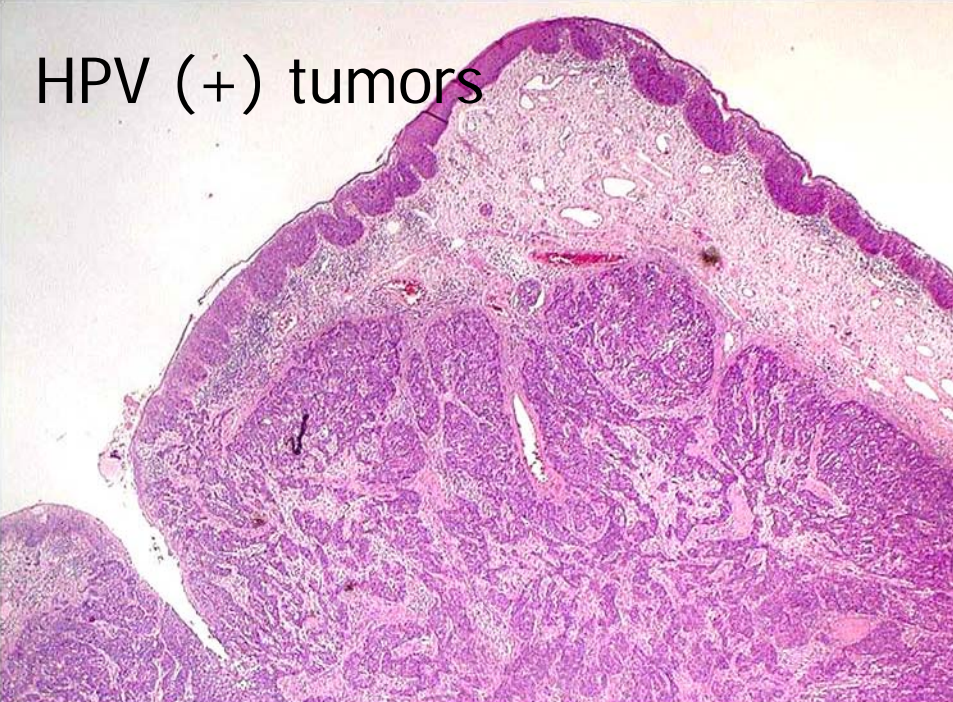




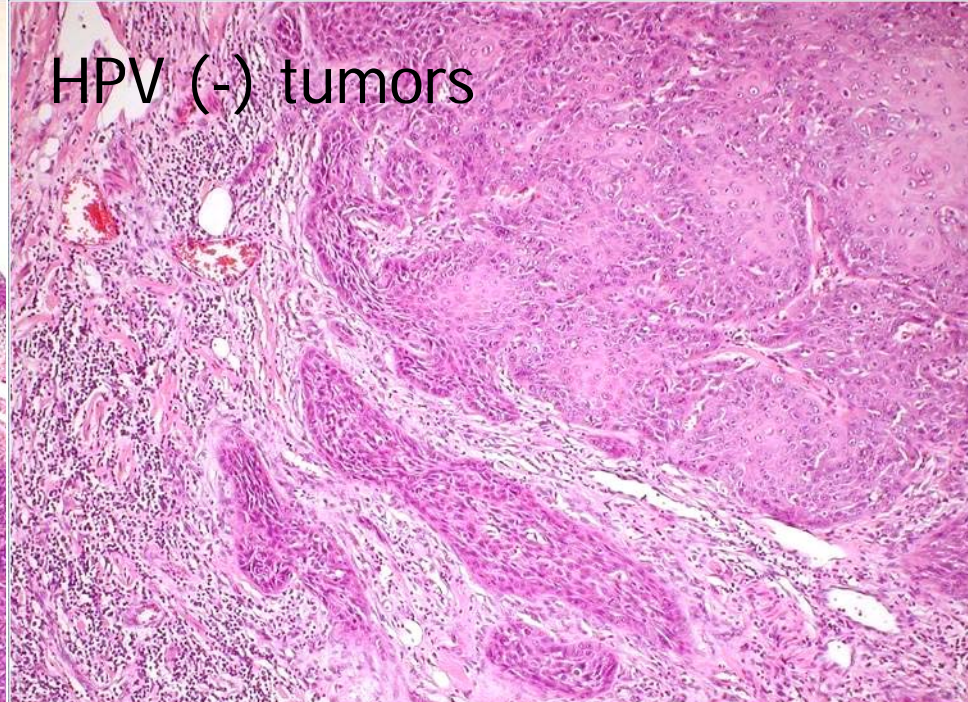
HPV: Mechanisms of transformation



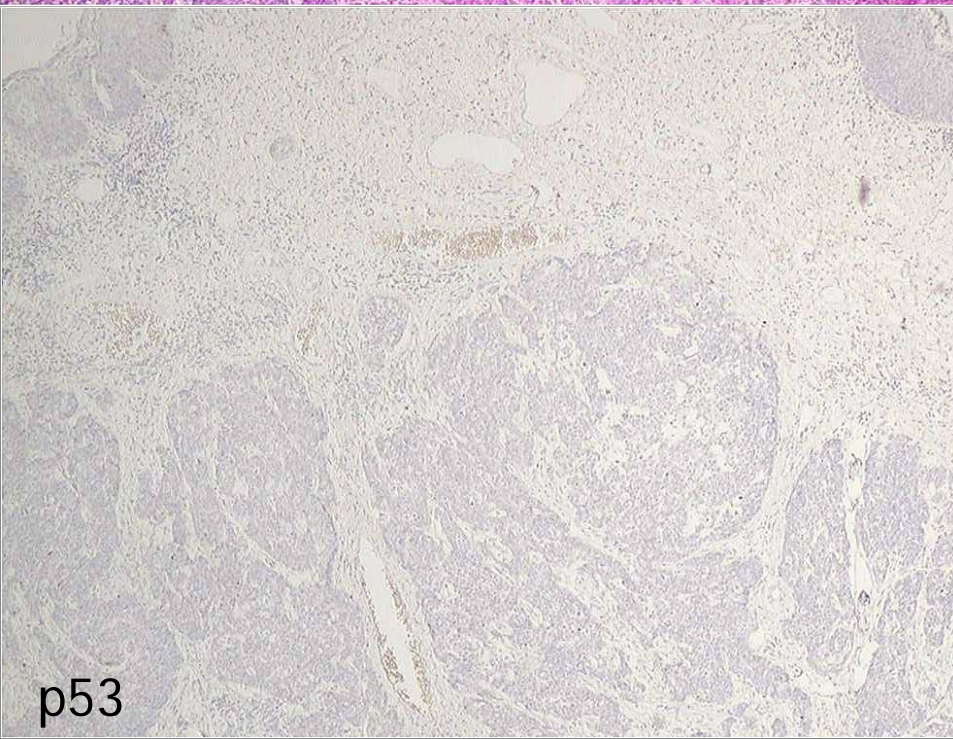
HPV (+) tumors



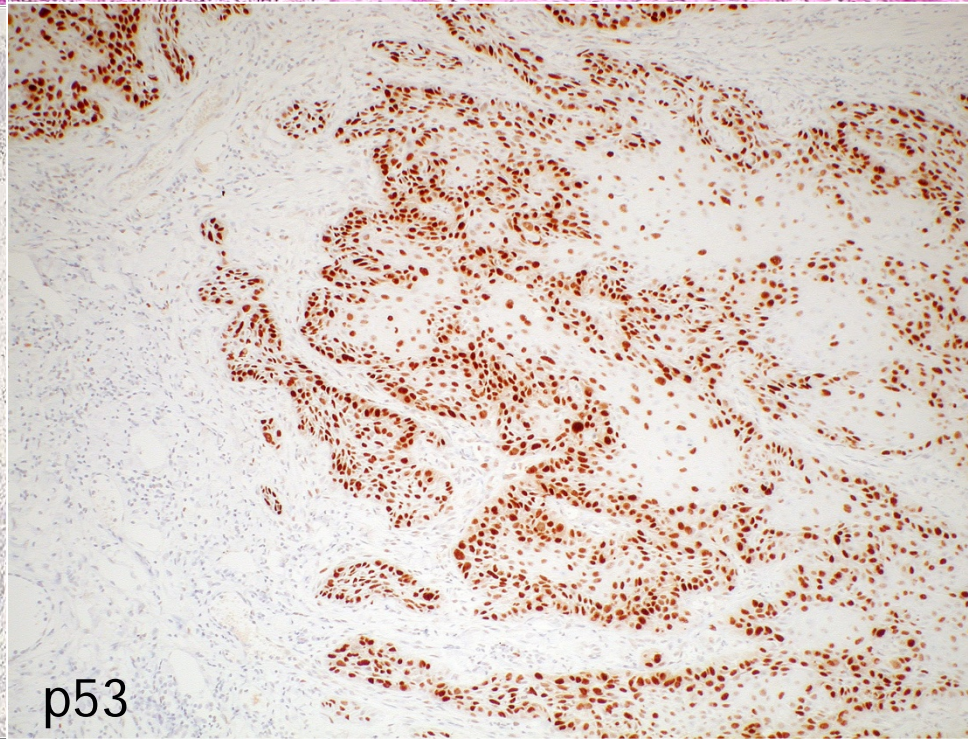
HPV (-) tumors



p53

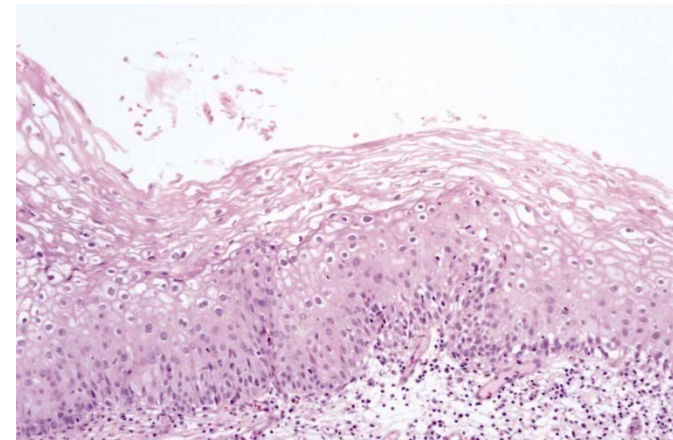
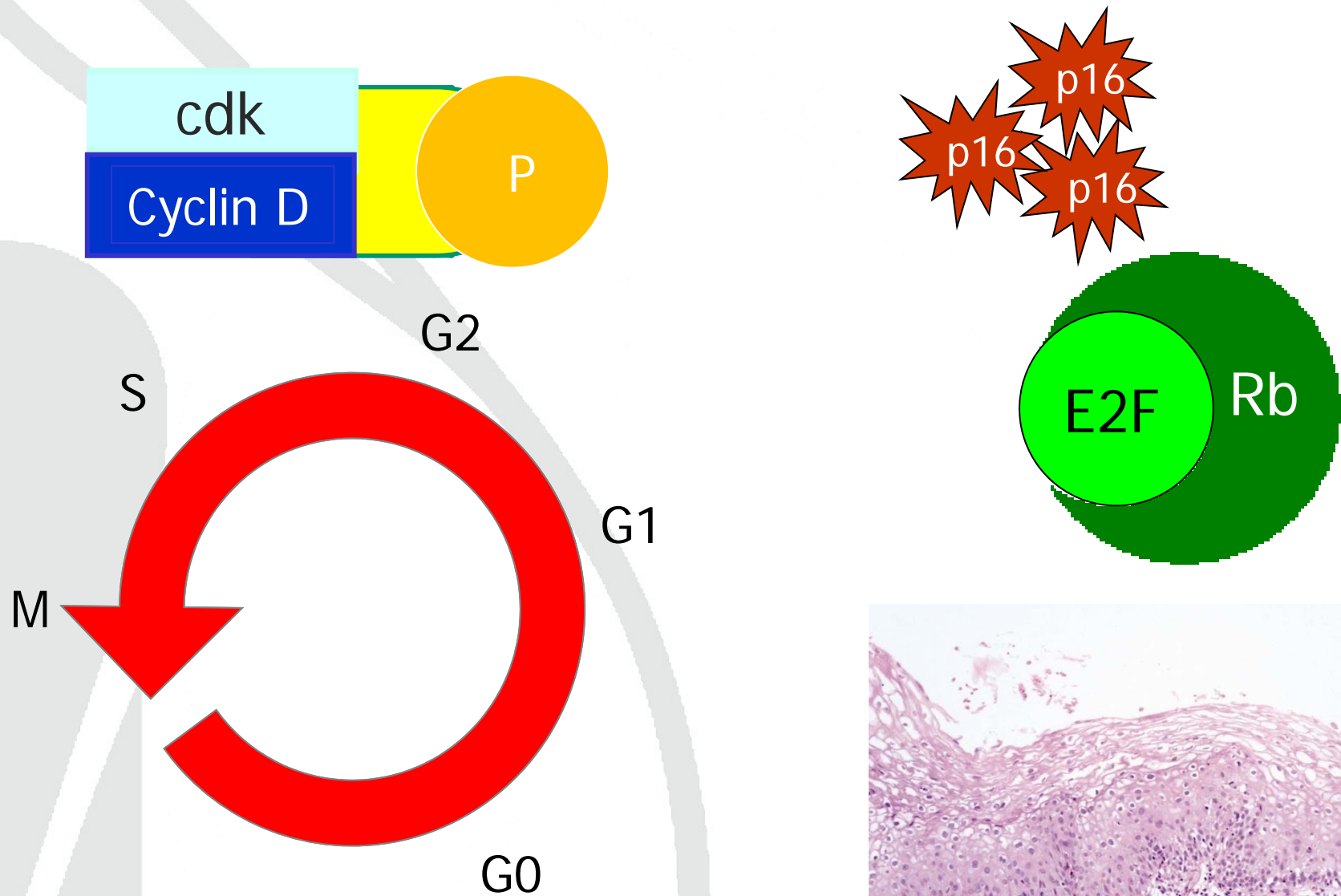


p53



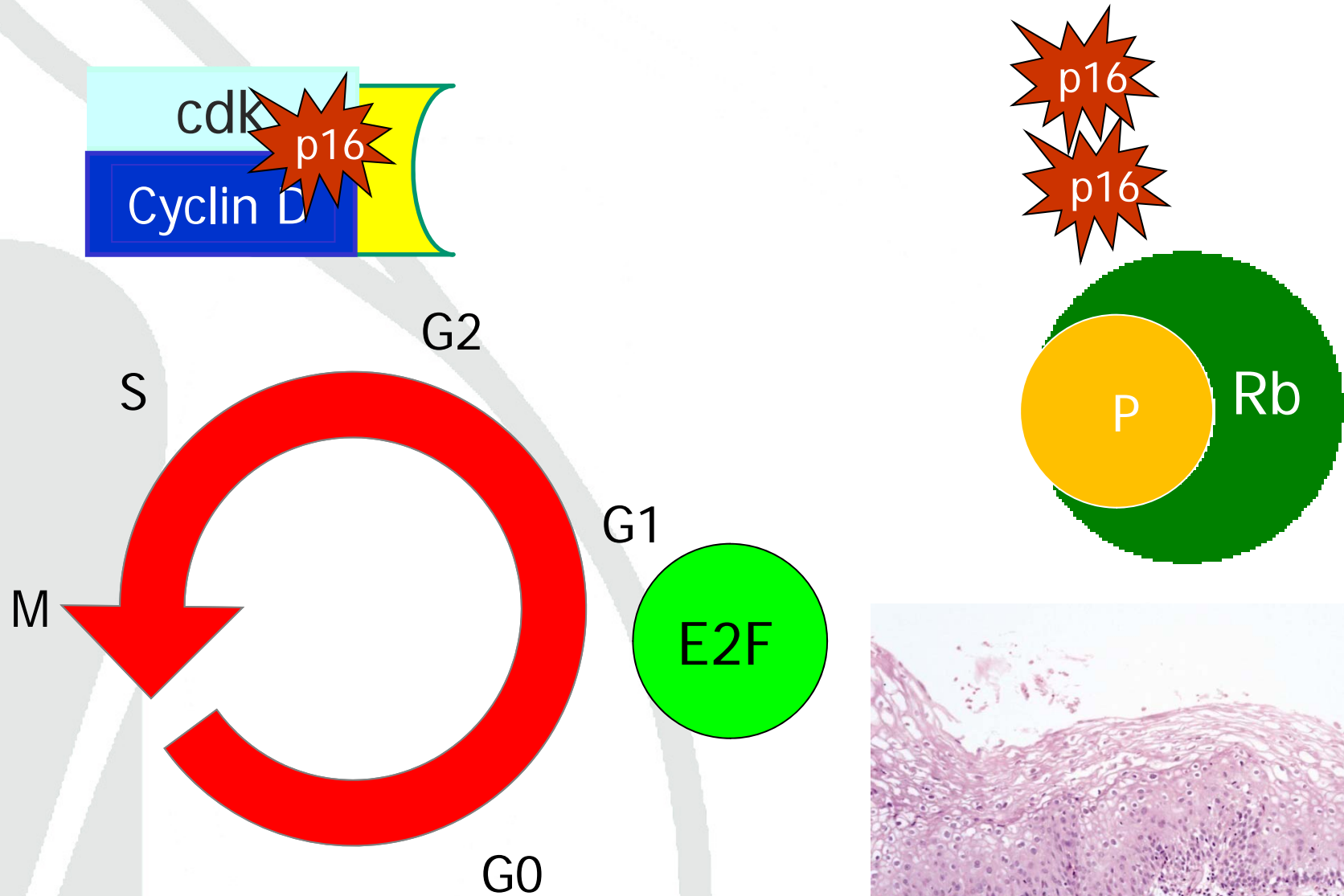


HPV: Mechanisms of transformation

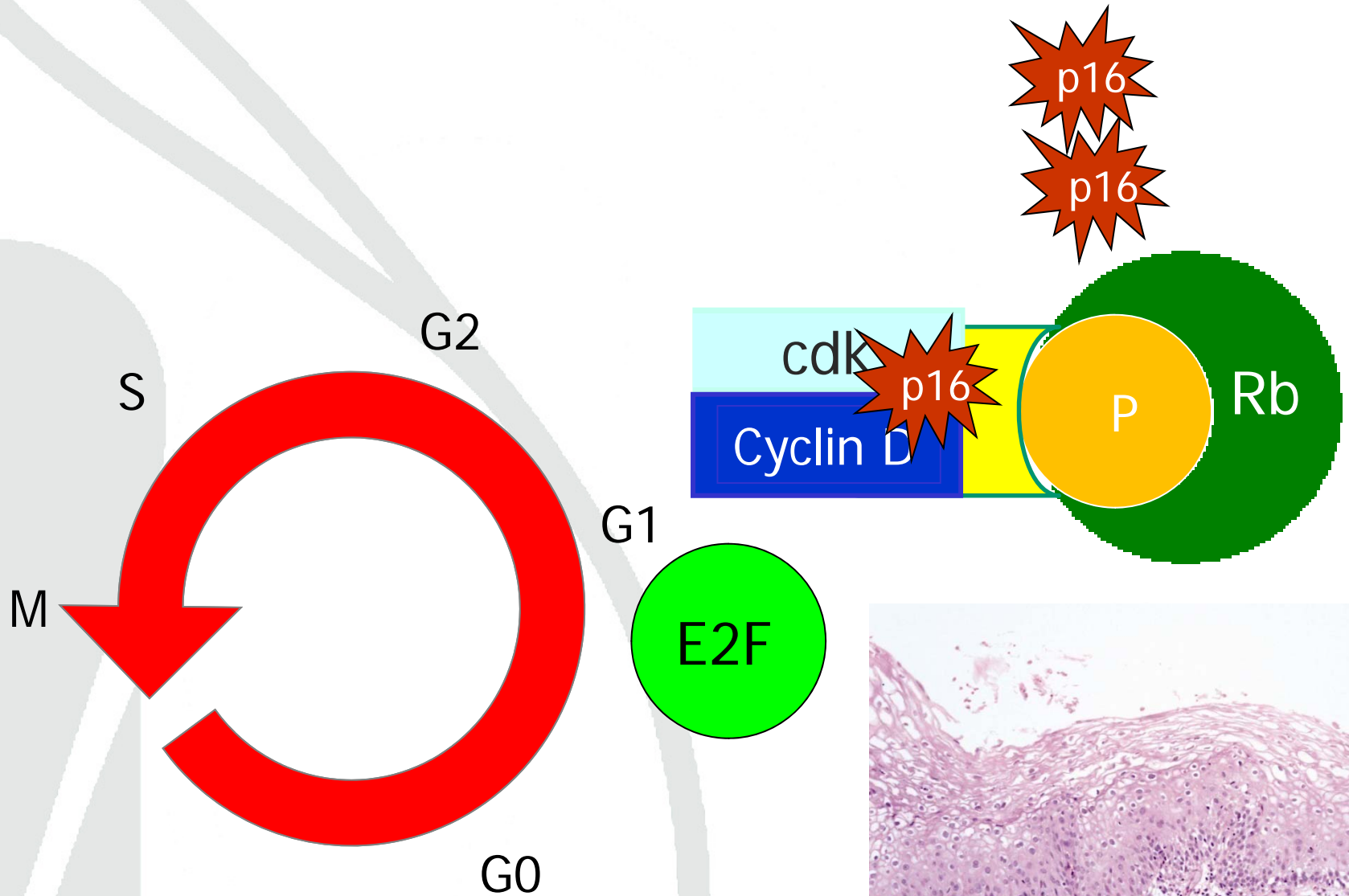




HPV: Mechanisms of transformation

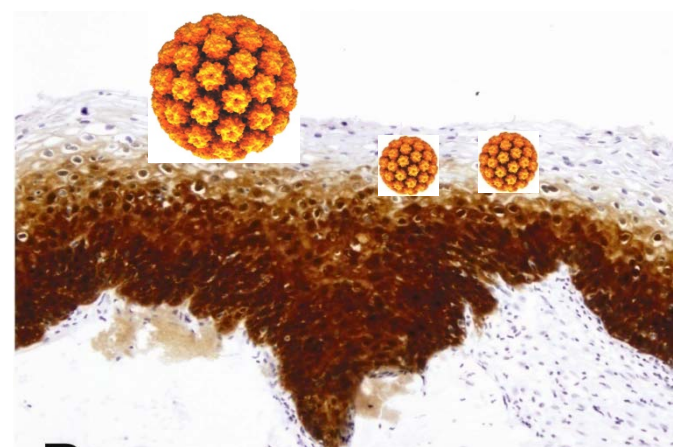
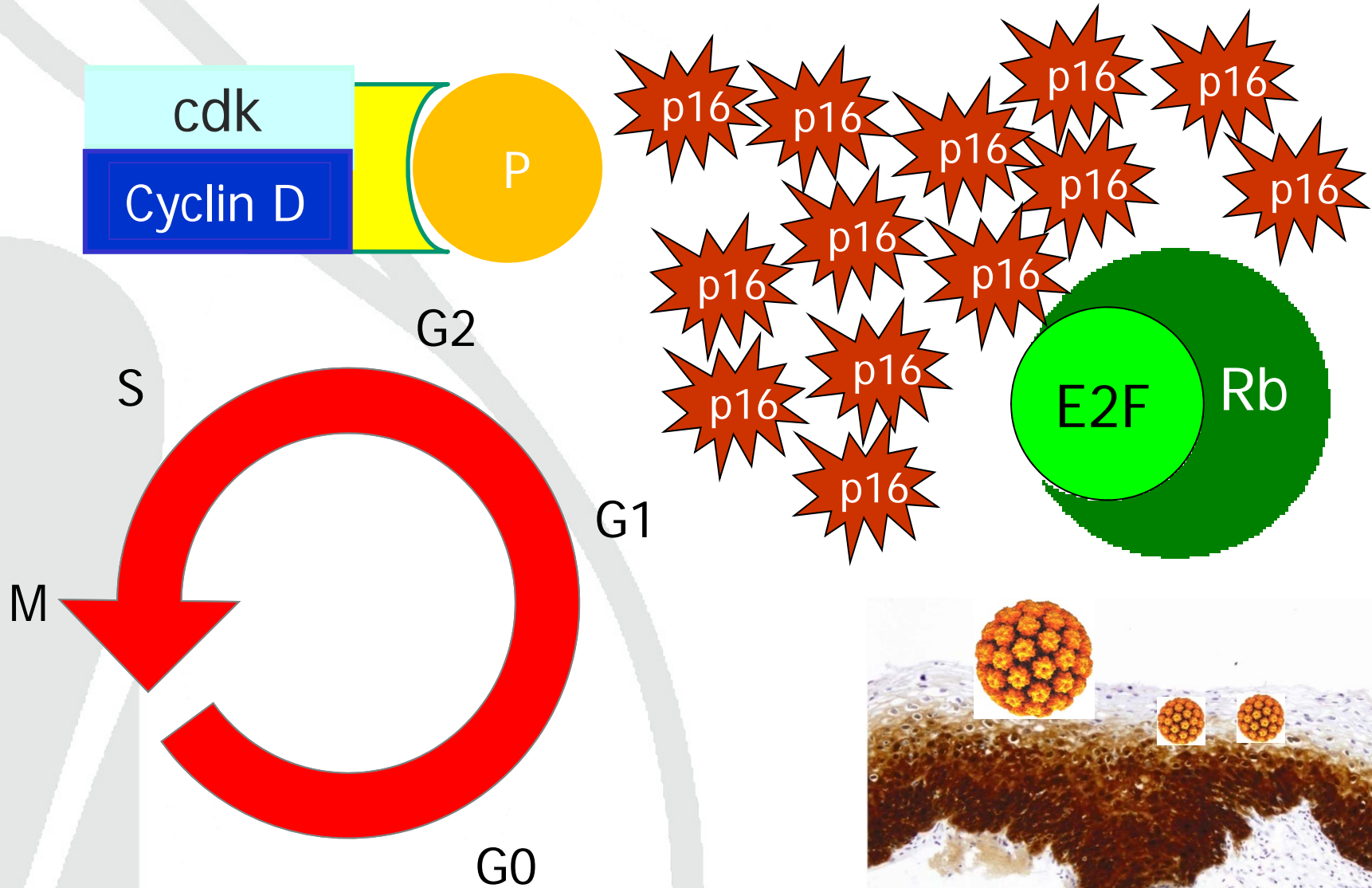


HPV: Mechanisms of transformation

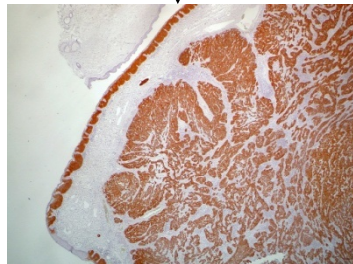




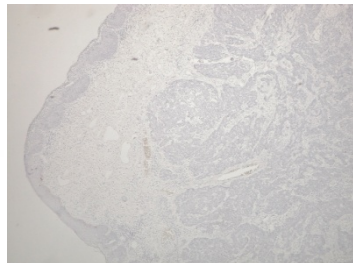
HPV: Mechanisms of transformation



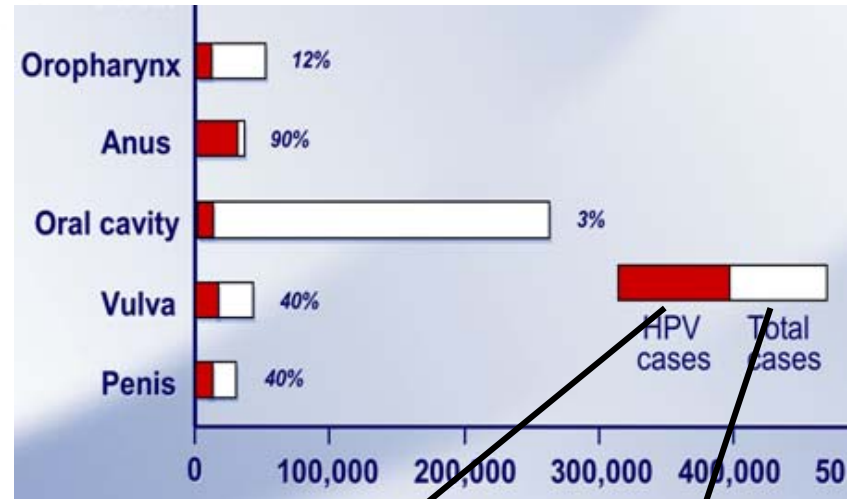
p16^{INK4a} and p53 in SCC



P16 (+)



P53 (-)



P16 (+)

P53 (-)

P16 (-)

P53 (+)



Càncer associat a VPH genital

- Carcinoma escatós de vulva
- Carcinoma escatós de vagina
- Carcinoma escatós de penis
- Carcinoma escatós anal
- Carcinoma escatós de cap i coll



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Carcinoma de la vulva

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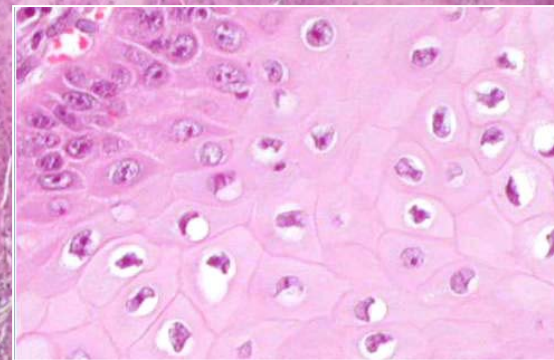
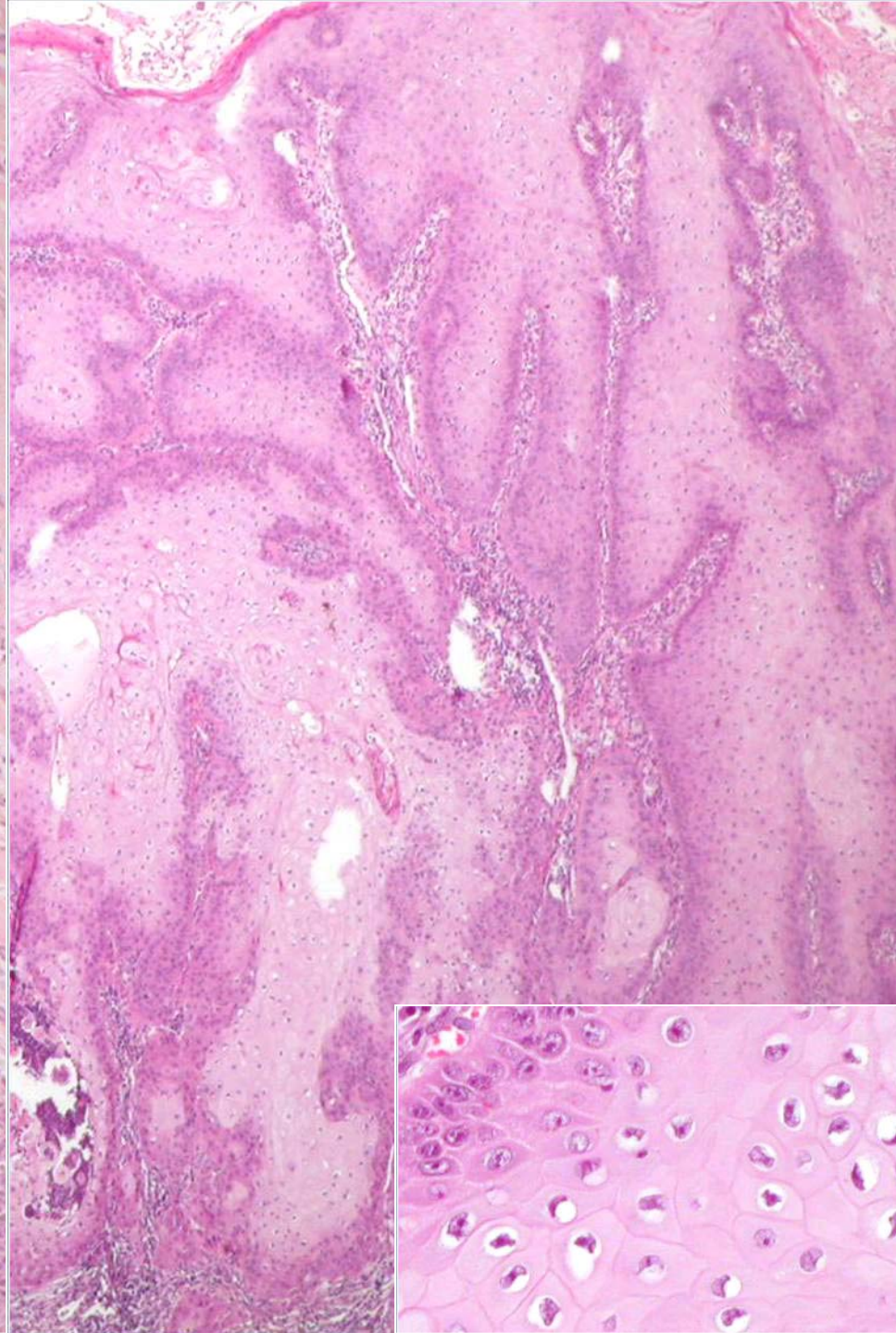
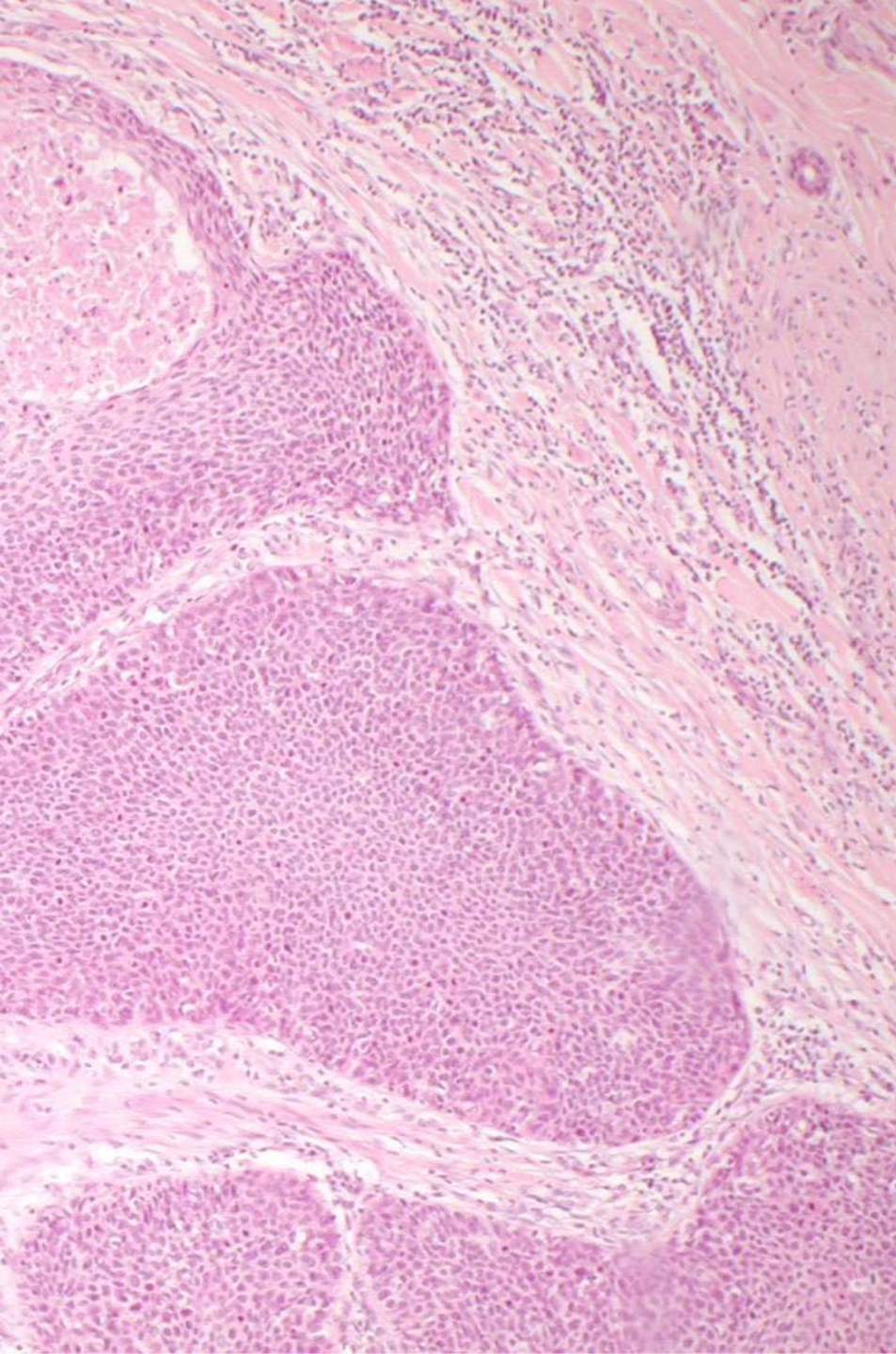


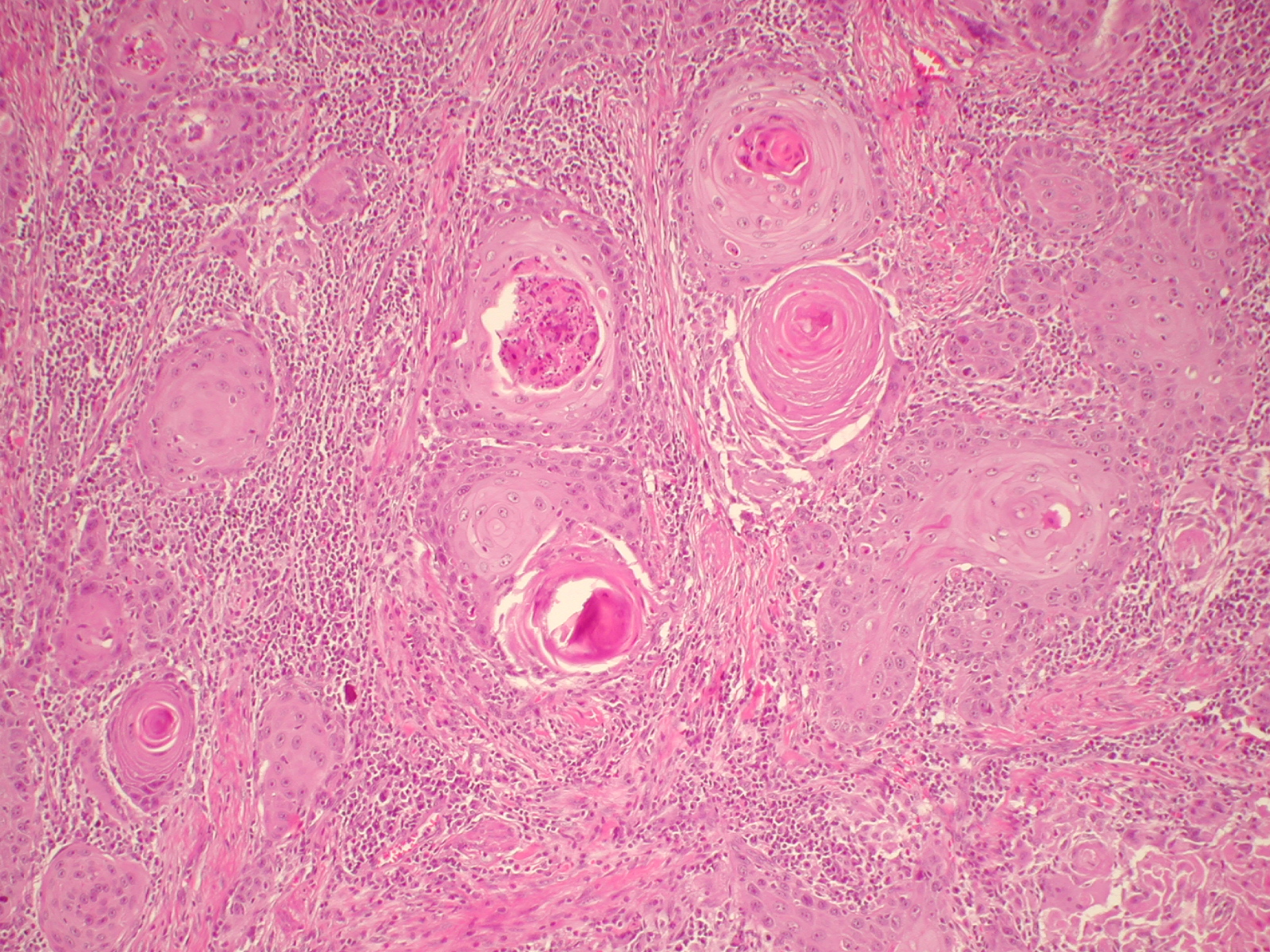
Carcinoma of the vulva

- Low frequency
 - < 4% GYN neoplasms
 - Incidence 20 : 100.000 women (Sturgeon et al. *Am J Obstet Gynecol* 1992; 166: 1482)
- Squamous cell carcinoma (SCC) >95%
- Two different etiopathogenic types (Kurman et al, *Am J Surg Pathol* 1993; 17:133) (Toki et al, *Int J Gynecol Pathol* 1991; 10:107)
 - HPV-positive
 - HPV-negative

SCC of the vulva (vSCC)

	HPV-positive	HPV-negative
Frequency	1/3	2/3
Age	Young	Old
Skin lesions	No	Lichen sclerosis Squamous cell hyperplasia
Histolog. type	Basaloid/warty	Keratinizing
VIN	Basaloid/warty	Differentiated
Molecular changes	Inactivation of p53 & Rb by products of HPV	Mutations of p53

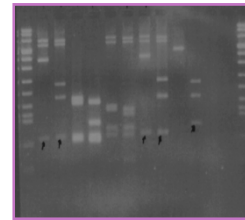




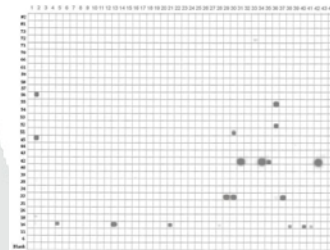
SCC of the vulva: HPV

- 92 invasive SCC of HCP
- Extraction of DNA from formalin-fixed, paraffin embedded tissue and detection of HPV by PCR

- PgMY09/11: 450 bp



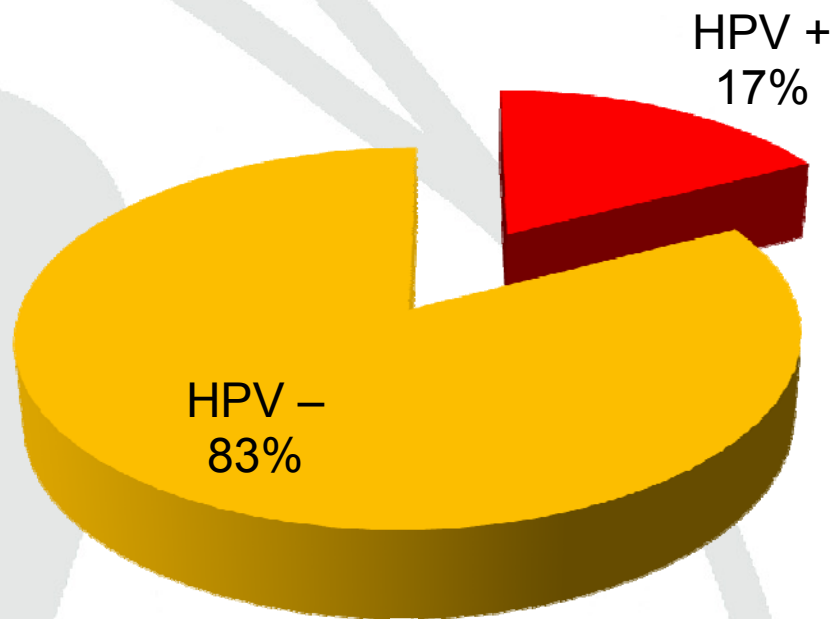
- GP5+/GP6+: 155 bp



- SPF10: 65 bp



SCC of the vulva: HPV

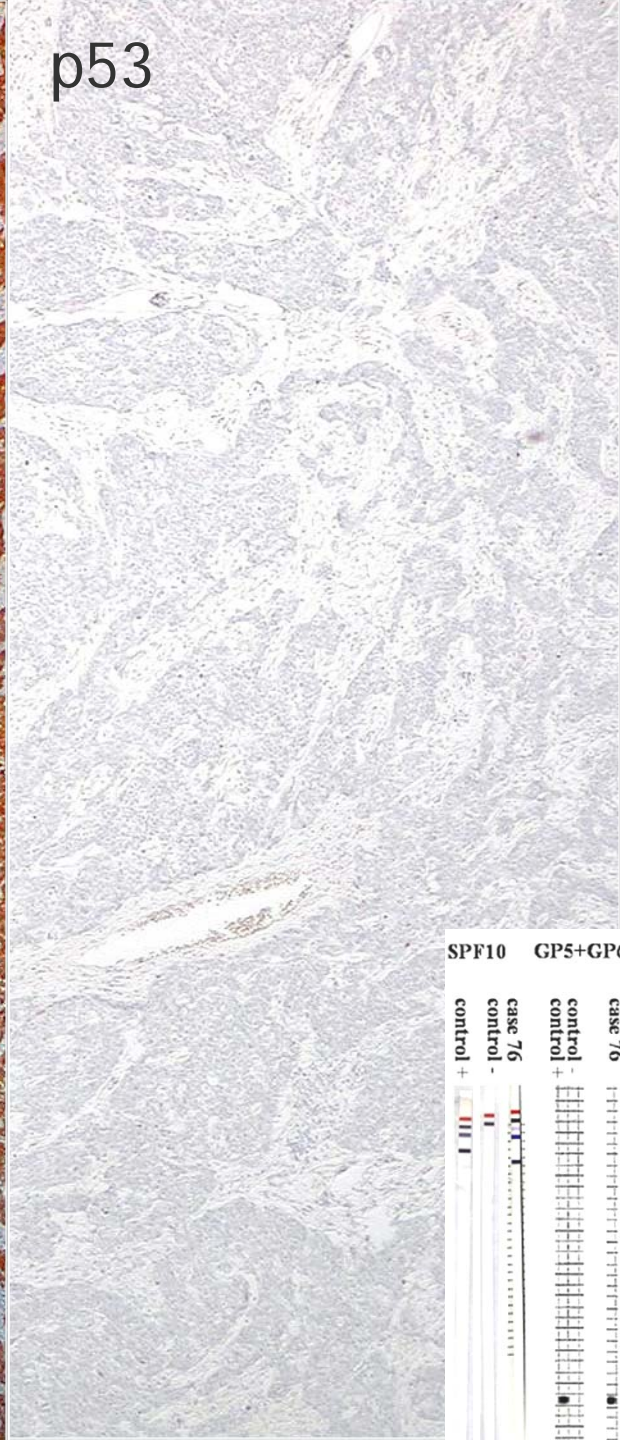
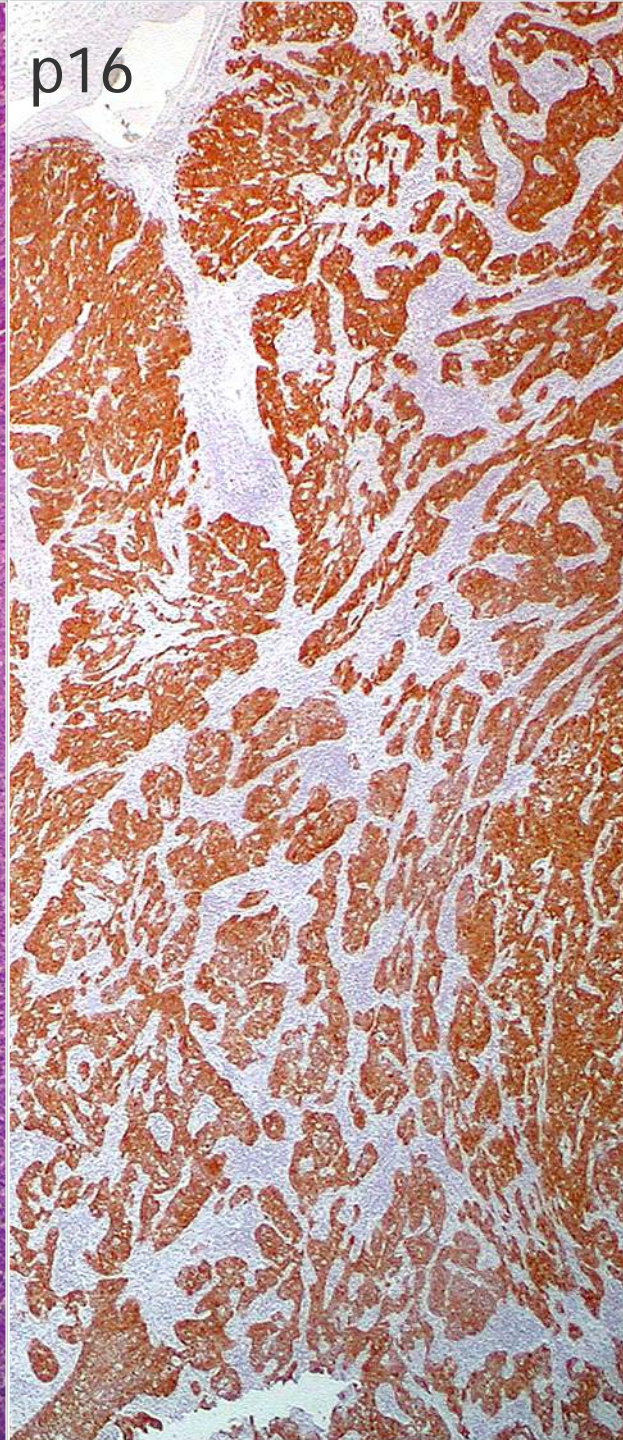
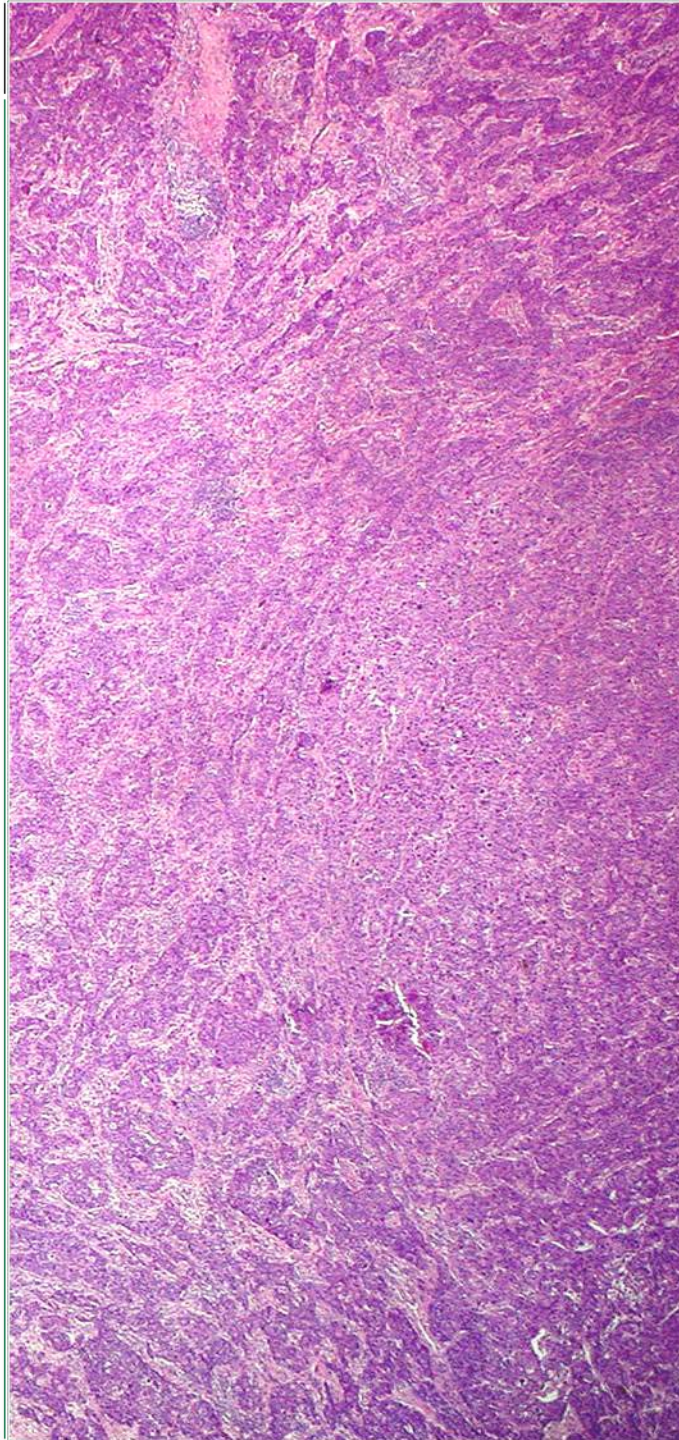


Case number	HPV
C14	33
C23	16
C32	33
C46	16
C62	16
C75	16
C76	16
C22	51
C49	16
C83	31
C33	16
C34	6 and 16
C35	16
C36	6 and 16
C56	16
C84	16

Santos M, et al. *Am J Surg Pathol* 2006; 30: 1347-1356

vSCC: p16^{INK4a}, p53

		High-risk human papillomavirus		
		Positive(n=16)	Negative (n=76)	p value
IHC	p16 +	16 (100.0 %)	1 (1.3 %)	<0.000001
	p53 +	1 (6.2 %)	49 (64.5 %)	0.00007

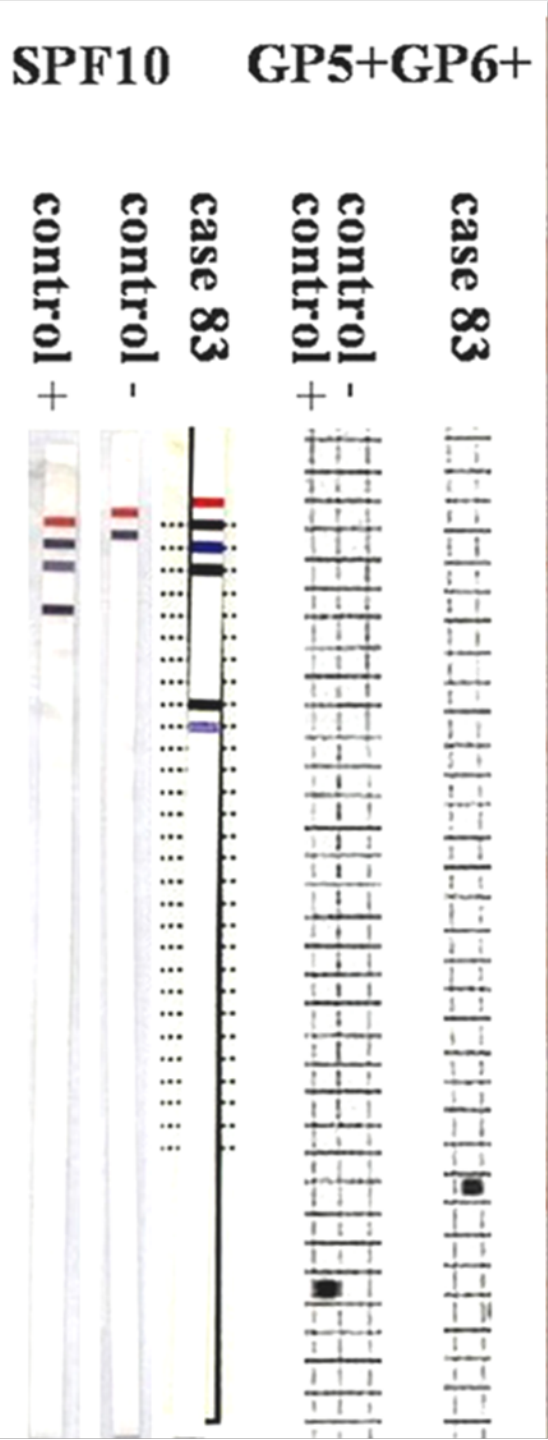
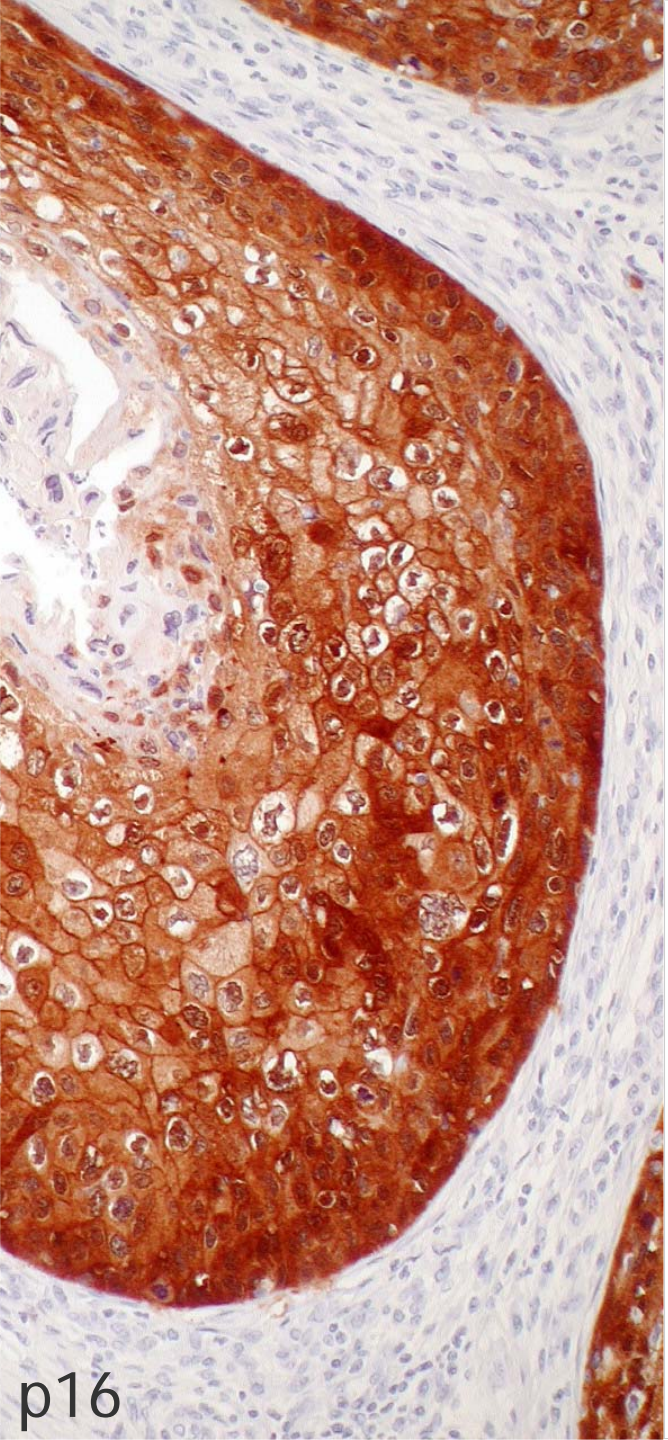
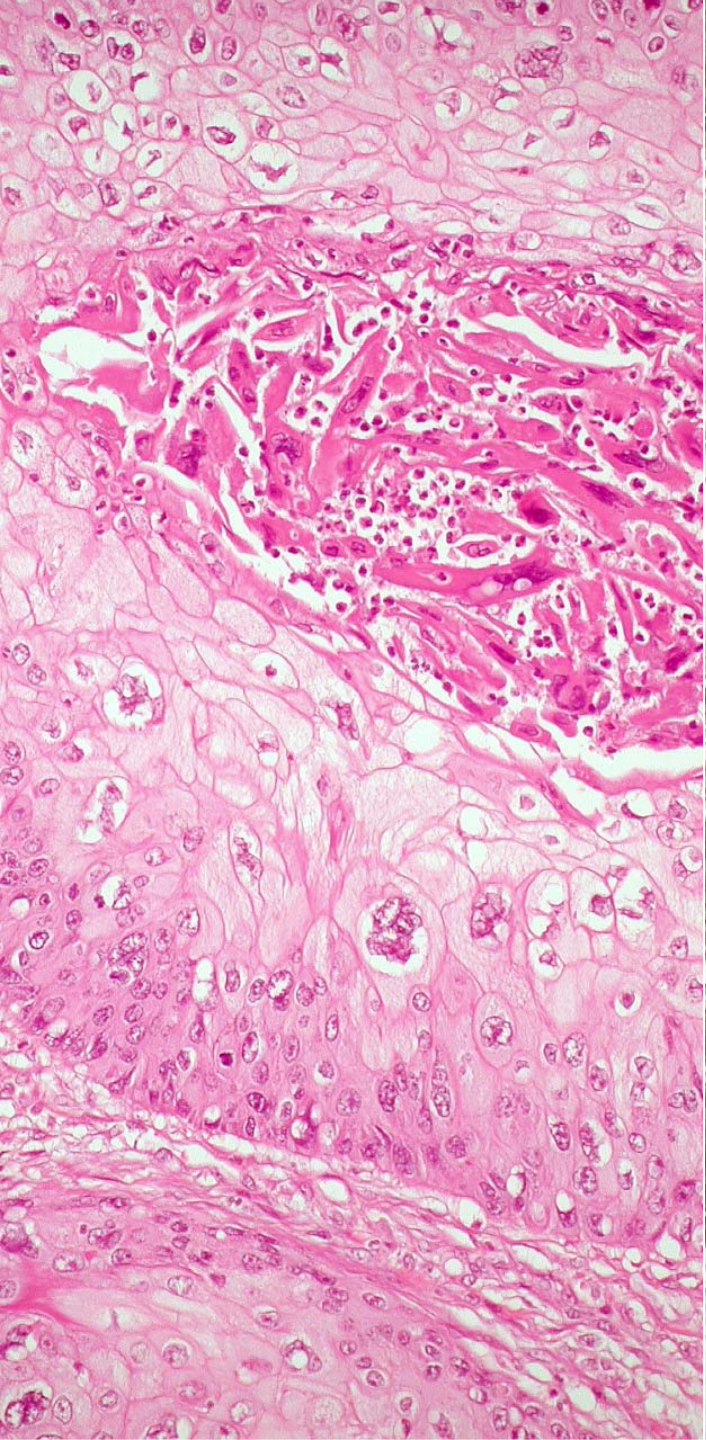


p16

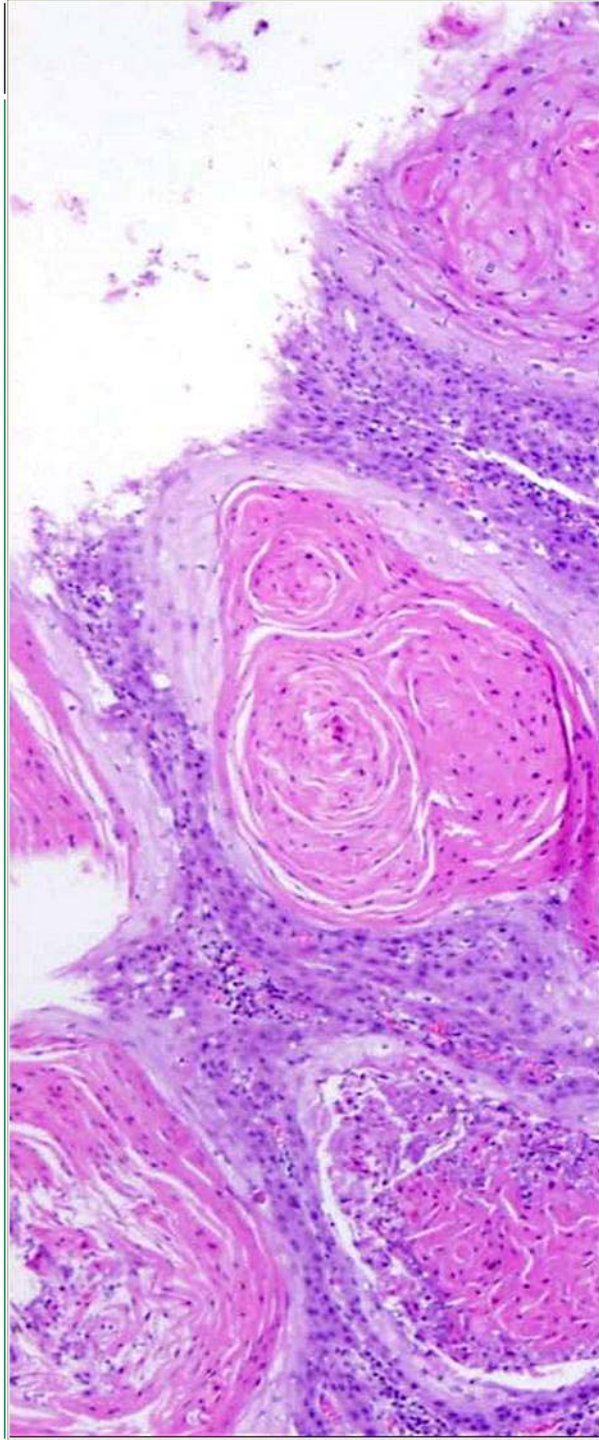
p53

SPF10 GP5+GP6

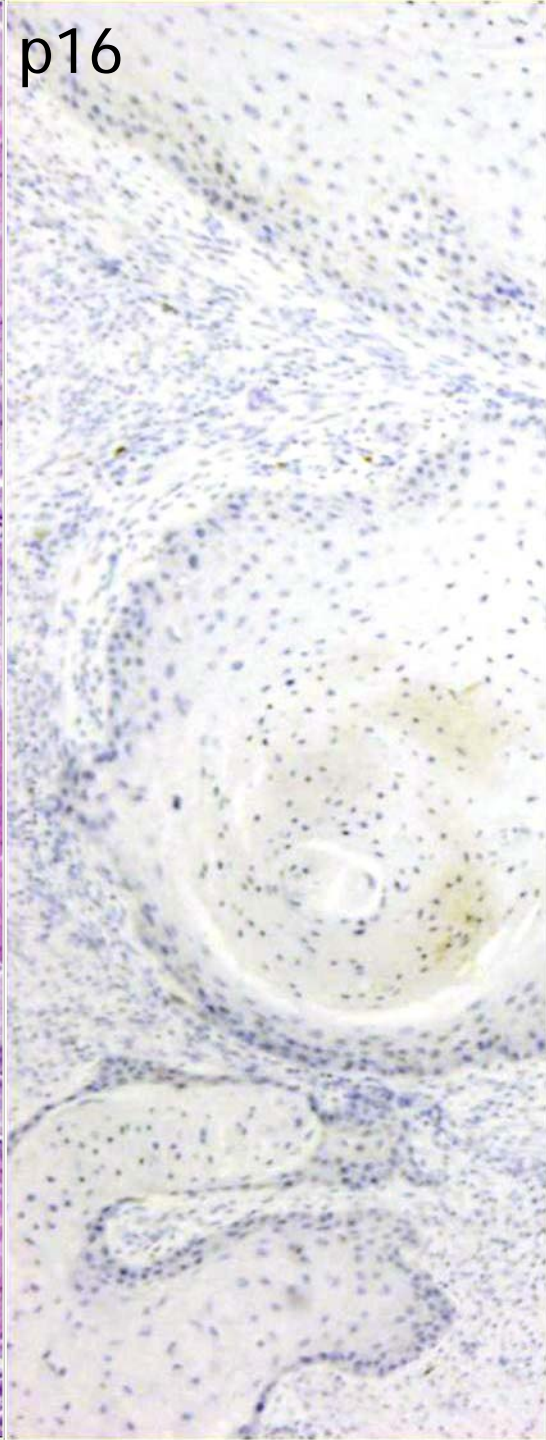
Case	SPF10	GP5+GP6
control	+	+
case 76	-	+
control	-	-
control	+	-



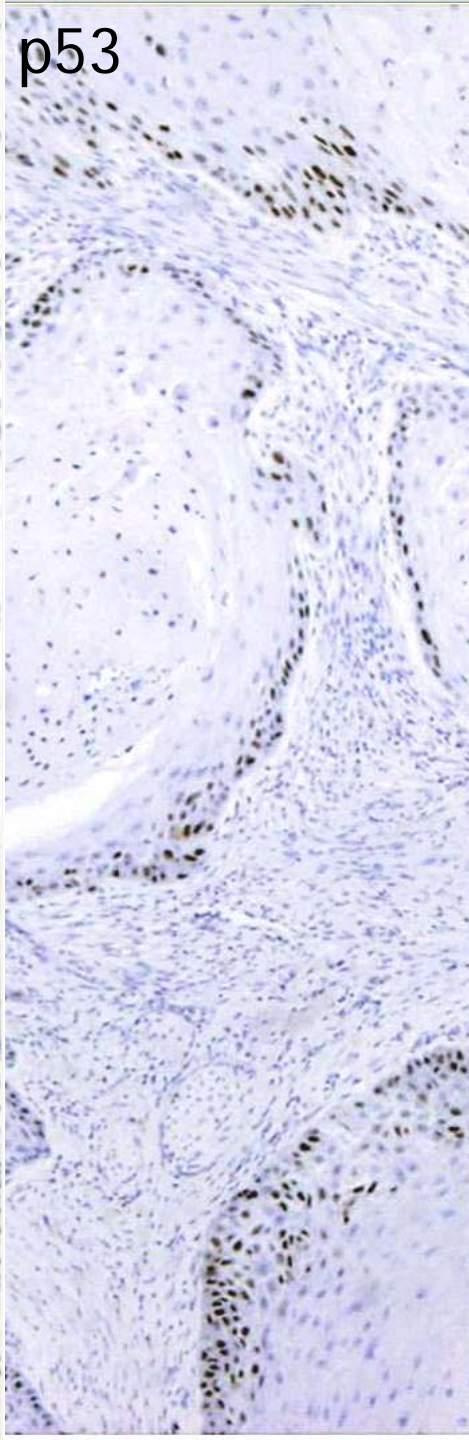
p16



p16



p53



SPF10

control +

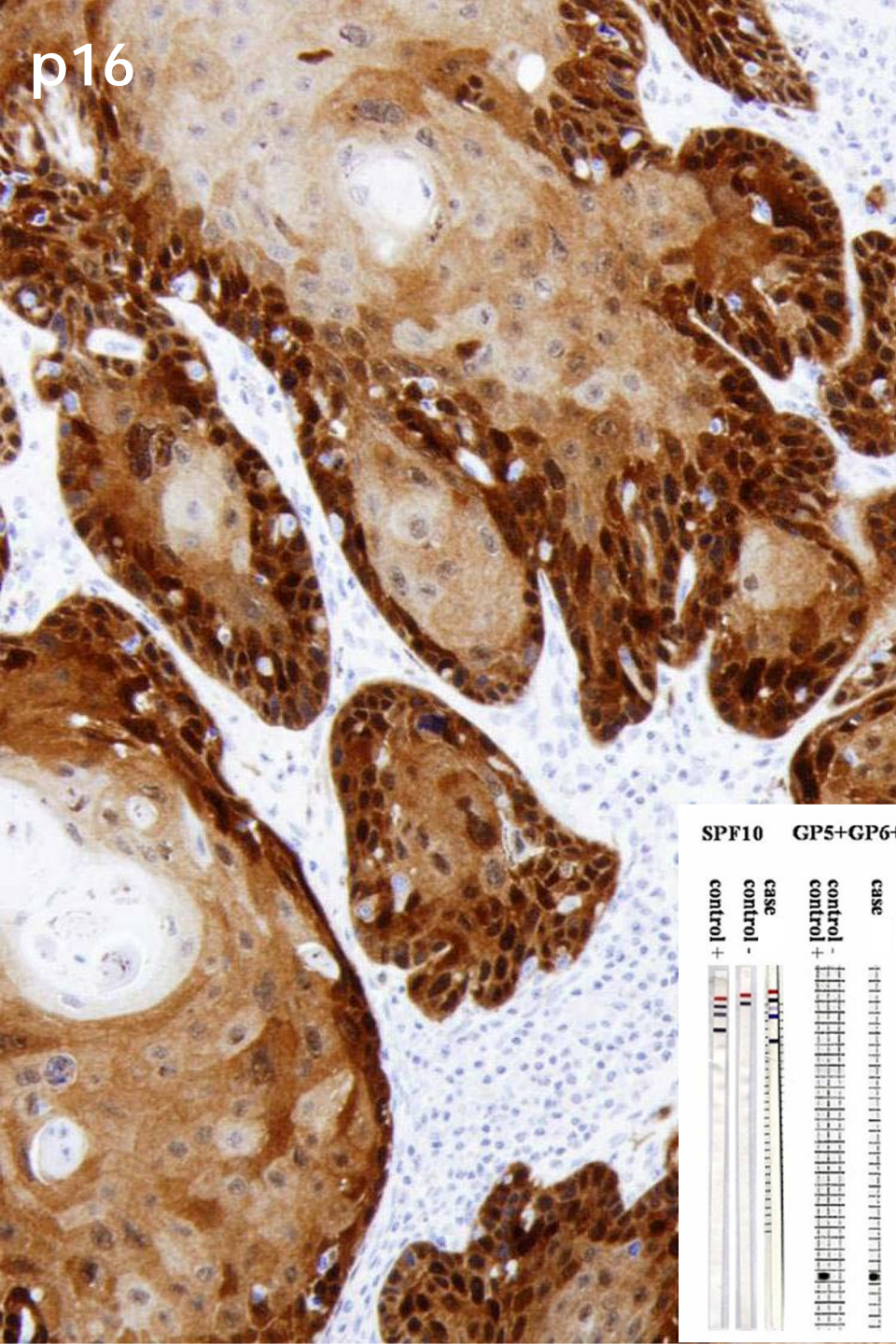
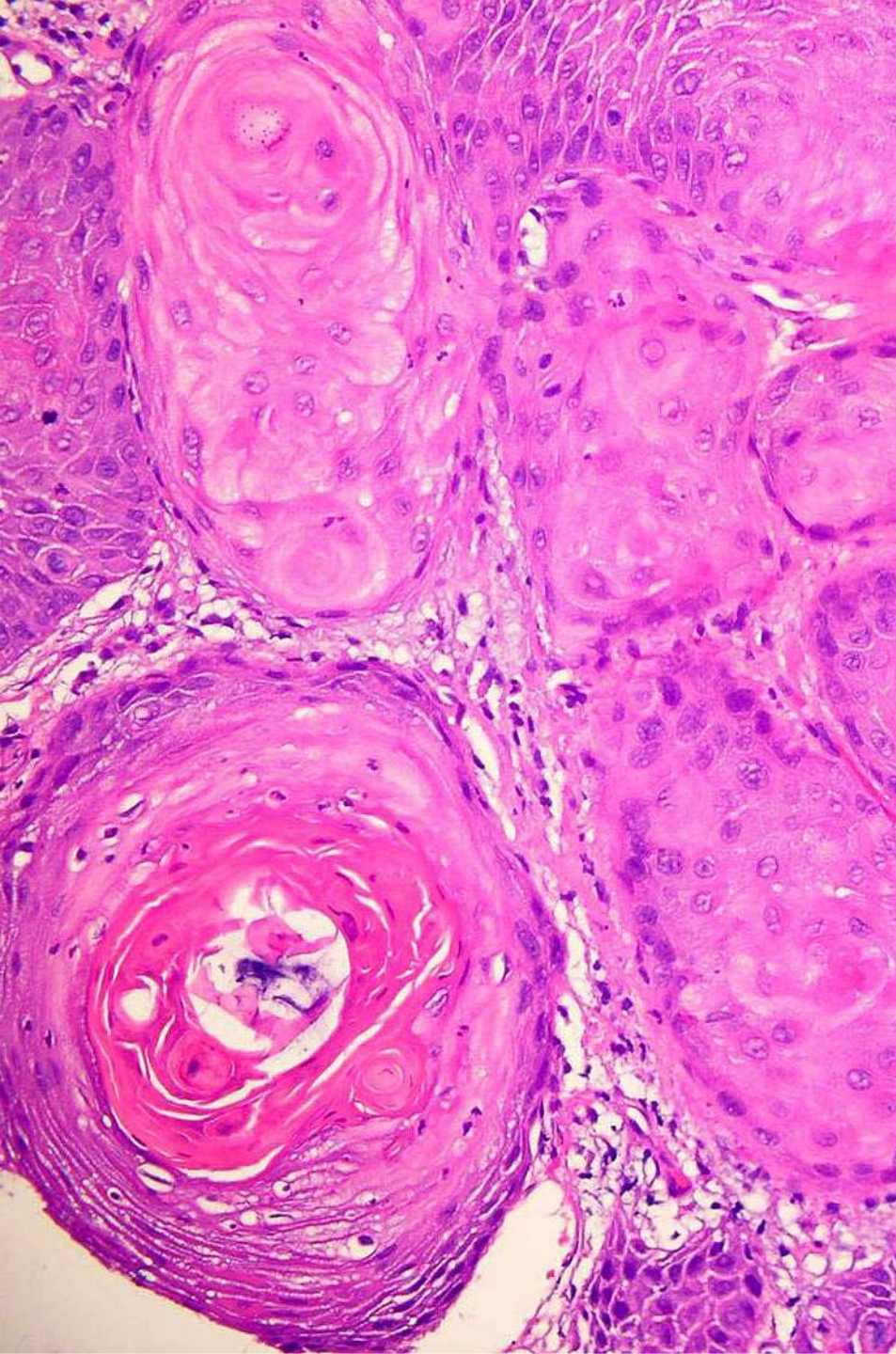


control -

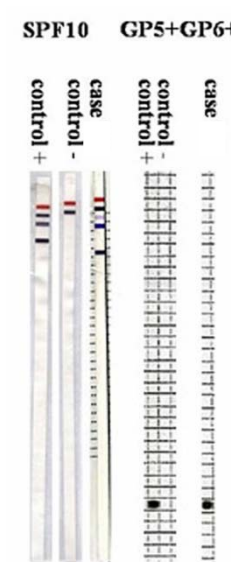


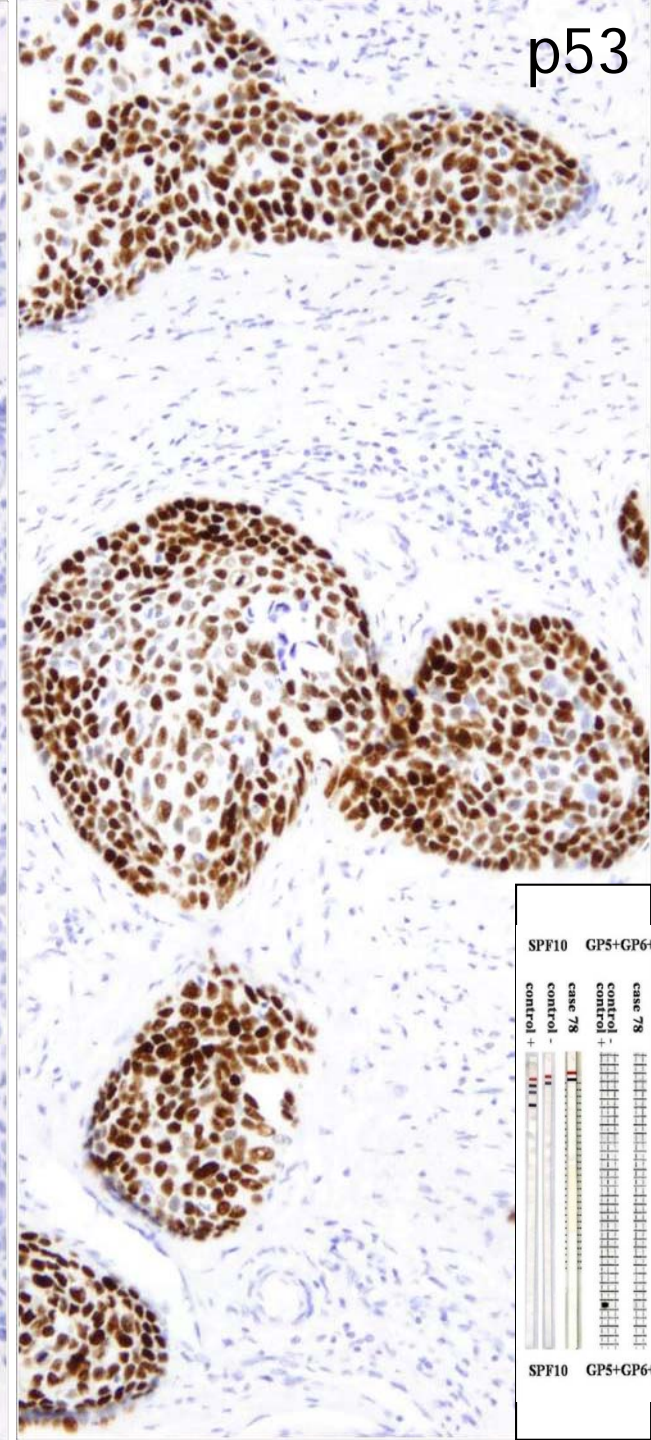
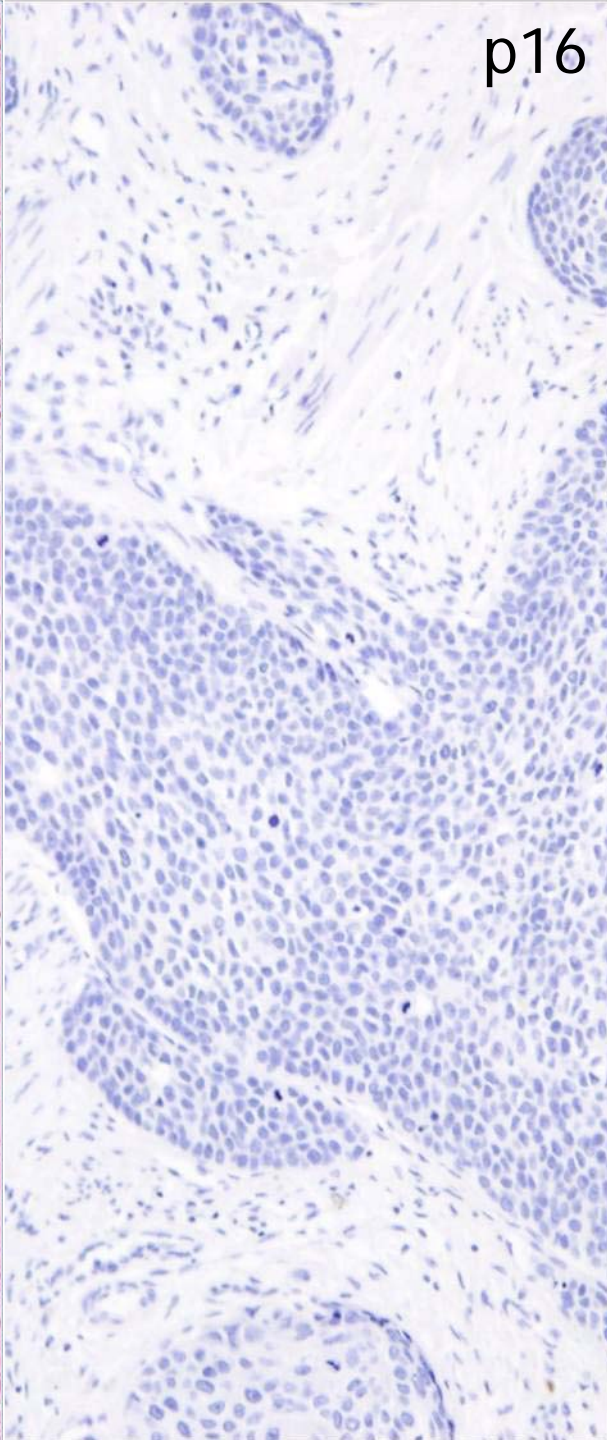
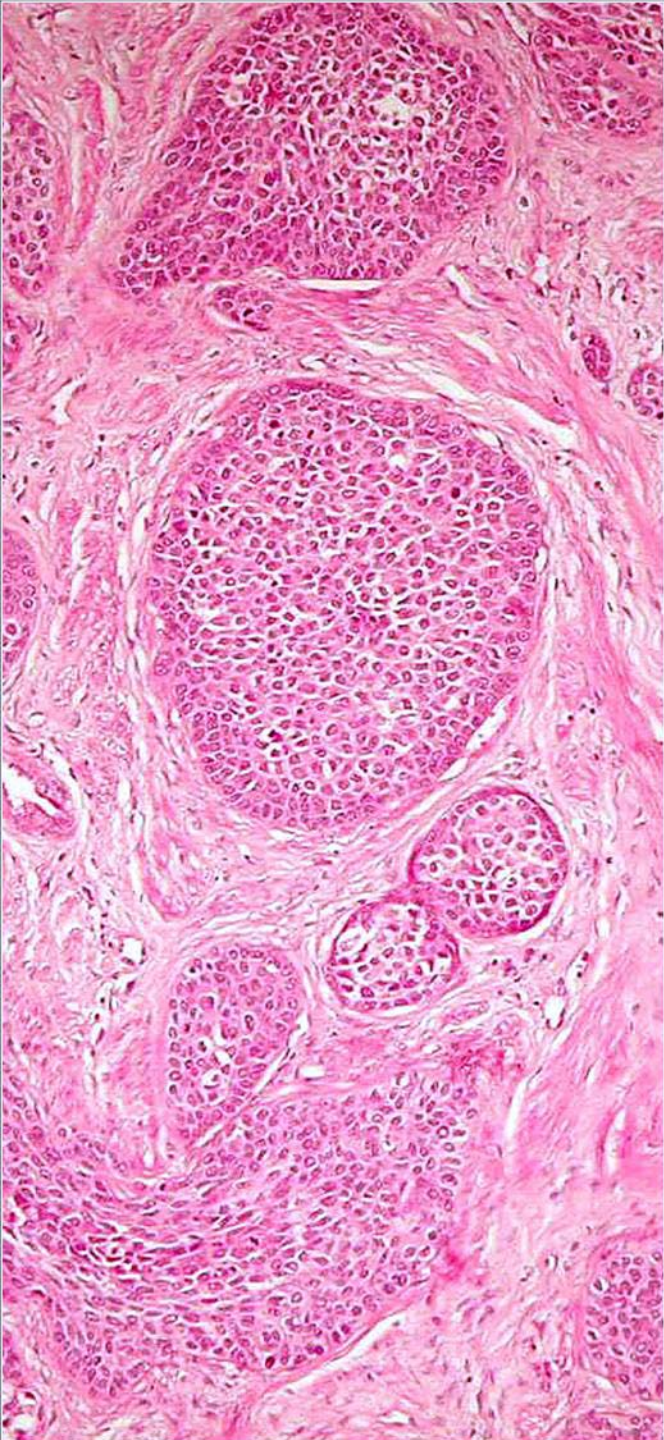
case 50





p16





vSCC: Histology, p16^{INK4a}, p53

	High-risk human papillomavirus				p value
	Positive(n=16)		Negative (n=76)		
Histologic type					
Basaloid	7	(43.7 %)	4	(5.3 %)	0.0003
Warty	3	(18.7 %)	3	(3.9 %)	NS
Keratinizing	6	(37.5 %)	69	(90.8 %)	0.00001
IHC					
p16 +	16	(100.0 %)	1	(1.3 %)	<0.000001
p53 +	1	(6.2 %)	49	(64.5 %)	0.00007

Santos M, et al. *Am J Surg Pathol* 2006; 30: 1347-1356



Identification of HPV relationship

	p16 (+ + +)	p53 (-)	basaloid/warty histology
Sensitivity	100%	93.8%	62.5%
Specificity	98.7%	35.5%	93.4%
Positive PV	94.1%	23.4%	66.7%
Negative PV	100%	96.4%	92.2%

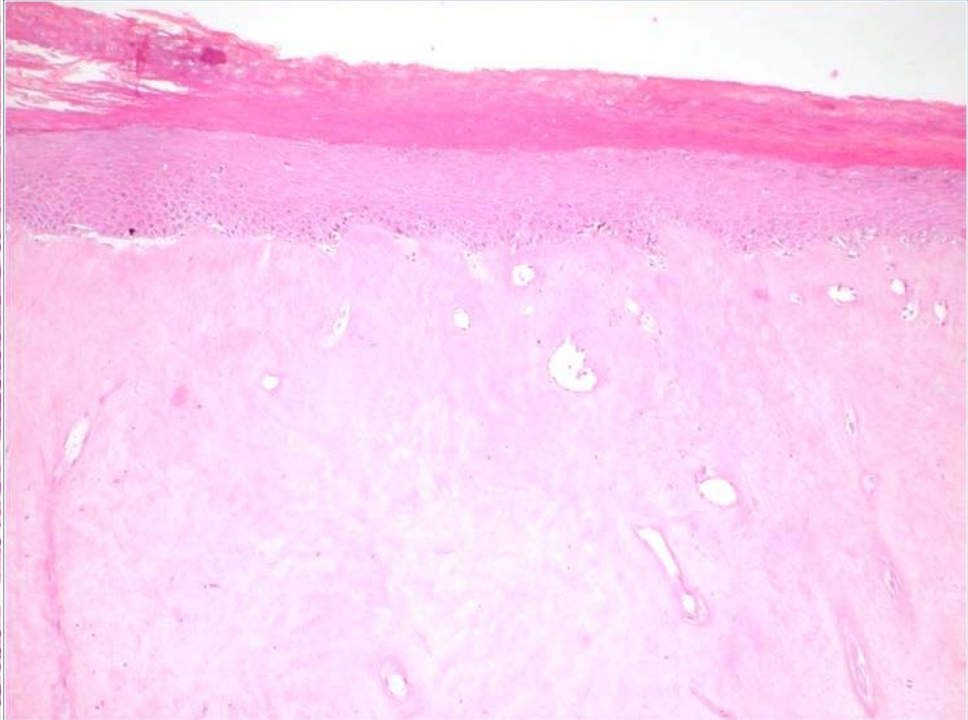
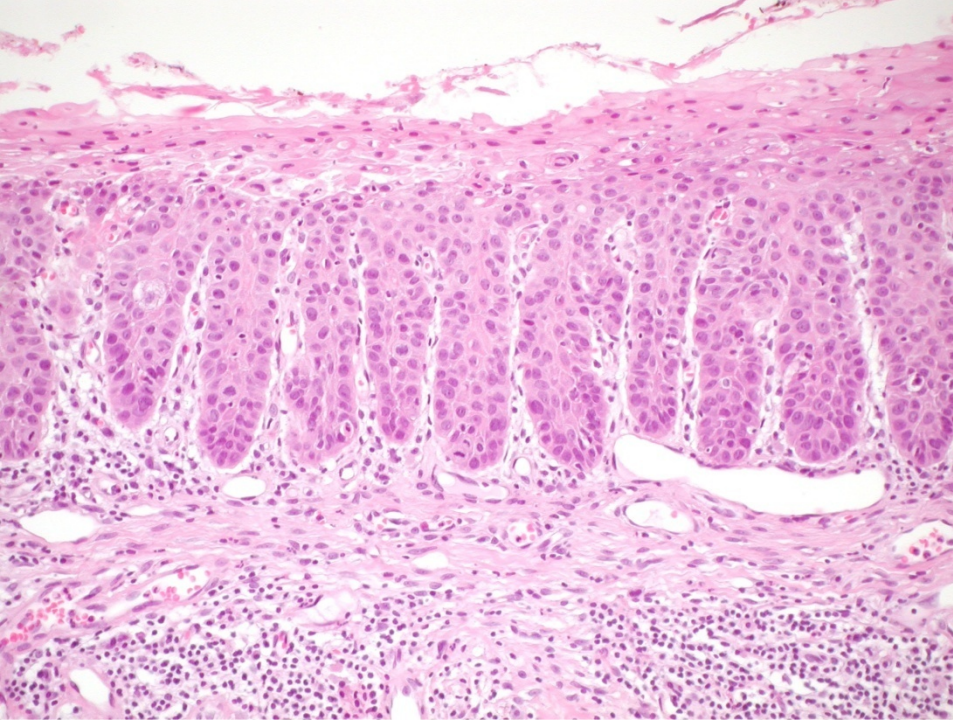
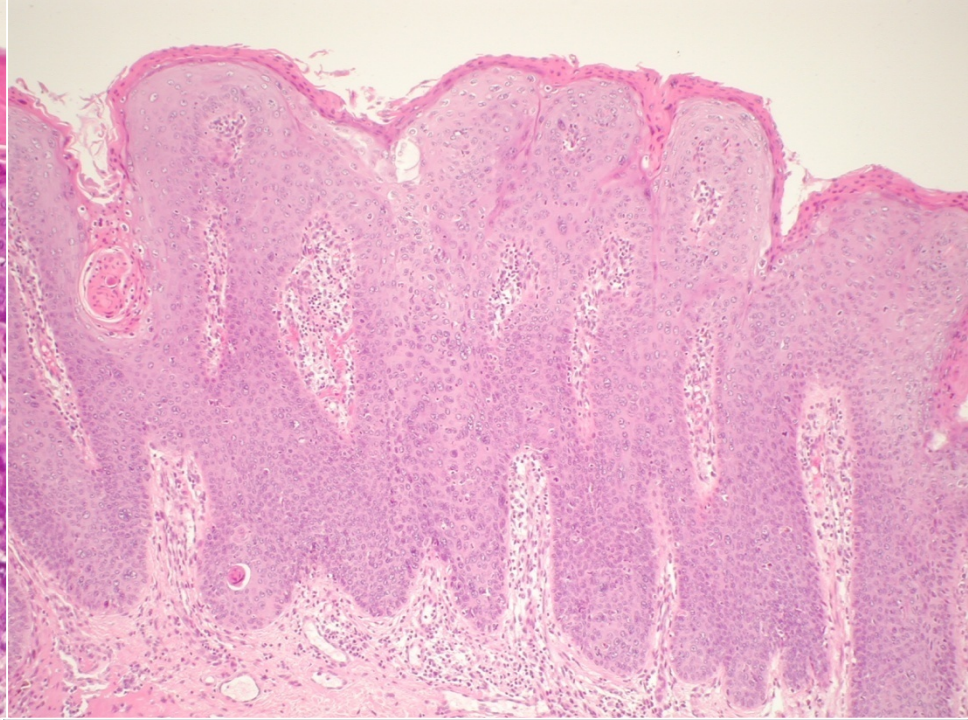
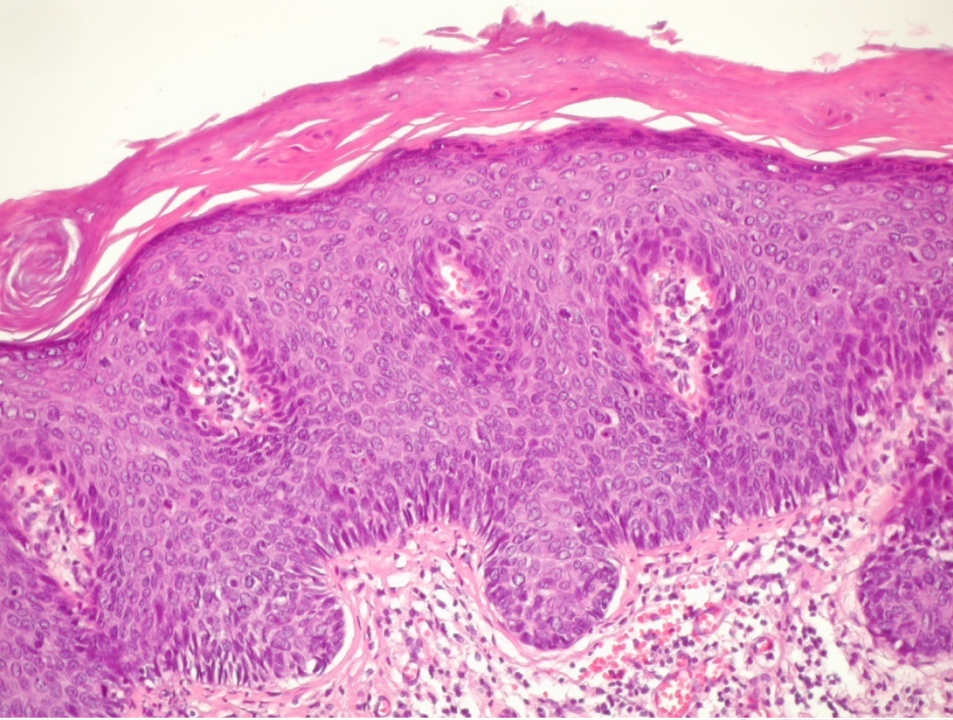
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Vulvar SCC: Associated lesions

Premalignant and other associated skin lesions	High-risk human papillomavirus				p value
	Positive (n=13)		Negative (n=68)		
VIN basaloid/warty type	7	(53.8 %)	0	(0 %)	0.000005
VIN differentiated type	0	(0 %)	31	(45.6 %)	0.0012
Squamous cell hyperplasia	2	(15.4 %)	43	(63.2 %)	0.002
Lichen sclerosus	0	(0 %)	27	(39.7%)	0.0036

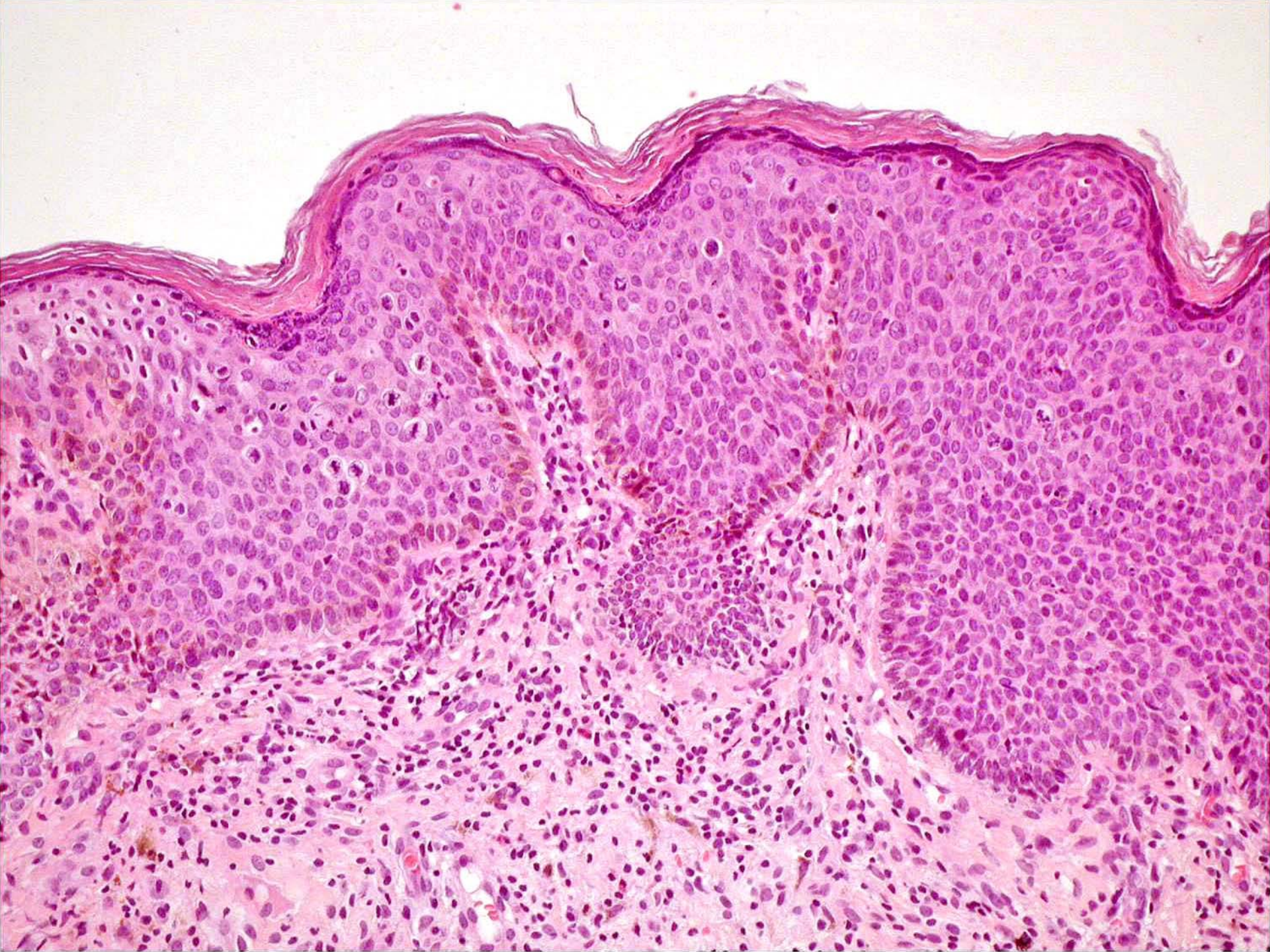
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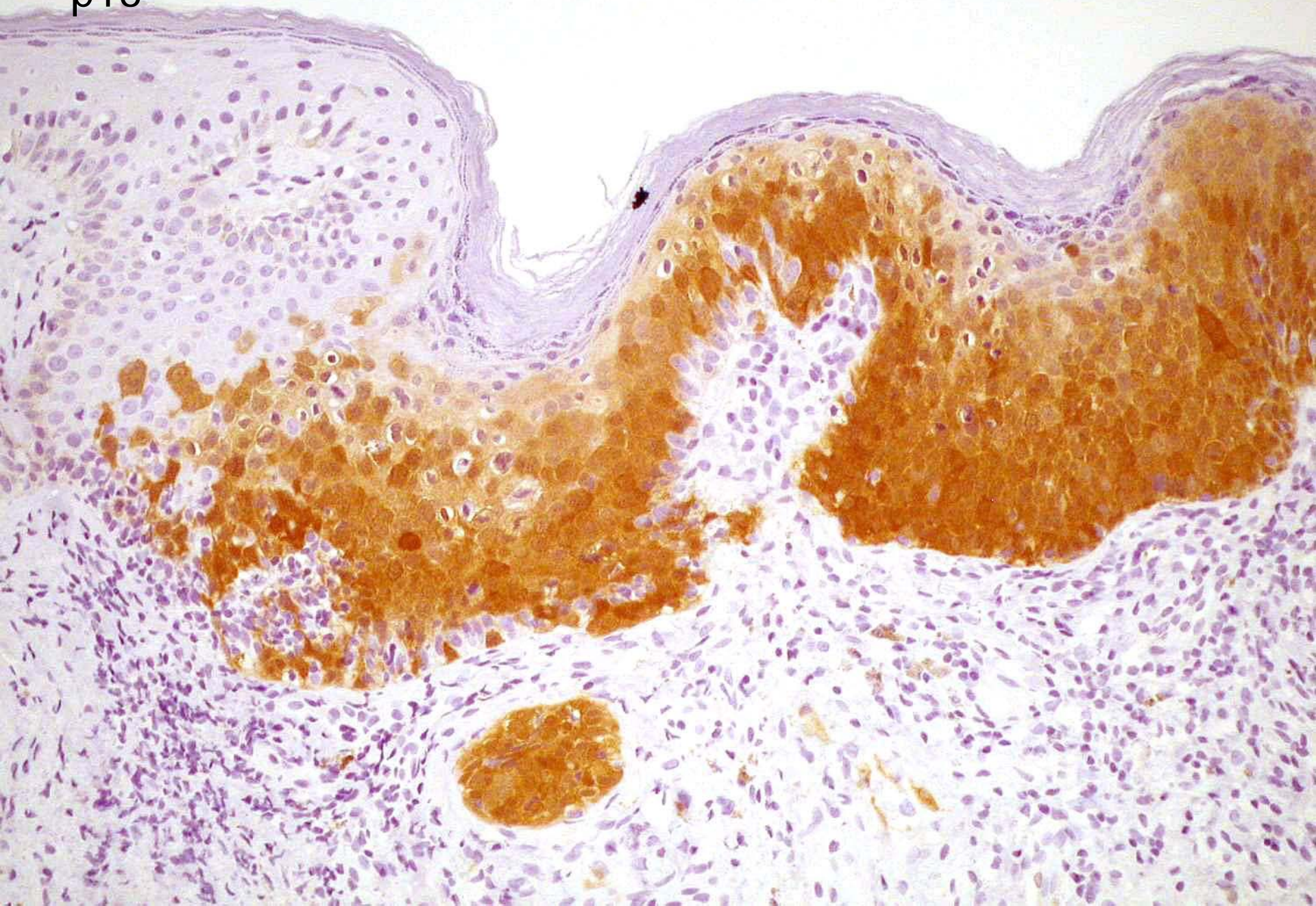
p16^{INK4a} in VIN and benign lesions

	p16 (%)	p53 (%)
Benign lesions		
Normal skin	0	2
Squamous cell hyperplasia	0	0
Lichen sclerosus	0	11
VIN		
VIN 3 basaloid / warty	100	0
VIN3 differentiated (simplex)	0	81

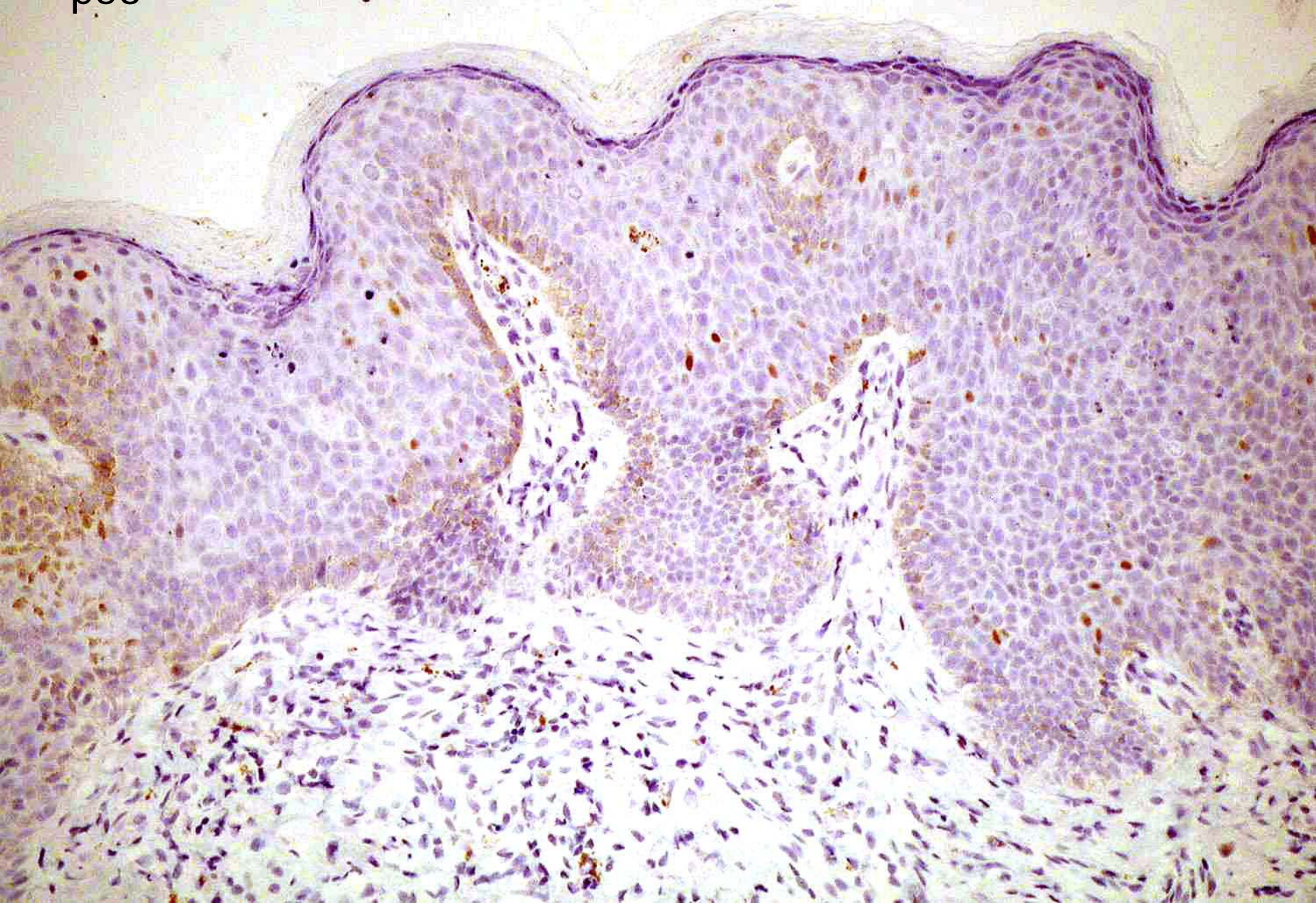
Santos M, et al *Int J Gynecol Pathol* 2004; 23:206-214

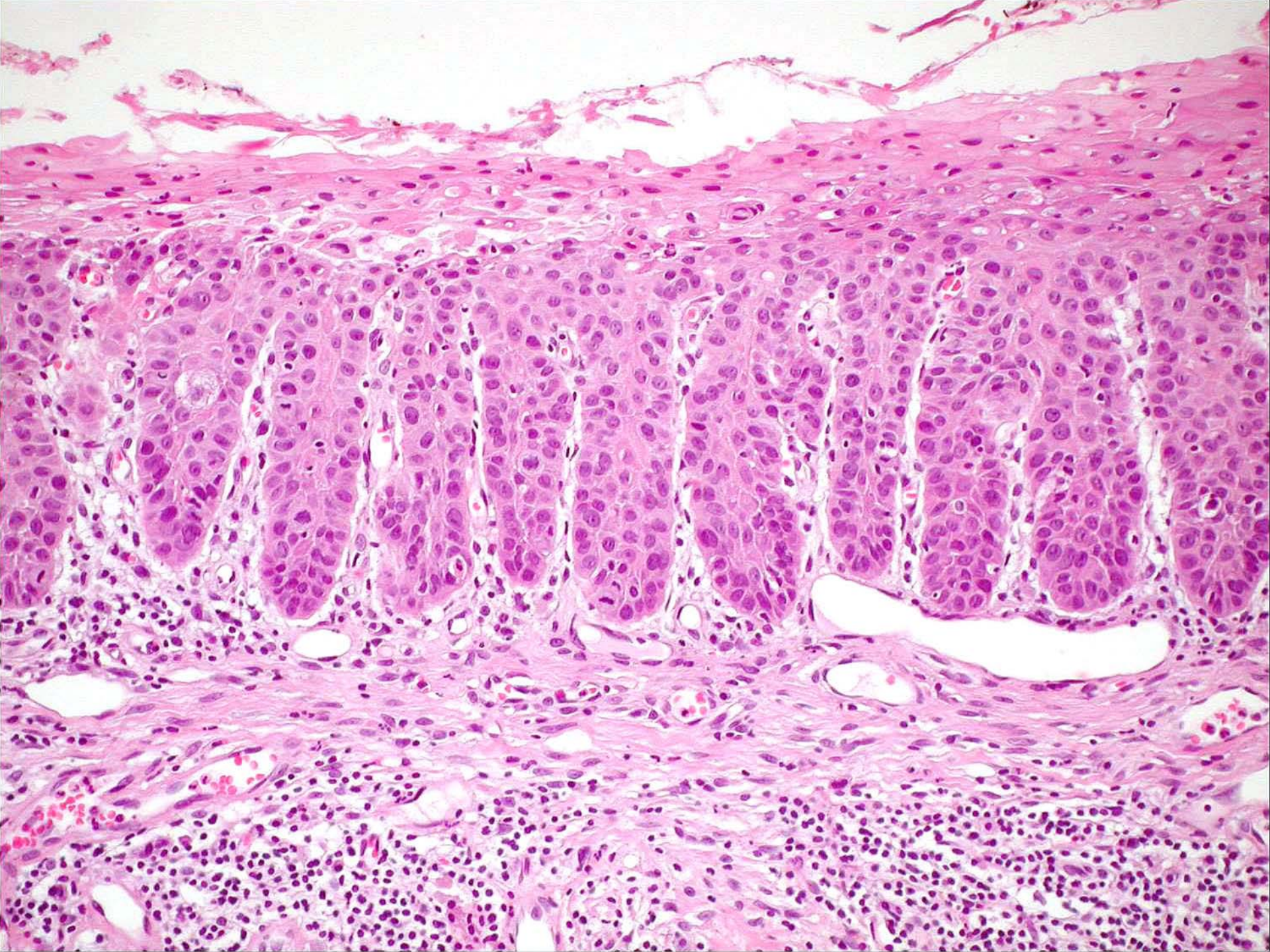


p16

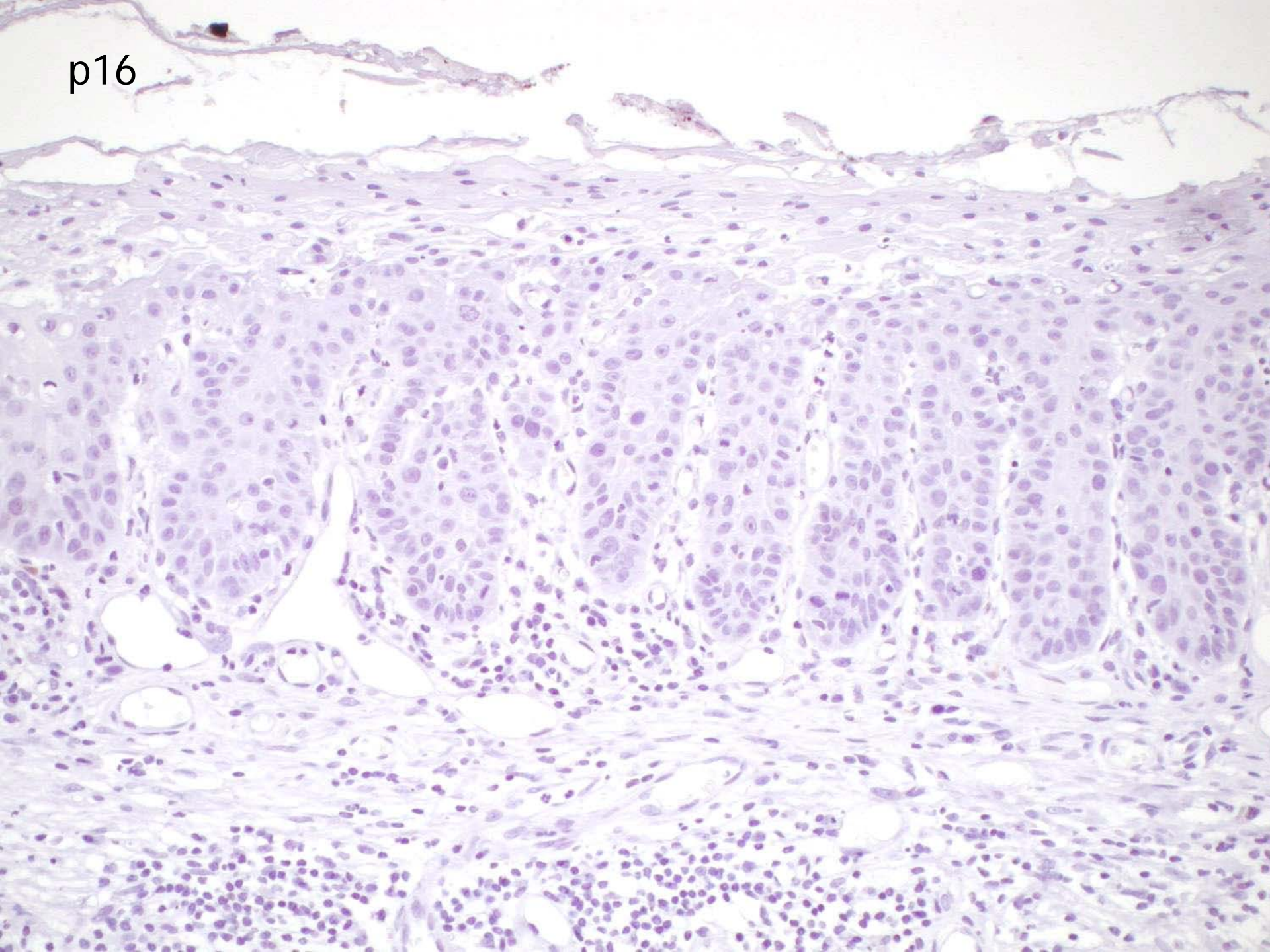


p53

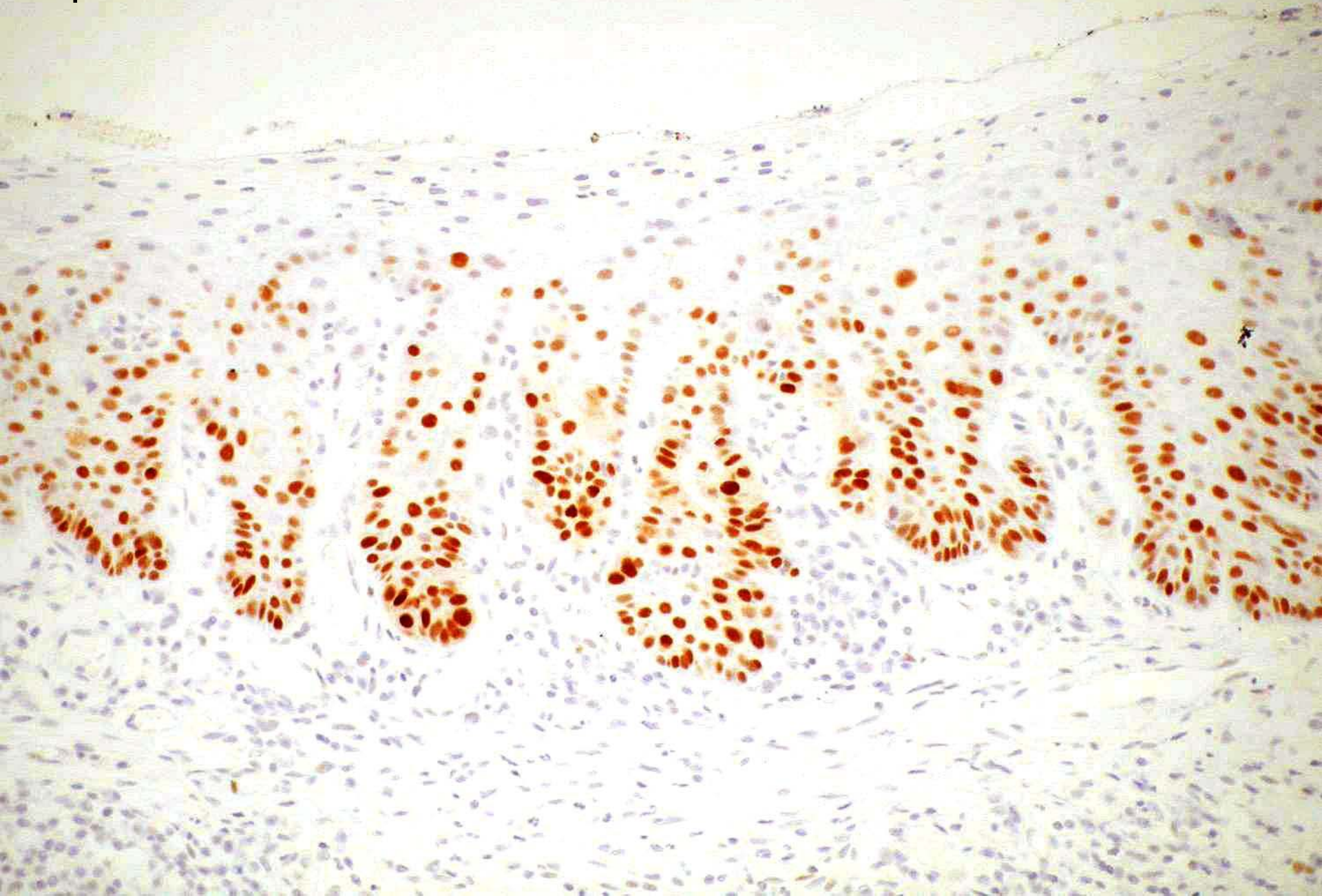




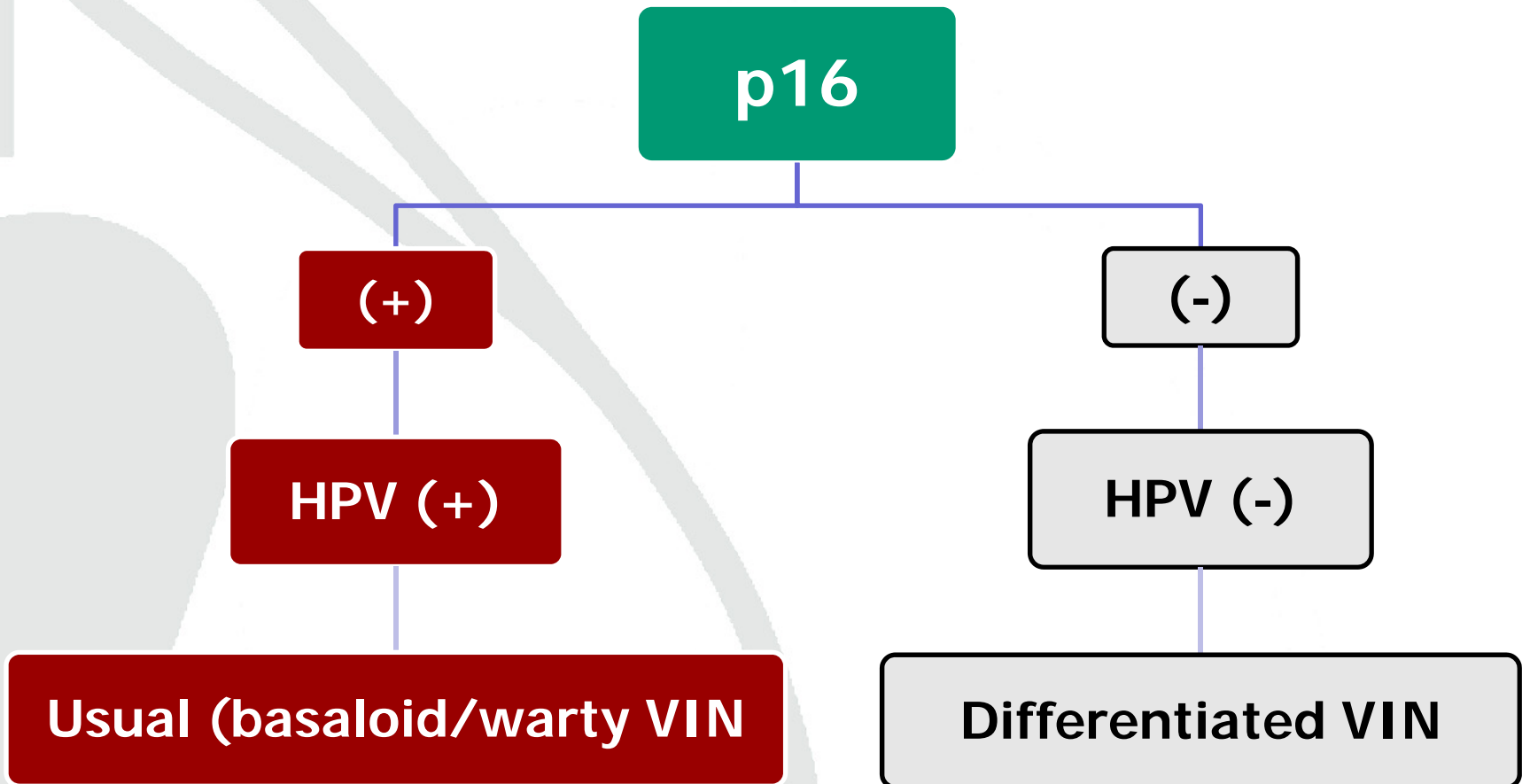
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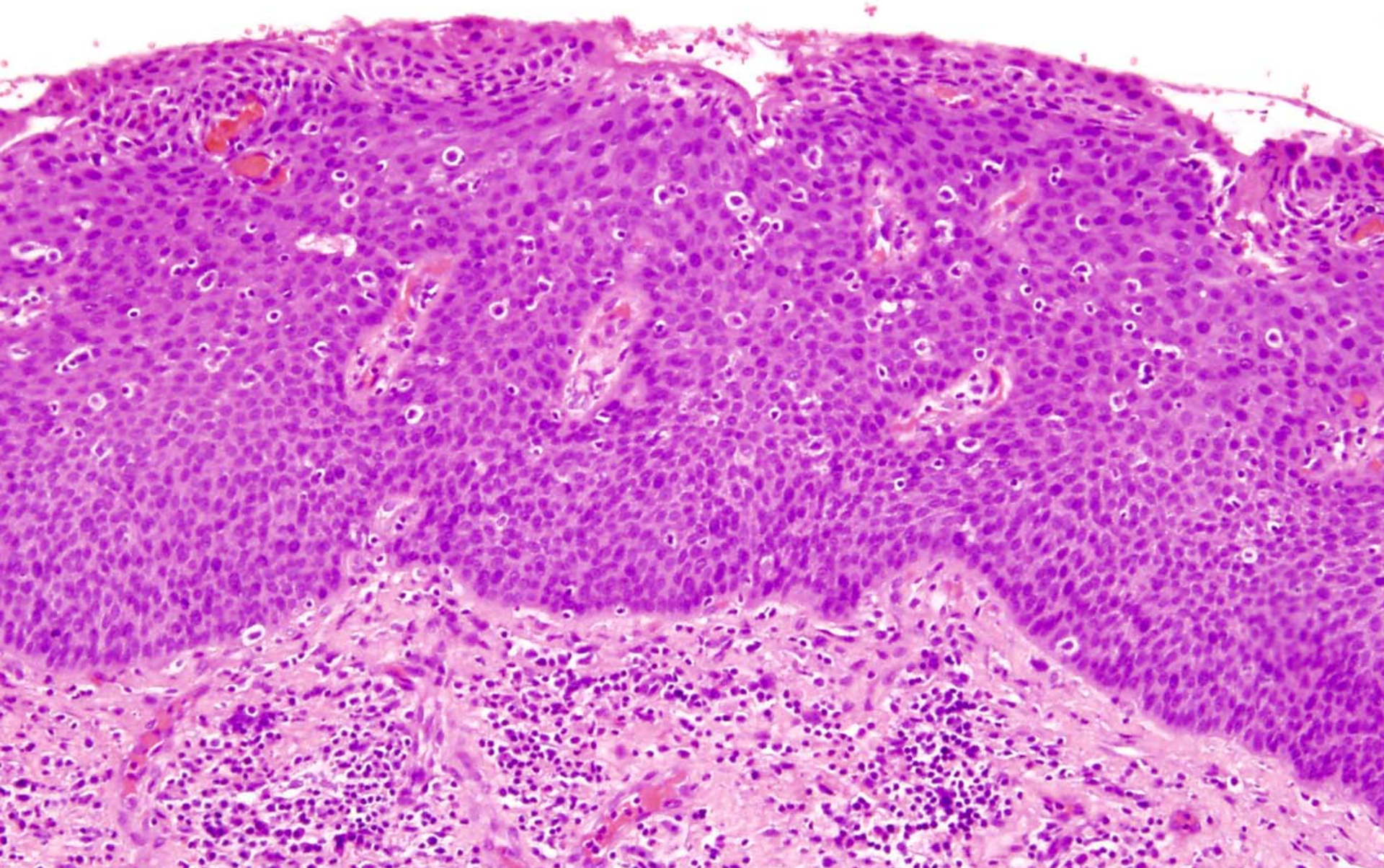


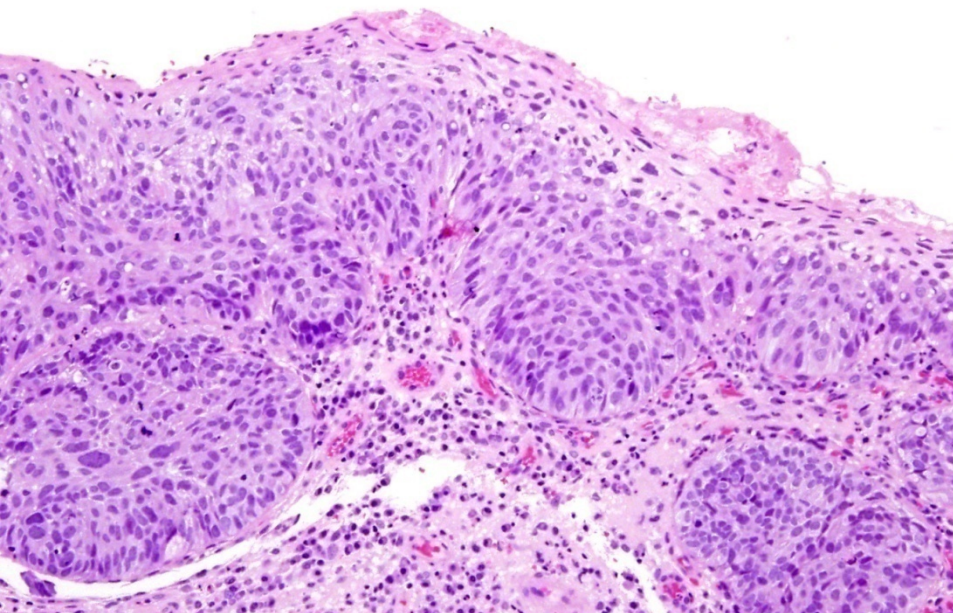
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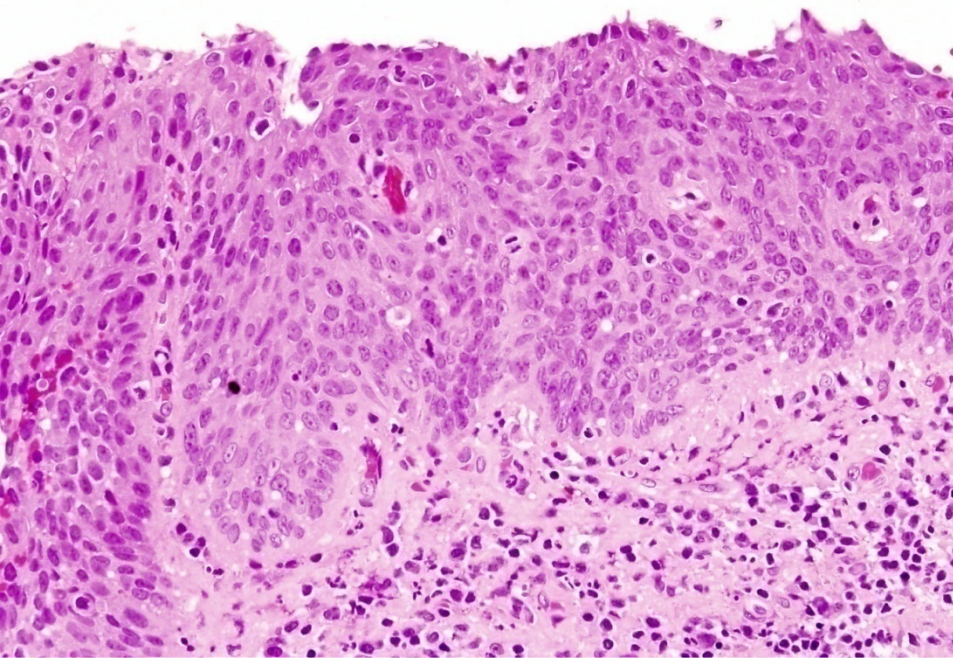
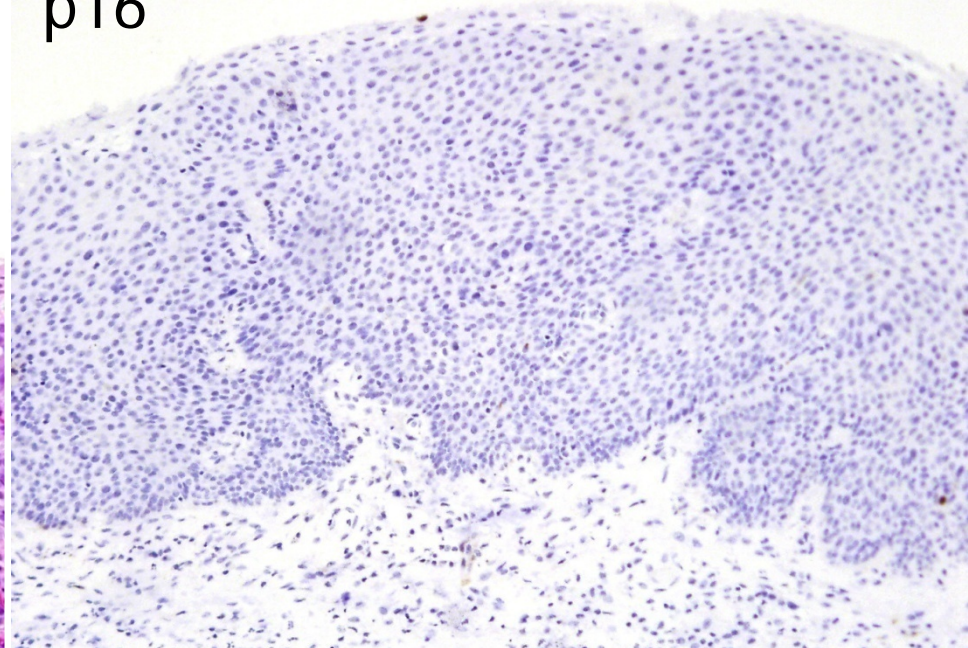
p16^{INK4a} and VIN



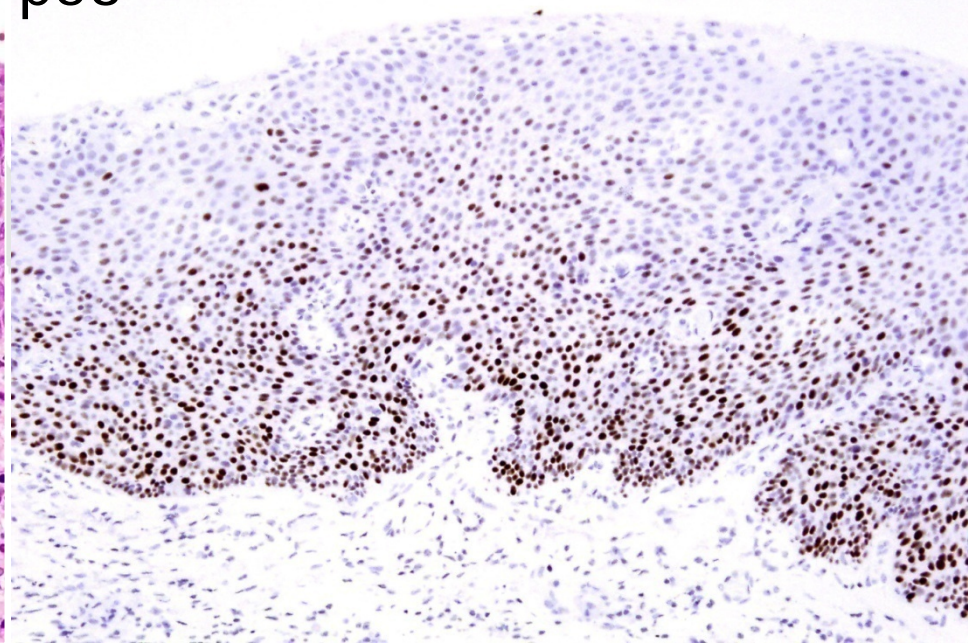




p16



p53



HPV (-) VIN with basaloid features

- 110 cases of HPV negative vSCC
 - 51 cases of differentiated VIN
 - 4/51 (7.8%) with basaloid features

	Age	Associated lesion	Invasive carcinoma	Grade
Case 1	60	Lichen sclerosus Squamous cell hyperplasia	Basaloid	3
Case 2	62	No	Keratinizing	3
Case 3	76	Squamous cell hyperplasia	Keratinizing	3
Case 4	45	Squamous cell hyperplasia	Keratinizing	2

Ordi J, et al. *Am J Surg Pathol* 2009; 33:1659-1665





Conclusions

- Approximately **1/5 SCC** of the vulva are related to **HPV** infection
- **HPV16** is the most prevalent type
- Current HPV vaccines will prevent approximately 2/3 of HPV positive vulvar carcinoma, but this will represent only 1/8 of all vulvar squamous cell carcinomas



Conclusions

- **p16^{INK4a} overexpression** has a sensitivity and a specificity close to 100% to identify HPV related SCC of the vulva and may be used as a **biomarker of HPV infection**. p16^{INK4a} is much **more specific than the histological pattern**
- A number of **HPV- VIN** may have a **basaloid morphology** and may be confused with classic (HPV+) VIN
- p16^{INK4a} negative staining allows to identify these cases



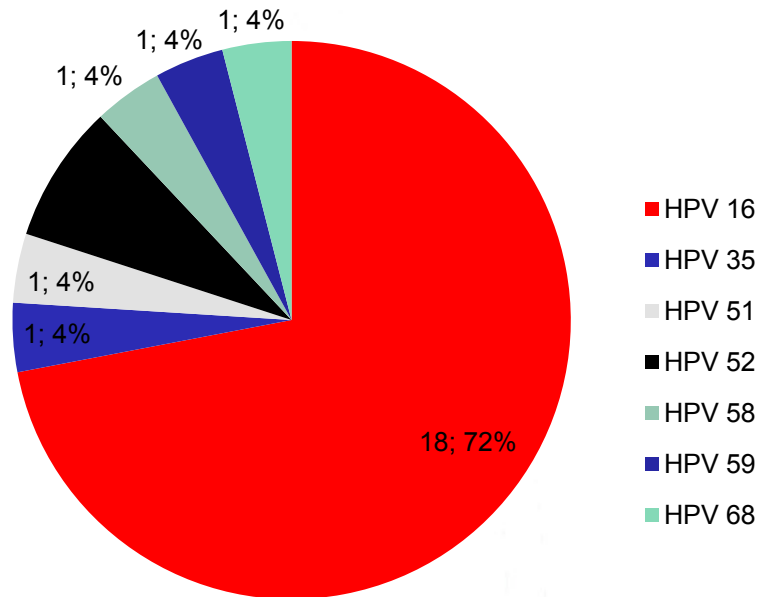
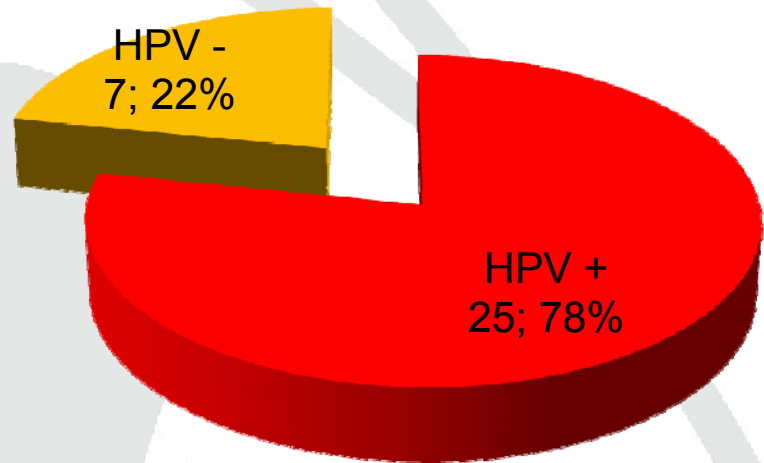
Carcinoma de la vagina

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SCC of the vagina: HPV

- 32 invasive SCC of HCP / HVH



Fuste V, et al. *Histopathology* 2010; in press

SCC of the vagina: HPV

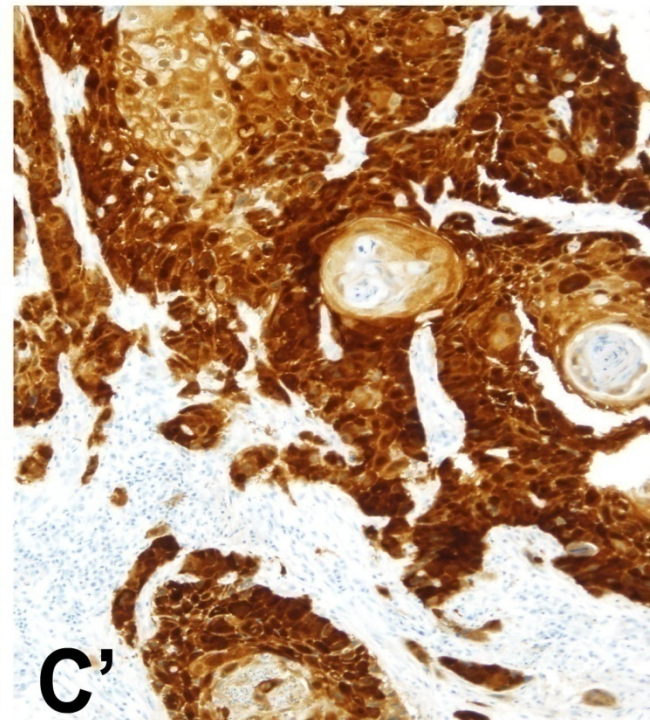
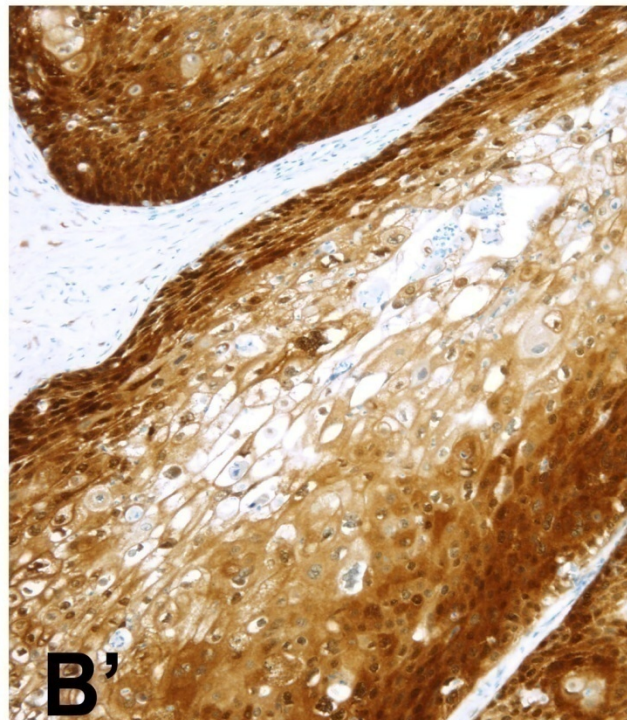
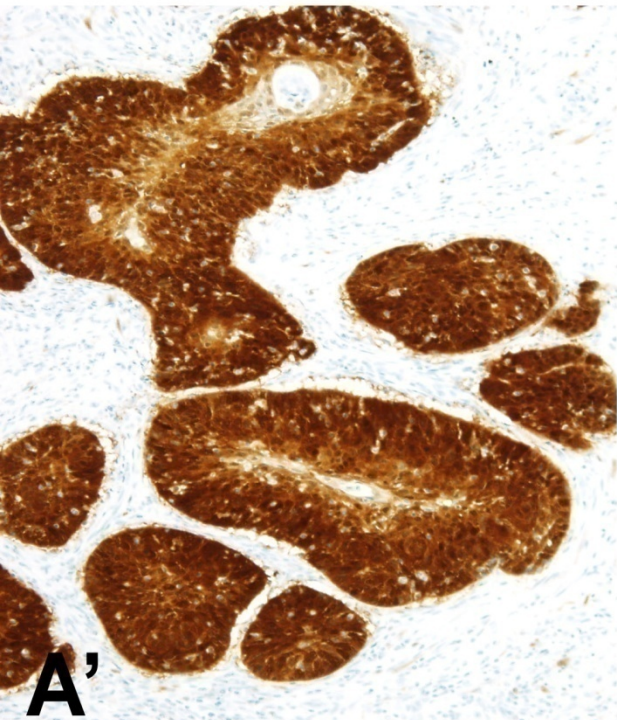
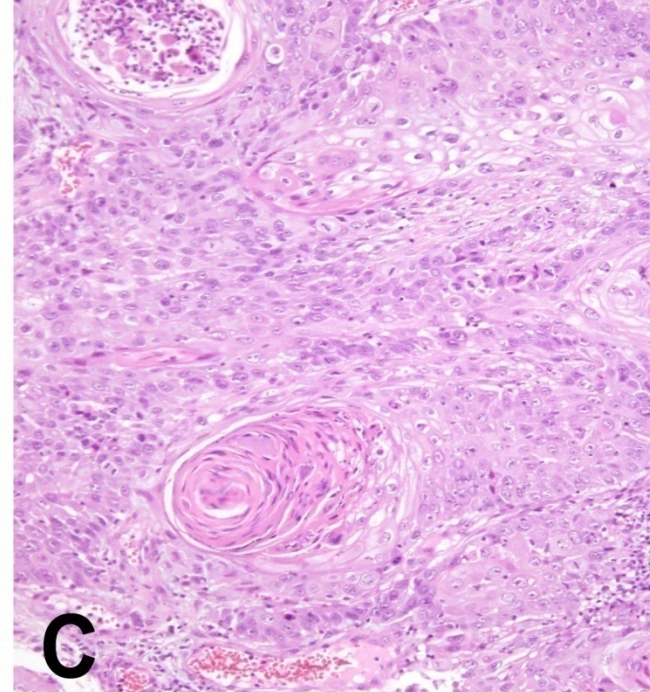
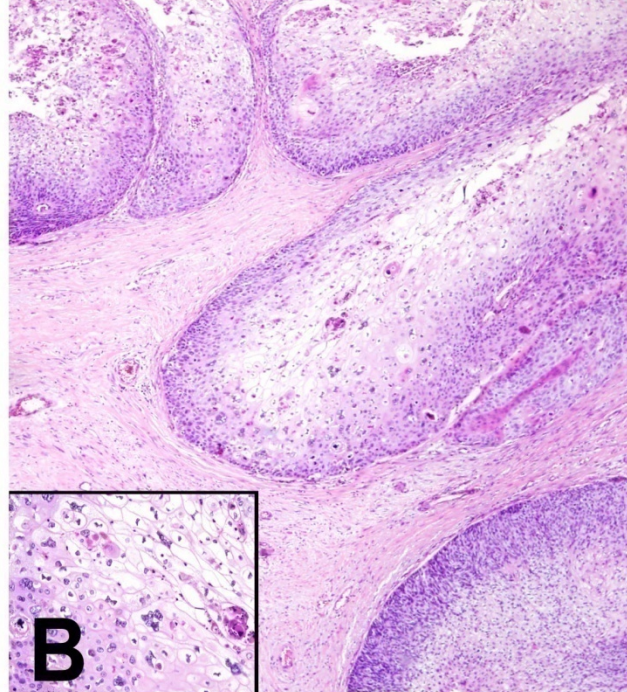
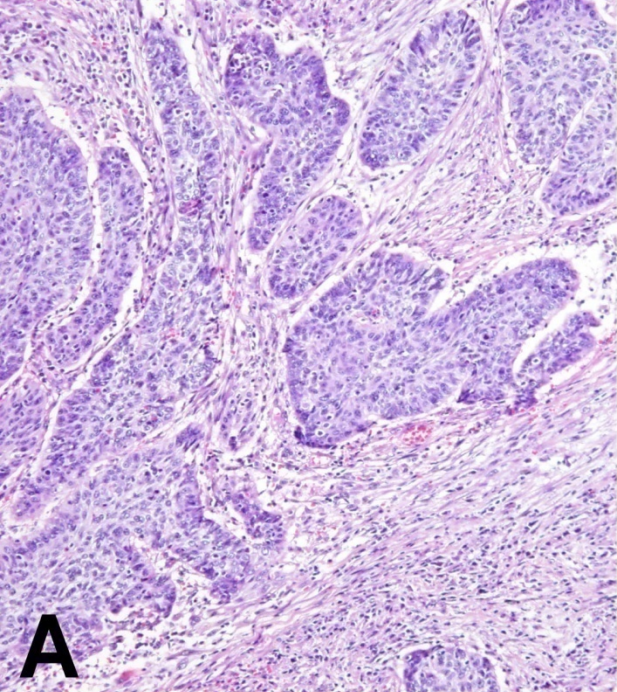
	High-risk human papillomavirus		p value
	Positive (n=25)	Negative (n=7)	
Histologic type			0.006
Keratinizing	4 (16.0 %)	6 (85.7 %)	
Non-keratinizing	14 (56.0%)	1 (14.3%)	
Basaloid	4 (16.0 %)	0 (0 %)	
Warty	3 (12.0 %)	0 (0 %)	
Immunohistochemistry			
p16 ^{INK4A} positivity	24 (96.0 %)	1 (14.3 %)	<0.001
p53 positivity	3 (12.0 %)	4 (64.5 %)	0.025

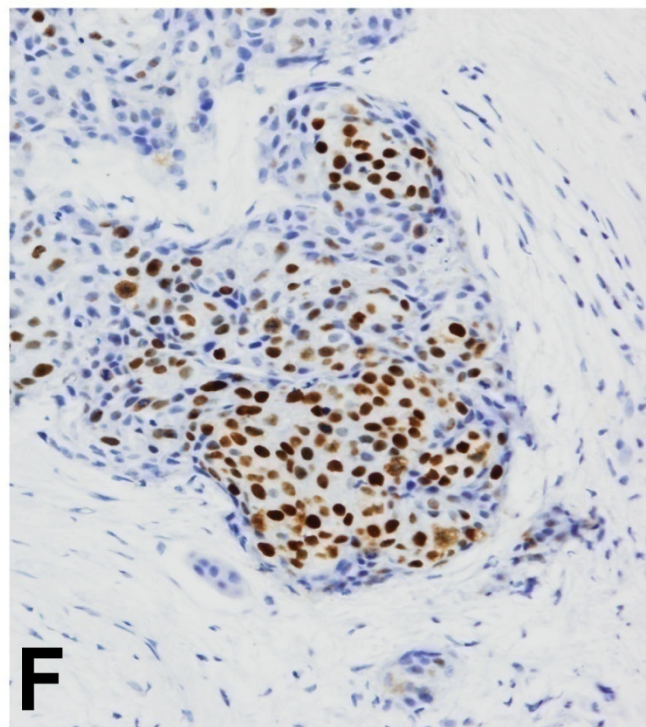
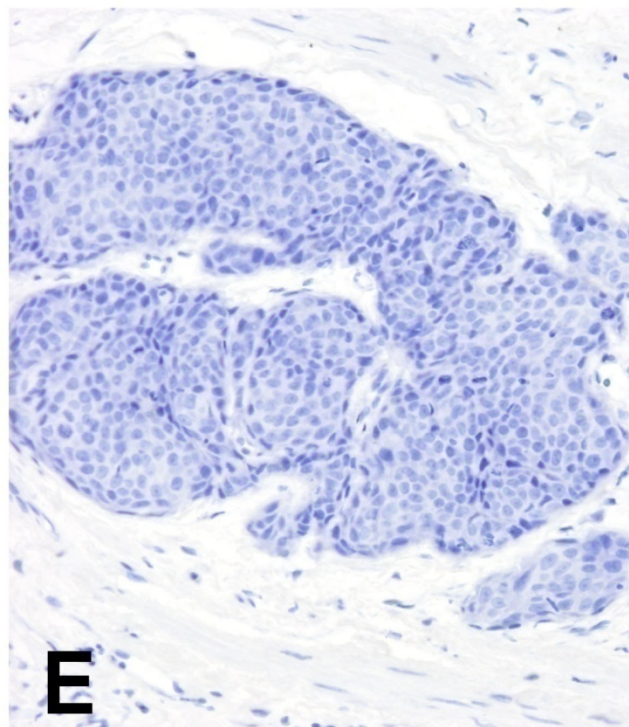
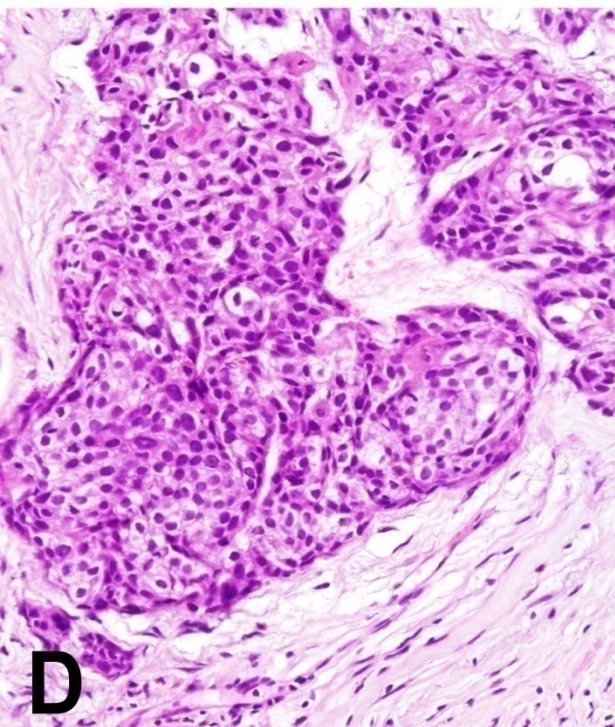
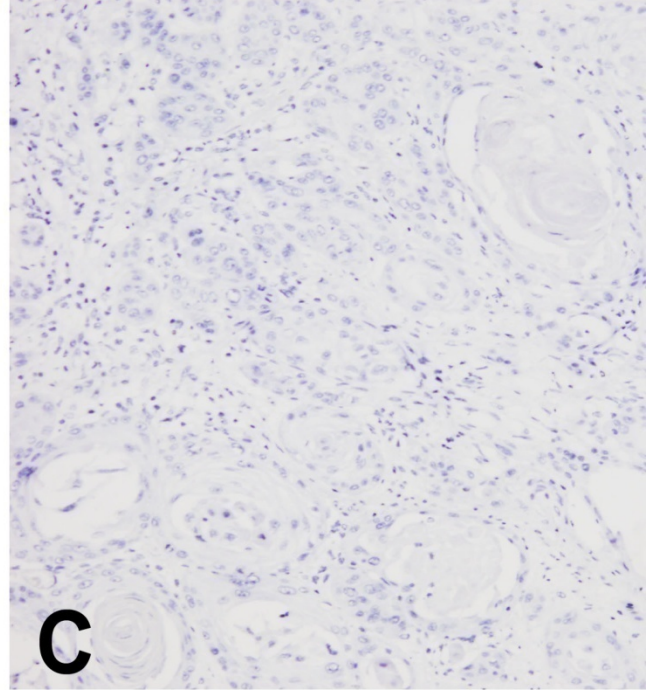
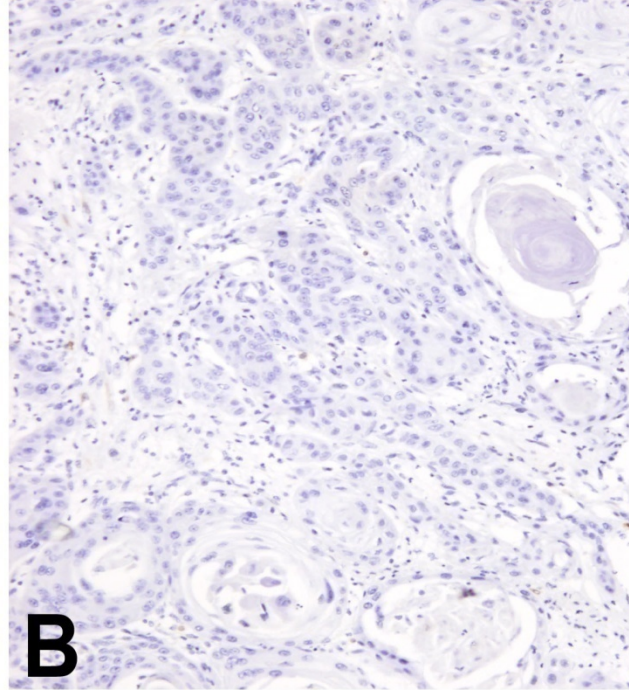
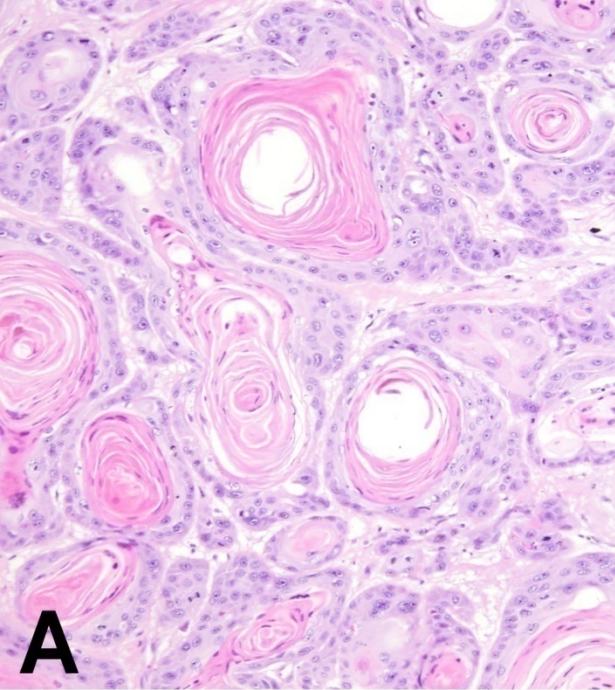
Fuste V, et al. *Histopathology* 2010; in press

SCC of the vagina: HPV

	p16 ^{INK4A} diffuse	p53 (-)	Non-keratinizing/ basaloid/warty histology
Sensitivity	96.0%	88.0%	95.5%
Specificity	85.7%	57.1%	60.0%
Positive predictive value	96.0%	88.0%	84.0%
Negative predictive value	85.7%	57.1%	85.7%

Fuste V, et al. *Histopathology* 2010; in press





SCC of the vagina: HPV

	High-risk human papillomavirus		p value
	Positive (n=25)	Negative (n=7)	
Age	62.6 ± 13.8	74.0 ± 8.5	0.049
History of cervical lesion	14 (56.0%)	0 (0%)	0.010

Fuste V, et al. *Histopathology* 2010; in press



Conclusions

- Approximately **4/5 SCC** of the vagina are related to **HPV** infection. **HPV16** is the most prevalent type (72%)
- **p16^{INK4a} overexpression** may be used as a **biomarker of HPV infection**. p16^{INK4a} is **more specific than histological pattern**
- A high number of **HPV+ vaginal carcinomas** have a **previous history of cervical or vulvar lesion**



Human Papillomavirus in Head and Neck Cancer

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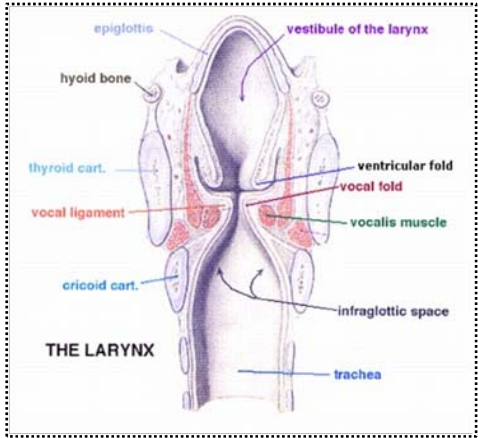
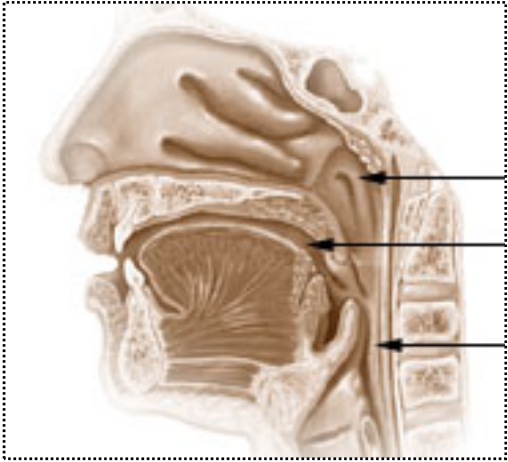
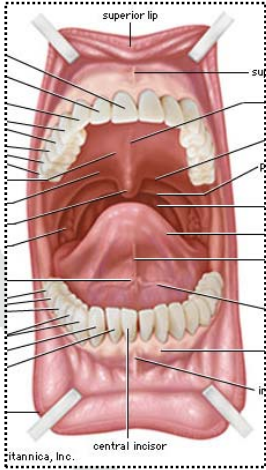
Squamous cell carcinoma of H&N

- Frequent neoplasm: 8th more prevalent cancer in the western world (6th in Spain): 500,000 new cases/year
- Marked clinical diversity
- Highly variable natural history



Squamous cell carcinoma of H&N

- Different locations
 - Sinonasal tract
 - Nasopharynx
 - Oral cavity
 - Tonsil
 - Oropharynx
 - Larynx





SCC of head & neck: etiology

- Smoke
- Alcohol

- **HPV infection**



SCC of head & neck: HPV

- First evidence: isolated cases in the nineties
- Marked methodological variability in the initial studies
- **Definite evidence in early 2000**
- Different implication of HPV in different areas of the head and neck region

SCC of head & neck: HPV

- Oropharynx 45%
 - Tonsil 58%
- } High frequency
- Sinonasal tract
 - Oral cavity 0- 8%
 - Nasopharynx 0-8%
 - Larynx 0- 7%
- } Low frequency

Van Houten MM, et al, *Int J Cancer* 2001; 93
Klussmann JP, et al. *Am J Pathol* 2003; 162
Scapoli et al. *Mod Pathol* 2008;



Laryngeal SCC in HIV+ patients

- All SCC of the larynx in HIV+ patients in the HCP of Barcelona: 6 cases
- DNA extraction from formalin-fixed, paraffin embedded material and HPV detection (PCR, SPF10)
- IHC staining for p16^{INK4a} and p53
- **All cases HPV negative and p16^{INK4a} negative**

Moyano S, et al, *J AIDS*, 2009; 10: 634-639

Laryngeal SCC in HIV+ patients

	Site	Histological type	Histological grade	Stage at diagnosis	Treatment	Relapse	Evolution
Case 1	Epiglottis	KSCC ^{a)}	2	T3N0M0	Total Laryngectomy	No	AWOD ^{b)} , 96 months
Case 2	Epiglottis	KSCC	2	T3N3M0	Supraglottic laryngectomy, chemotherapy	12 months	DOD ^{c)} , 22 months
Case 3	Epiglottis	KSCC	2	T2N1M0	Partial resection Radiotherapy	48 months	AWOD, 70 months
Case 4	Epiglottis	KSCC	2	T3N3M0	Partial Laryngectomy Radiotherapy	8 months	DOD, 16 months
Case 5	Right cord	KSCC	2	T2N0M0	Partial resection	No	AWOD, 29 months
Case 6	Epiglottis	KSCC	3	T4N2M0	Laryngectomy Radiotherapy, Chemotherapy	No	AWOD ^{c)} , 12 months

Moyano S, et al, *J AIDS*, 2009; 10: 634-639

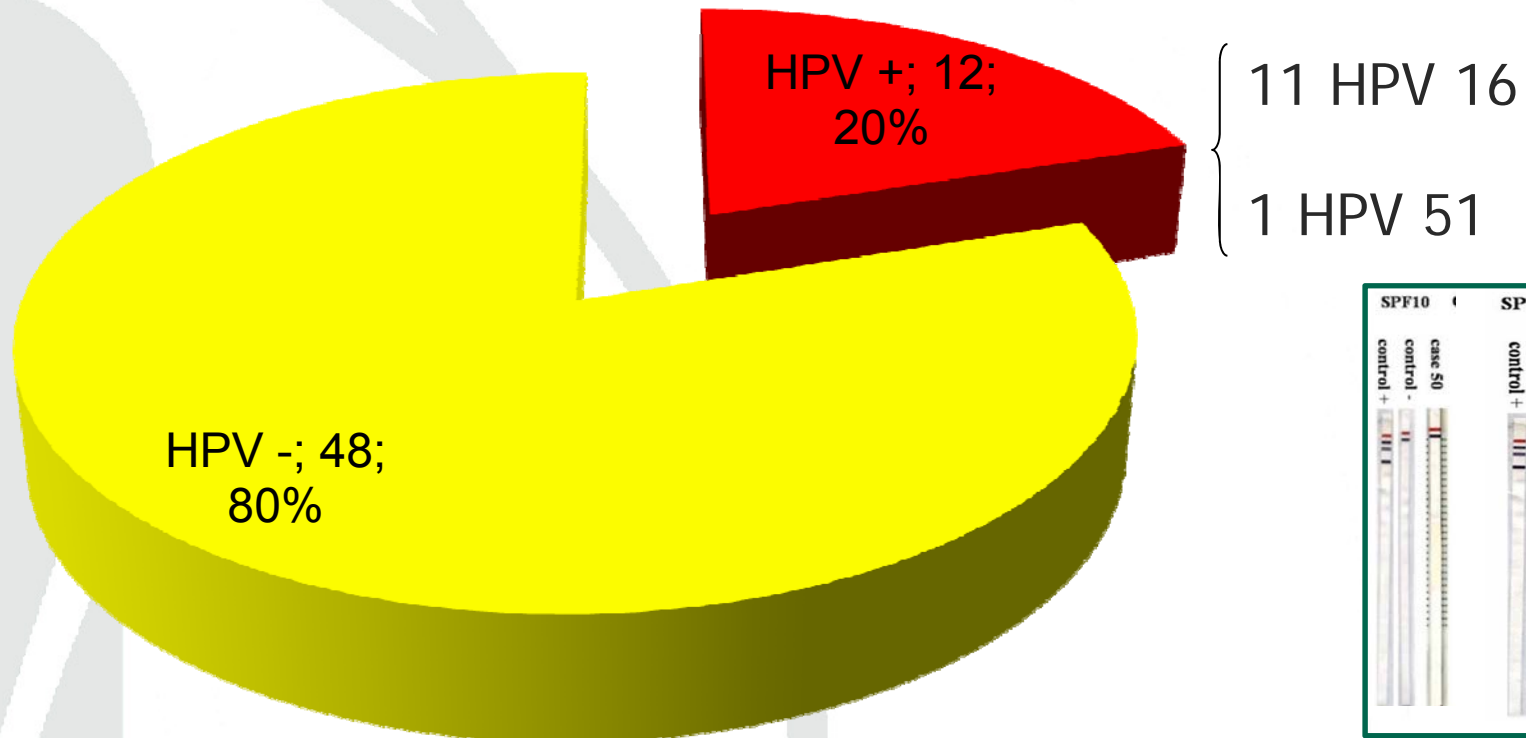


Sinonasal SCC

- Over 90% of all rinosinusal carcinomas
- Low frequency
 - 3% of neoplasms of head and neck
 - Incidence $<1.5 : 100,000$ (Sisson & Beck, 1981)
- Relationship with HPV not clearly established
 - Few publications (isolated cases)
 - Discrepant results
 - 19% tumors HPV+ (El-Mofty & Lu. *Am J Surg Pathol* 2005; 29)

Sinonasal SCC: HPV

- All rinosinusal SCC diagnosed and treated at the Hospital Clinic of Barcelona between 1981 and 2006: **60 cases**

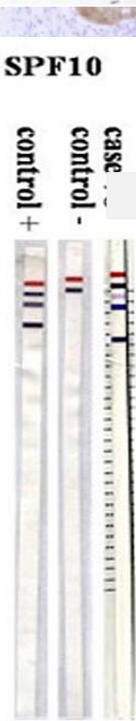
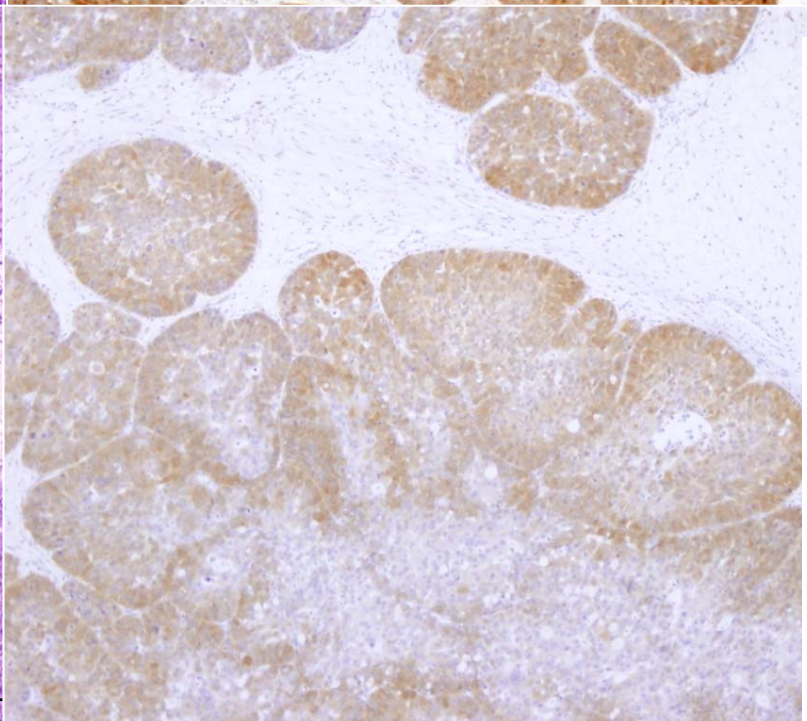
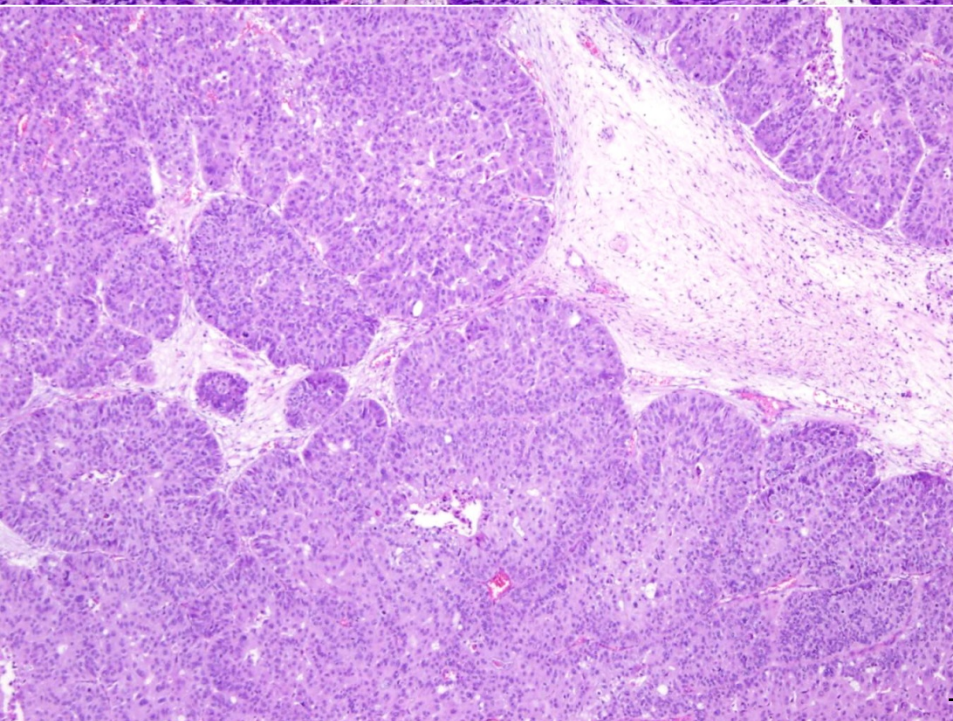
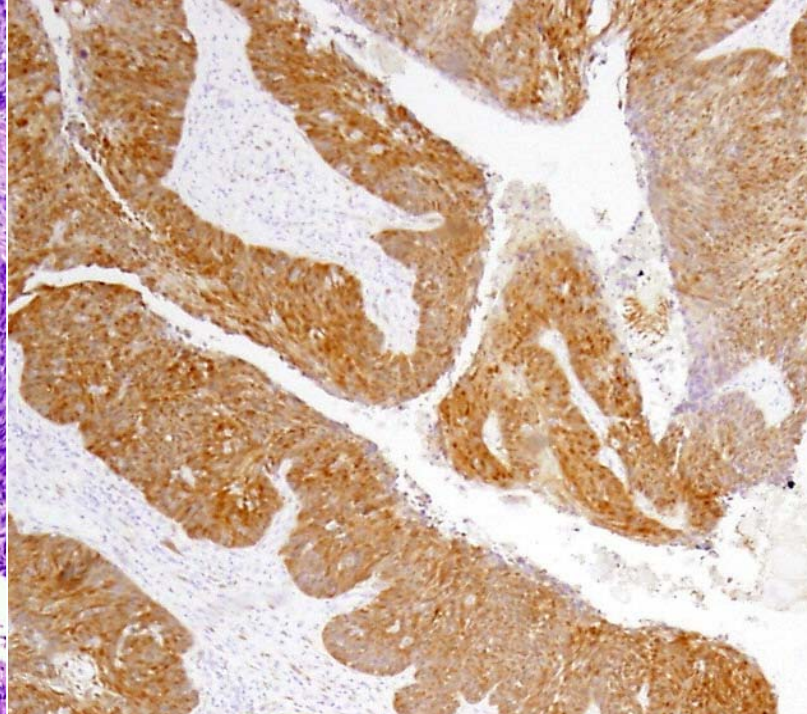
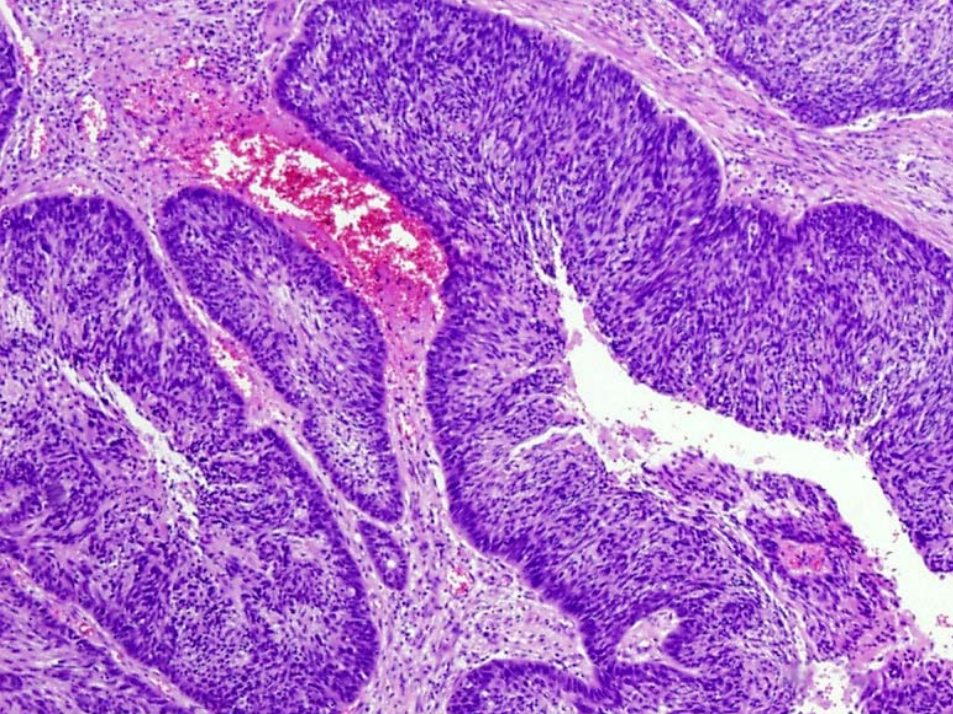


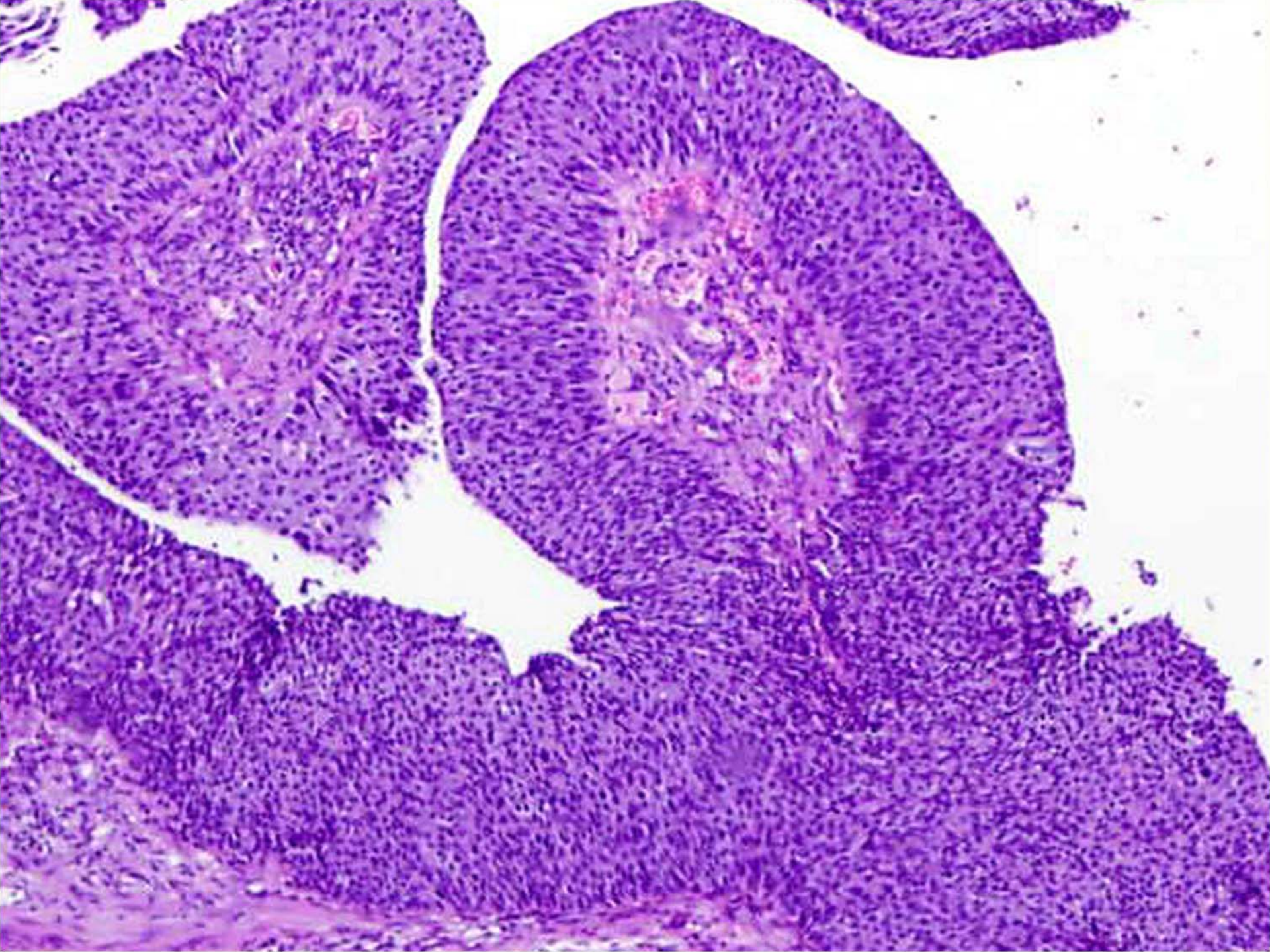
Alos L, et al. *Cancer* 2009; 115:2701-2709

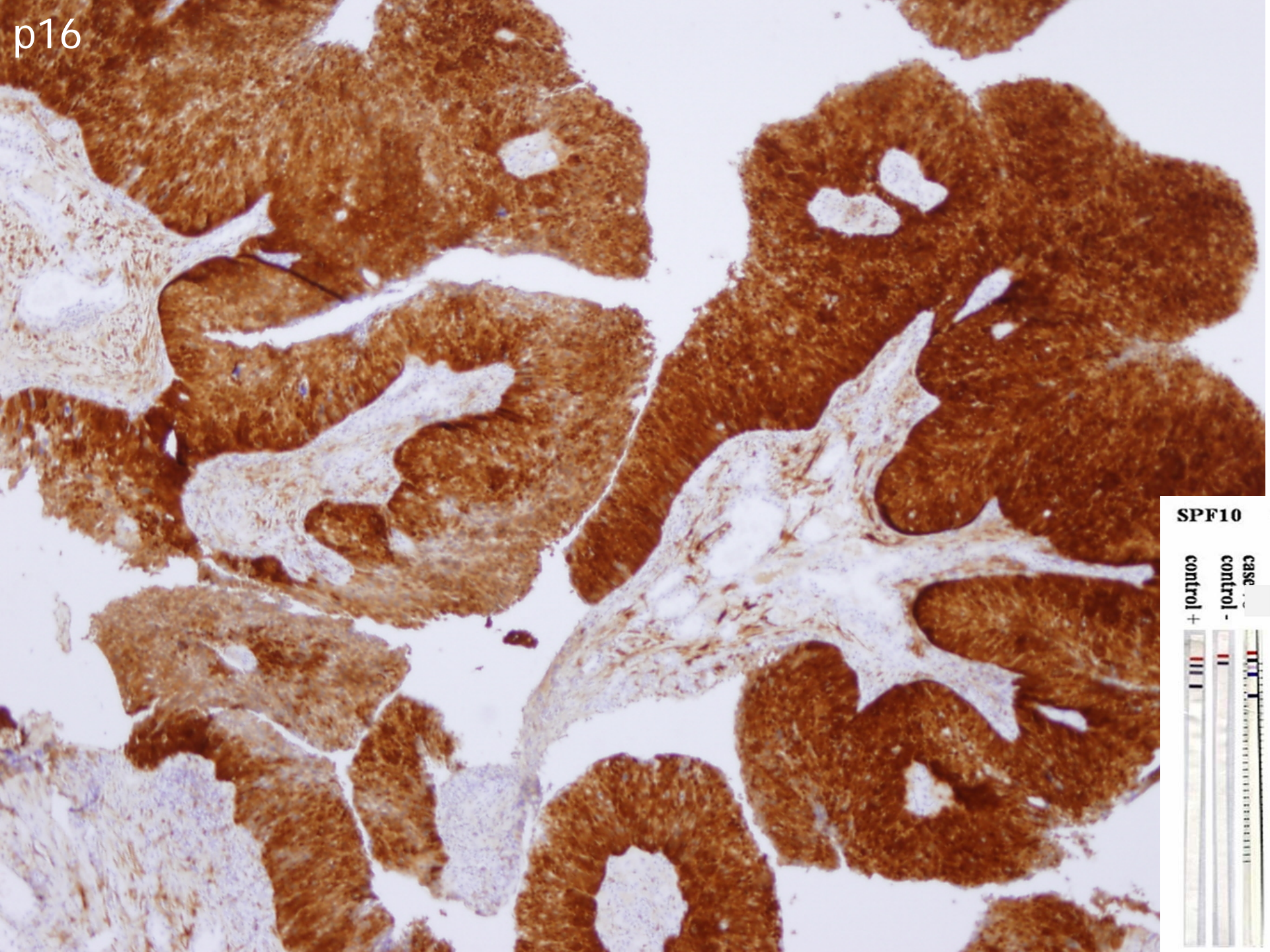
SN SCC: IHC p16^{INK4a} and p53

	HPV+ (n=12)		HPV- (n=48)		
	n	(%)	n	(%)	p
Immunohistochemistry					
p16 ^{INK4a} positive	12	(100)	0	(0)	<.001
p53 positive	4	(33.4)	32	(66.6)	.05

Alos L, et al. *Cancer* 2009; 115:2701-2709



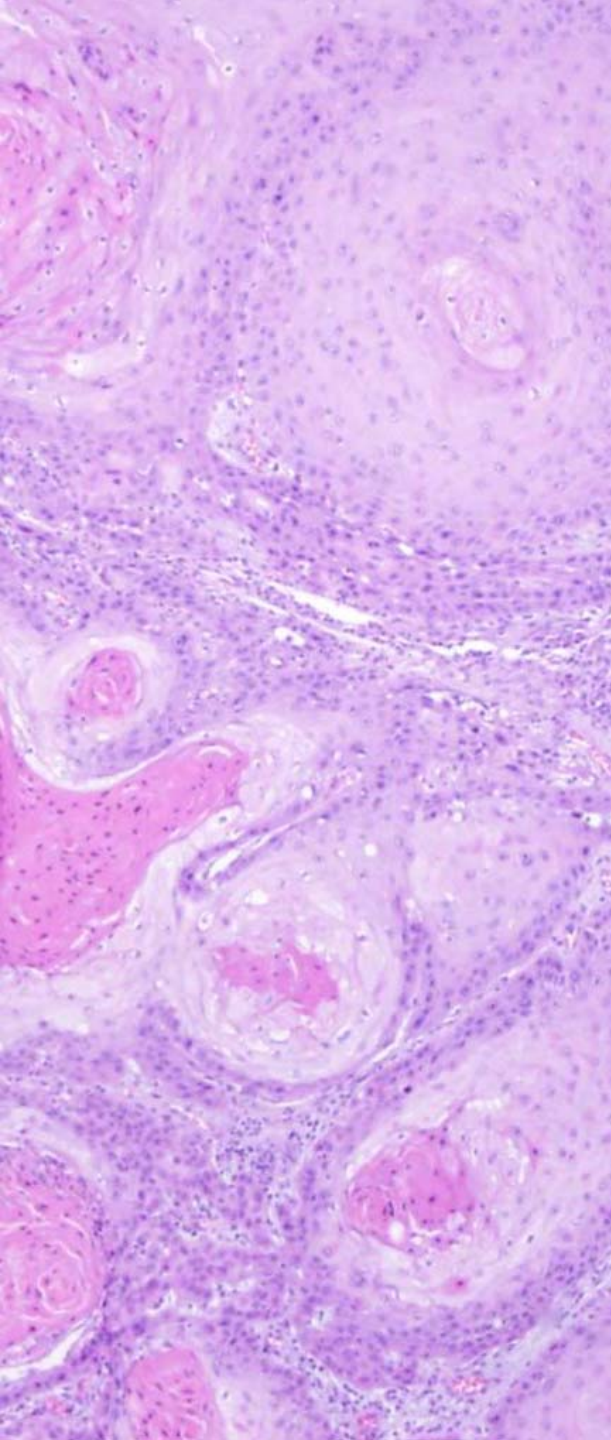




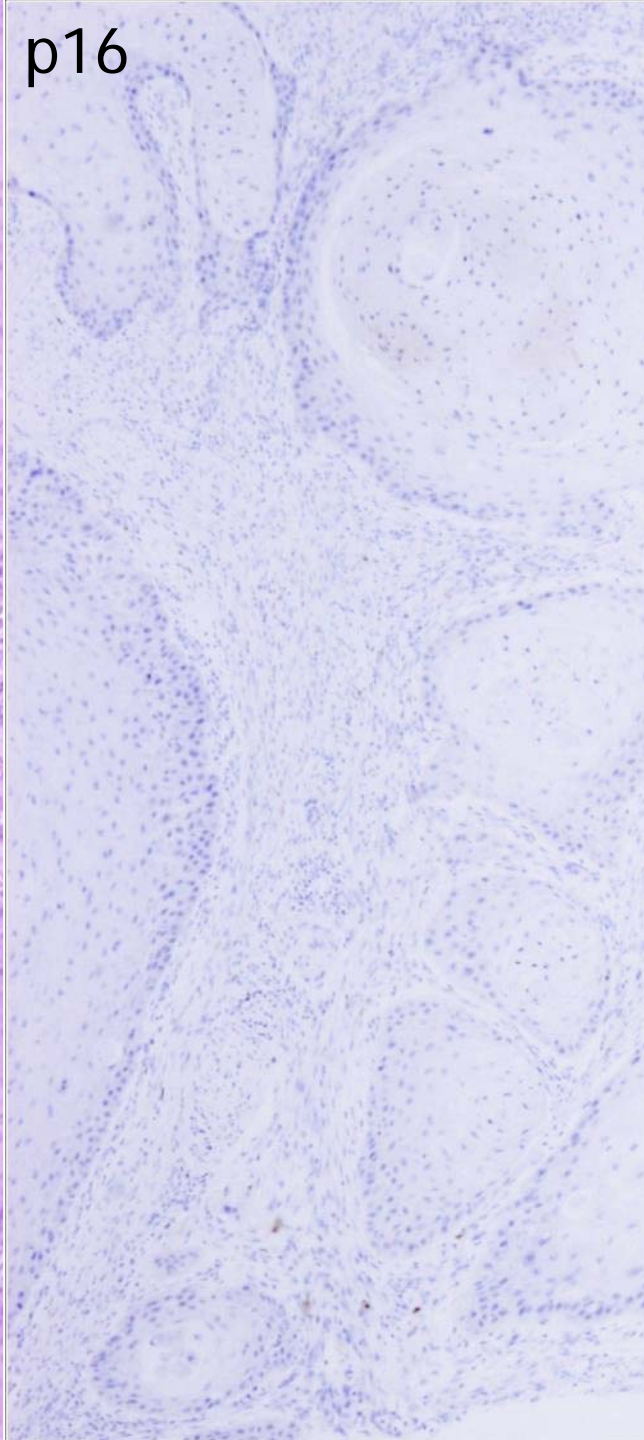
p16

SPF10

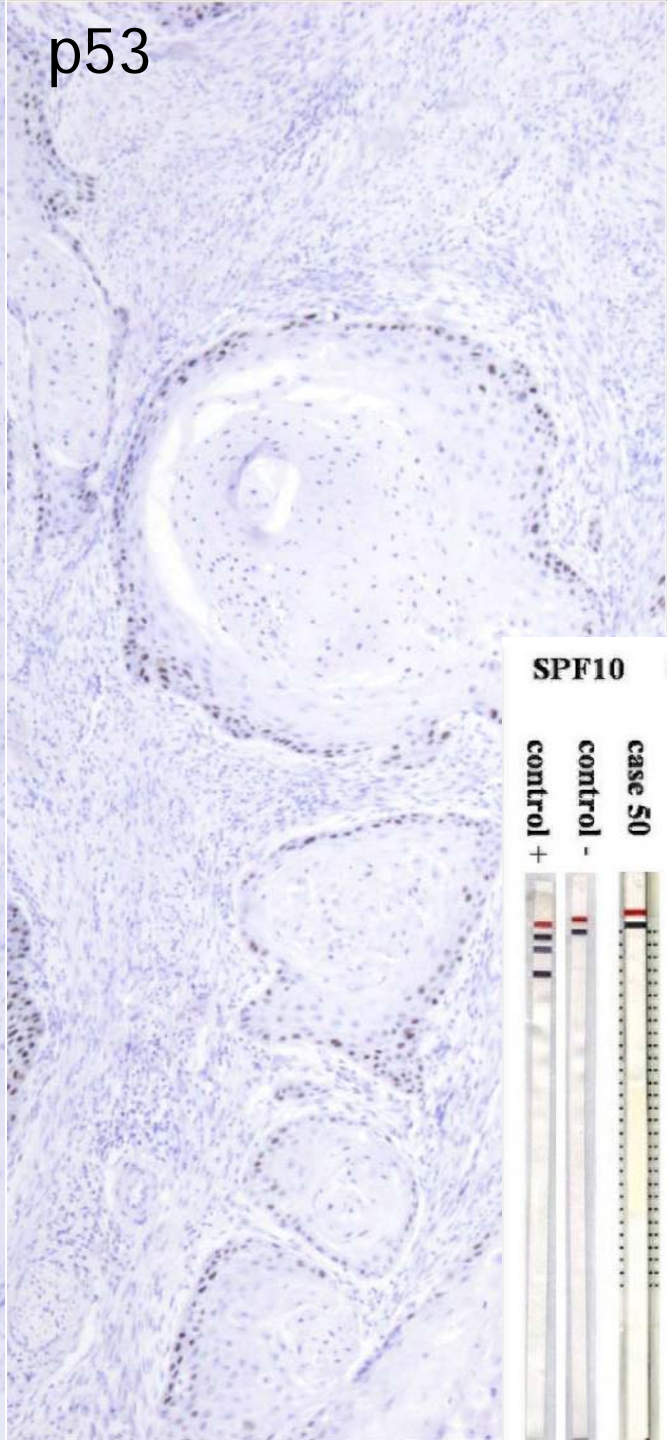
case	+	+++
control -	-	++
control +	+	++



p16



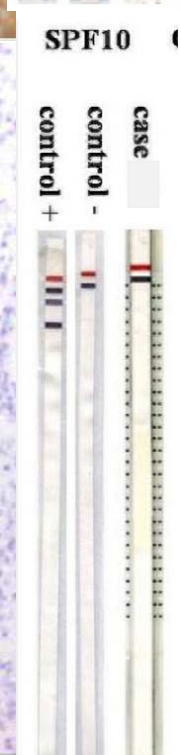
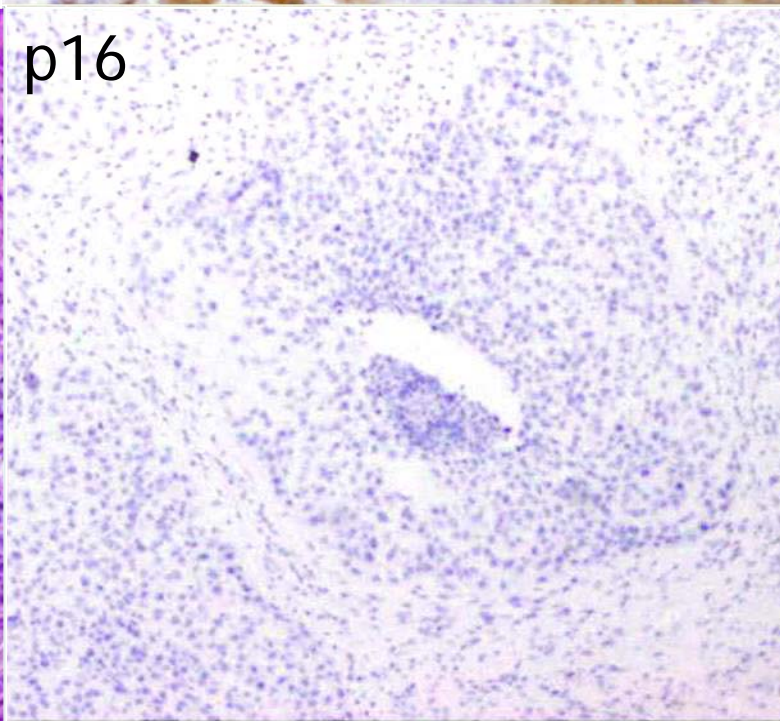
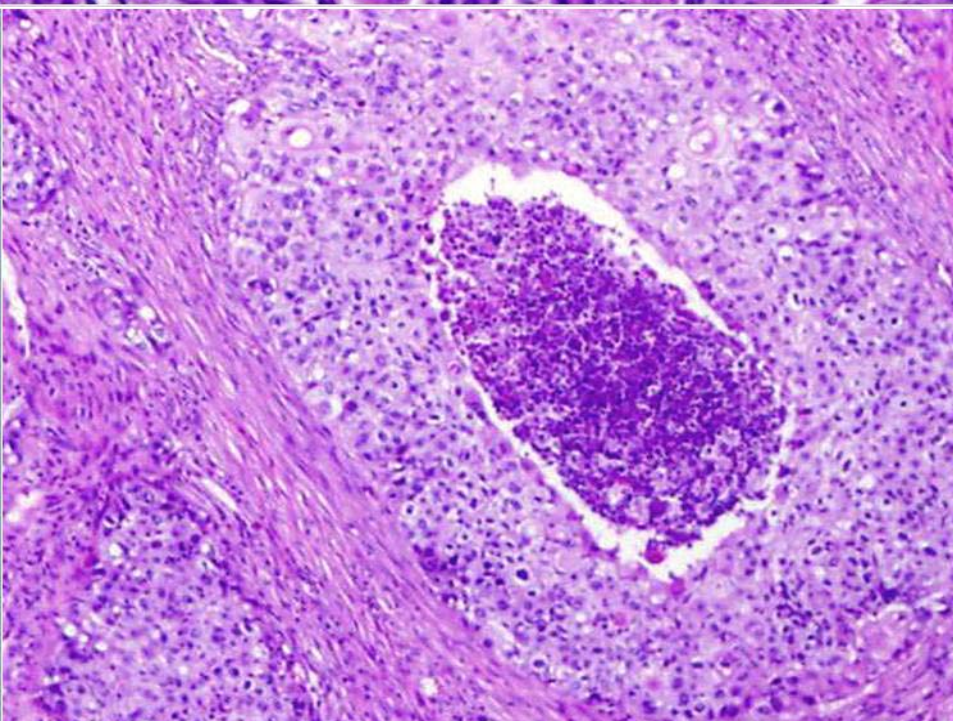
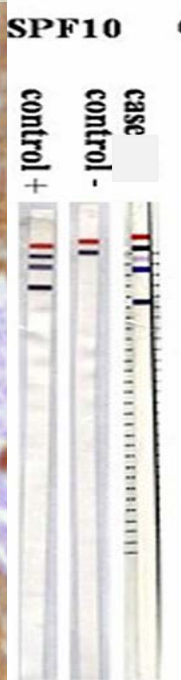
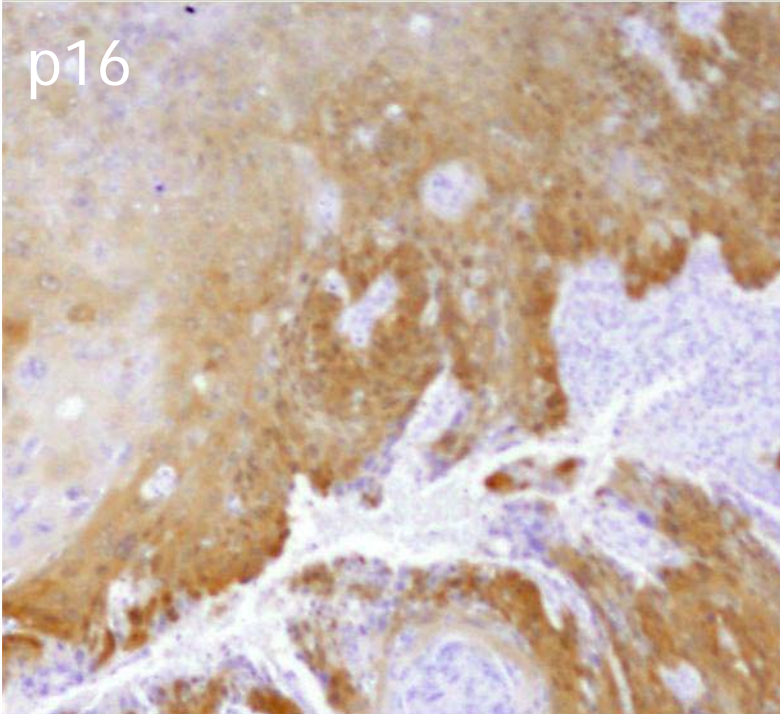
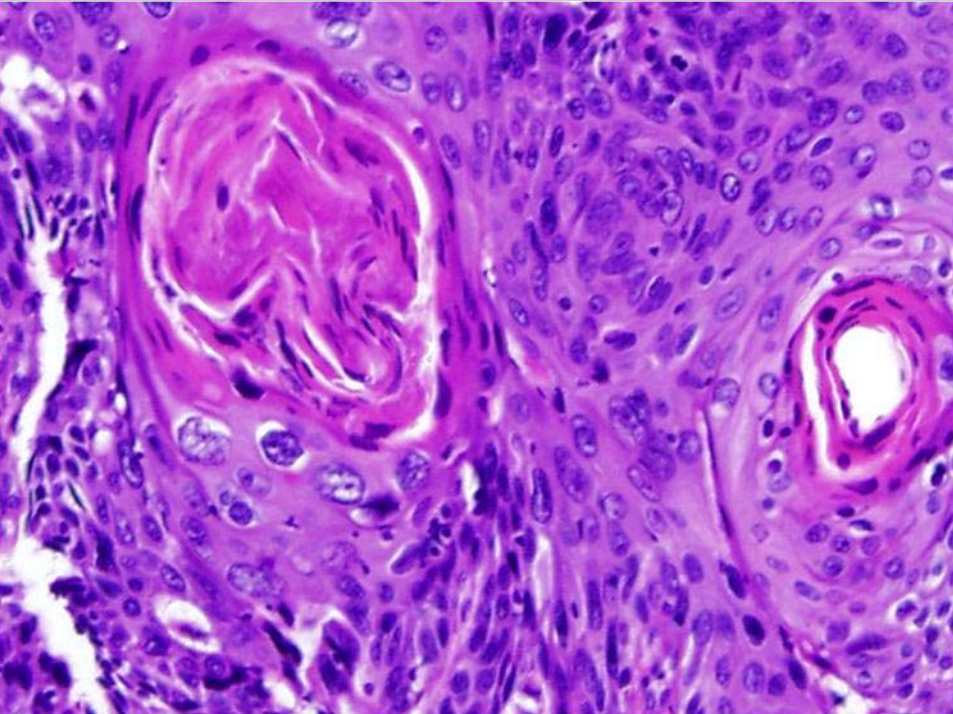
p53



SPF10

case 50
control -
control +





Sinonasal SCC: histological types

Histological type	HPV+ (n=12)		HPV- (n=48)		p
	n	(%)	n	(%)	
Keratinizing (n=42)	2	(16.7)	40	(83.3)	<.001
Non-keratinizing (n=11)	6	(50.0)	5	(10.4)	
Basaloid (n=5)	2	(16.7)	3	(6.3)	
Papillary (n=2)	2	(16.7)	0	(0)	

Alos L, et al. *Cancer* 2009; 115:2701-2709



Identification of HPV relationship

	p16 (+++)	p53 (-)	basaloid/warty histology
Sensitivity	100%	56.6%	88.9%
Specificity	100%	83.3%	83.3%
Positive PV	100%	56.6%	66.7%
Negative PV	100%	83.3%	95.2%

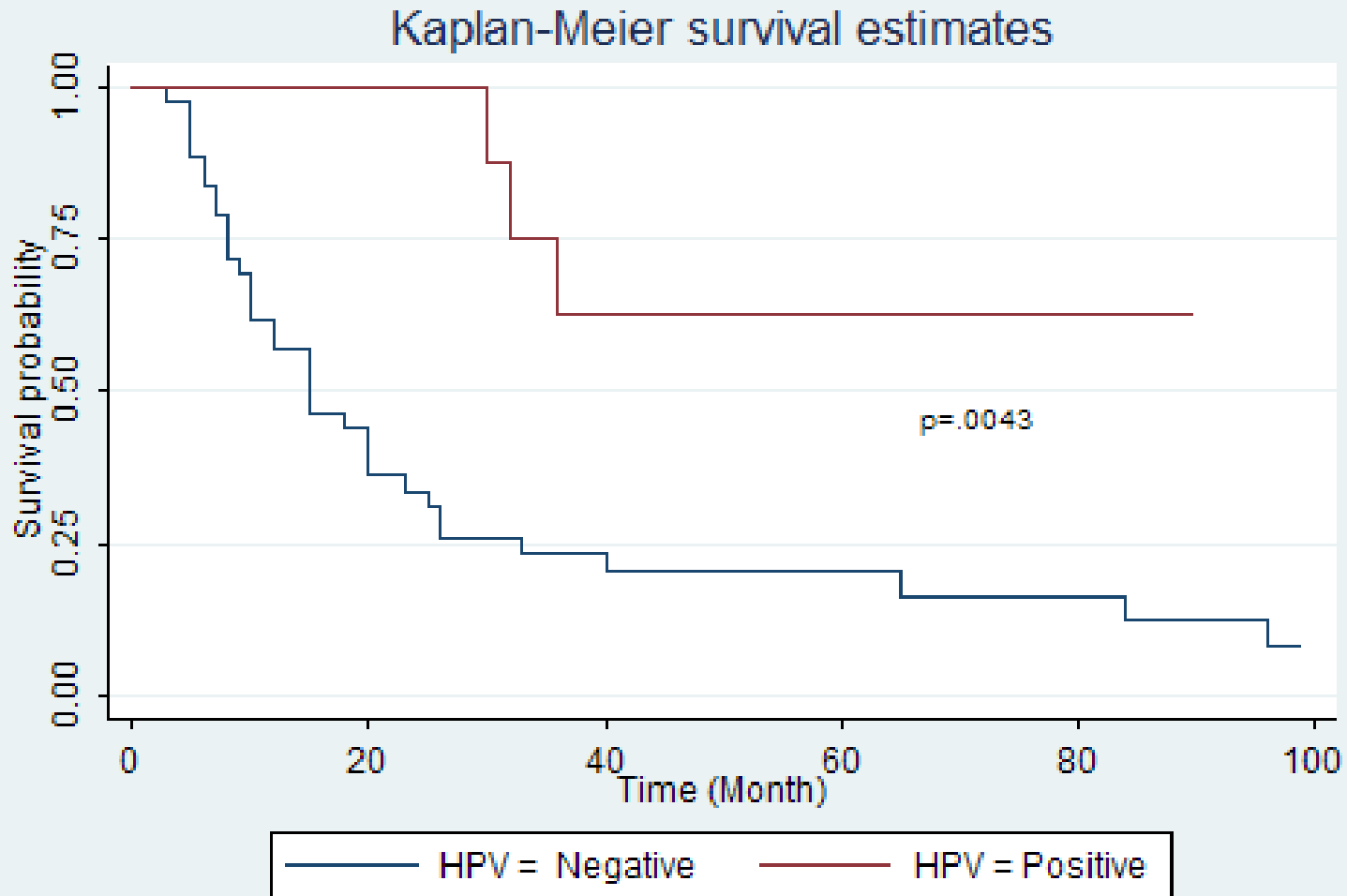
Alos L, et al. *Cancer* 2009; 115:2701-2709

Sinonasal SCC: Staging

	HPV positive (n=12)	HPV negative (n=48)	p
Stage			.977
I	1 (8.4)	5 (10.4)	
II	4 (33.3)	13 (27.1)	
III	4 (33.3)	17 (35.4)	
IV	3 (25.0)	13 (27.1)	

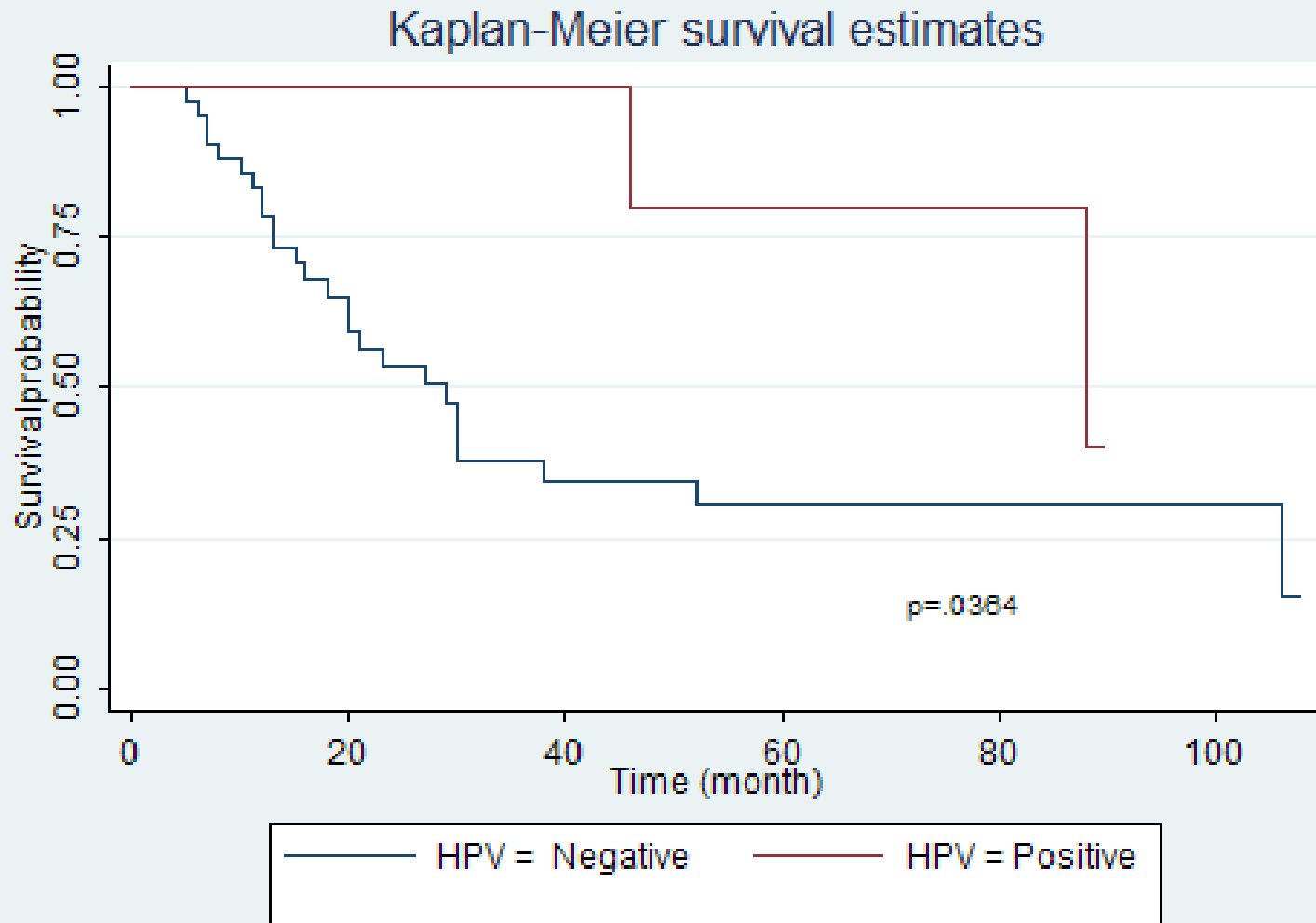
Alos L, et al. *Cancer* 2009; 115:2701-2709

SN SCC: disease-free survival



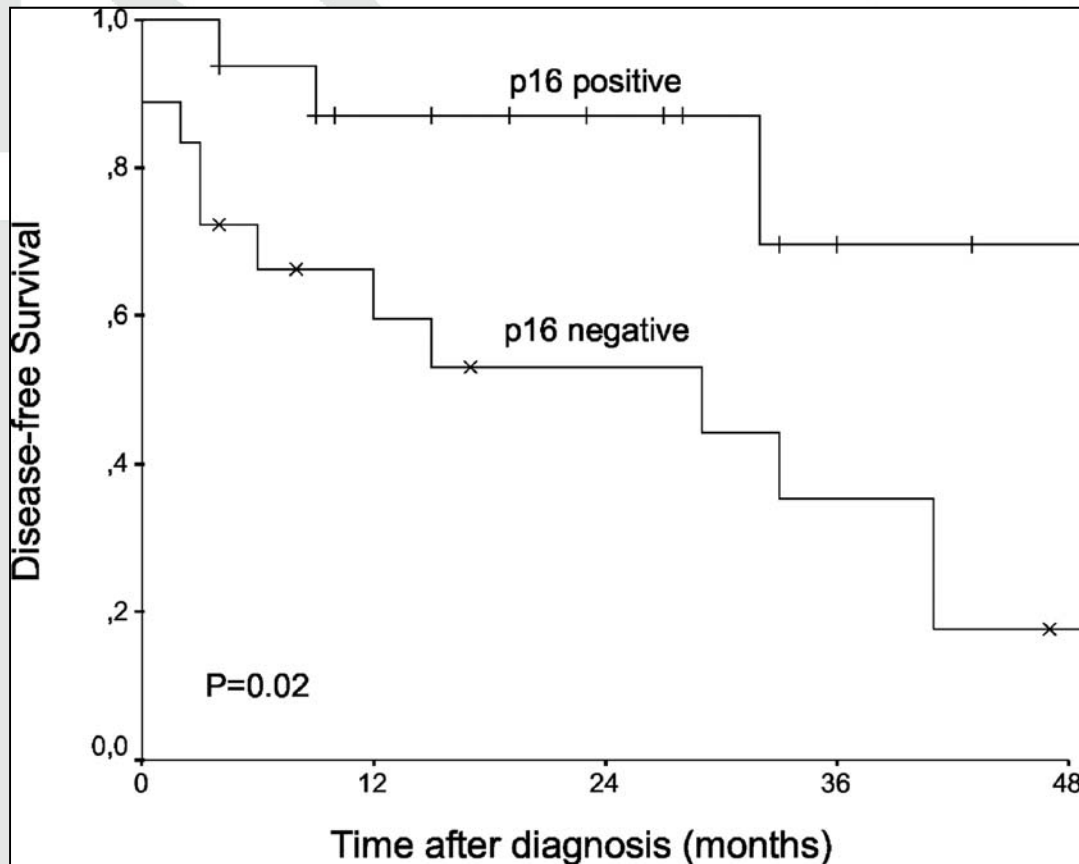
Alos L, et al. *Cancer* 2009; 115:2701-2709

SN SCC: overall survival



Alos L, et al. *Cancer* 2009; 115:2701-2709

Oropharyngeal SCC: survival

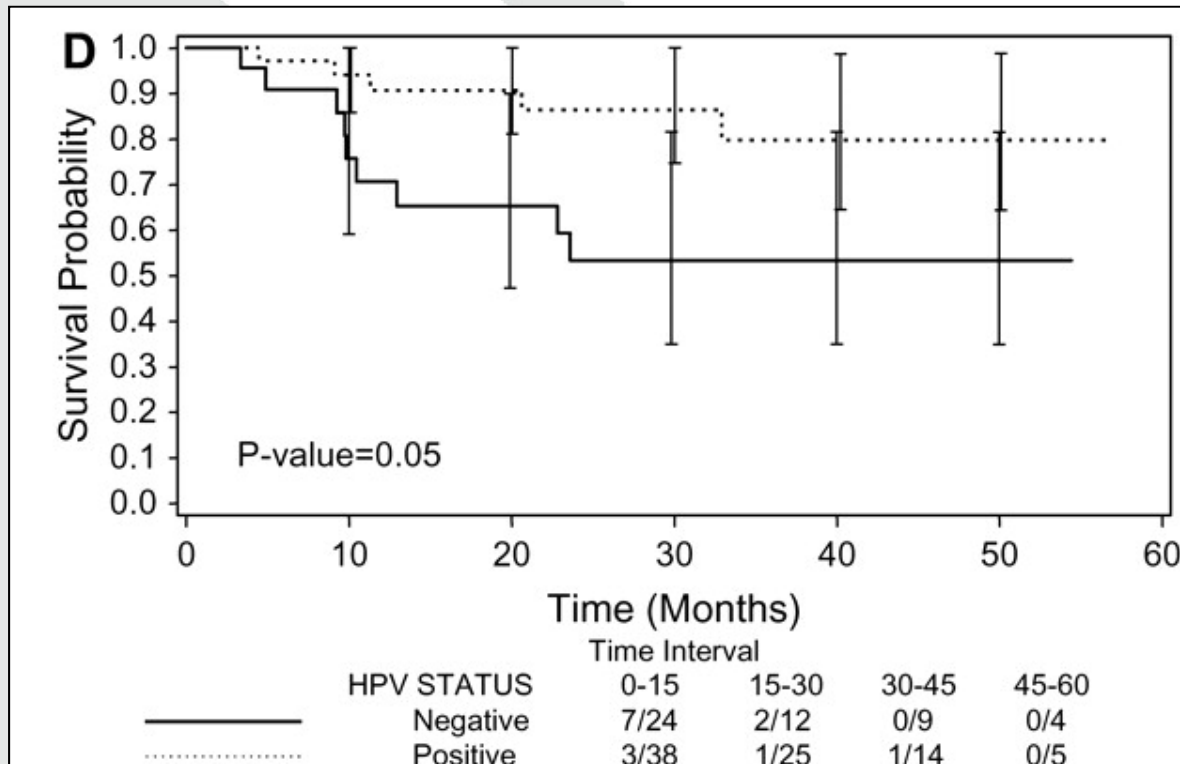


- Better disease-free survival in HPV+ patients ($p=0.02$)

Klussmann JP, et al. *Am J Pathol* 2003; 162

Oropharyngeal SCC: survival

- Better response to chemotherapy induction (82% vs. 55%)
- Better response to radio-chemotherapy treatment (84% vs. 57%)



Fakhry C, et al *J Natl Cancer Inst* 2008; 100

Lassen P, et al. *J Clin Oncol* 2009; 27:1-7

Laryngeal SCC in HIV+ patients

	Sex	Age	Smoking Packs/year	Alcohol consumption Per day	Risk factor	Years HIV ^{b)}	Antiretroviral treatment	Other lesions
Case 1	F	36	23	No	IVDA ^{a)} Heterosexual	9	Lamivudin Estavudin	HCV+ ^{e)} , Carcinoma uterine cervix, VIN3 ^{f)}
Case 2	M	54	20	No	Homosexual	12	Lamivudin Estavudin indinavir	-
Case 3	M	42	36	No	Homosexual	16	Lamivudin, Estavudin, indinavir, ritonavir	Pulmonary tuberculosis
Case 4	F	41	10	No	IVDA ^{a)}	7	Lamivudin, zidovudin, abacavir	HCV+ ^{e)} , PML ^{g)} , CIN3 ^{h)}
Case 5	M	46	25	No	Heterosexual	18	Zidovudin Didanosin, nevirapin	B-cell lymphoma, rynopharynx
Case 6	F	37	100	120 gr	IVDA ^{a)}	9	Tenofovir, emtricitavin, nevirapin	HCV+ ^{e)}



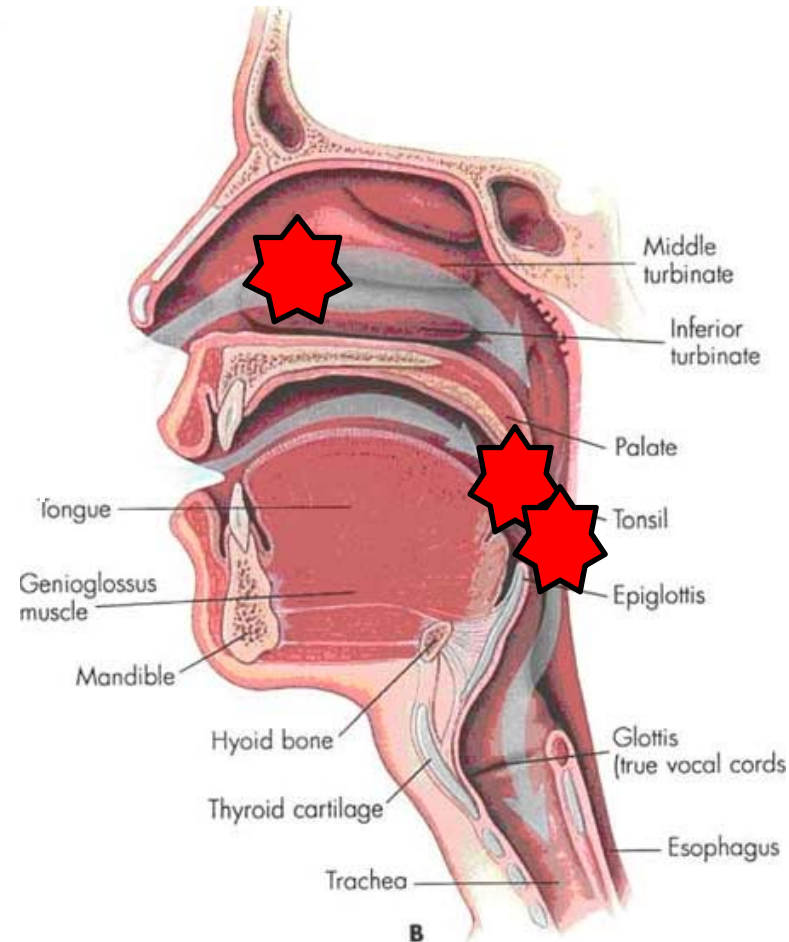
H&N SCC and HPV: epidemiology

- High number of sexual partners
 - Vaginal sex (26 or more) (OR 3.2; 95% CI 1.5-6.5, p=0.002)
 - Oral sex (6 or more) (OR 3.4; 95% CI 1.3-8.8, p=0.009)
- Evidence of HPV16 infection
 - Oral PCR for HPV type 16 (OR: 14.6, 95% CI 6.3-36.6)
 - Serum positive for L1 of HPV16 (OR: 32.2, 95%CI 14.6-71.3)
 - Positivity for E6 y E7 (64% of oropharyngeal tumors)
- Independent of smoking and alcohol

D'Souza et al, *N Engl J Med* 2007; 356:19

Conclusions

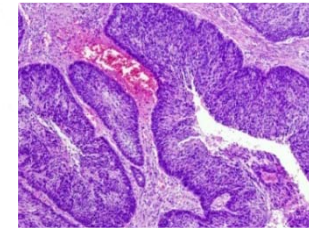
- **Variable proportion of HPV + tumors in different areas:**



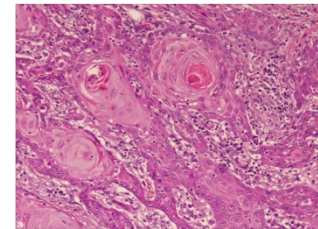
Conclusions

- **Relation HPV / histological type**

- HPV+ tumors: Non keratinizing

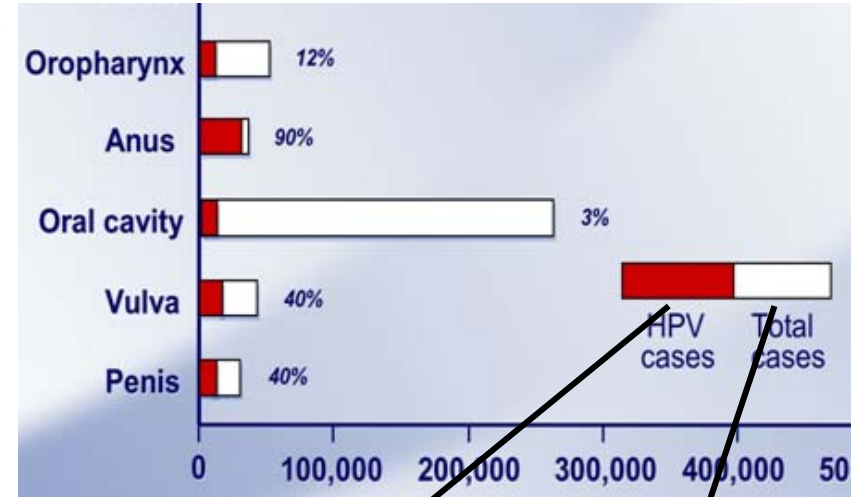


- HPV- tumors: Keratinizing



Conclusions

- **p16^{INK4a} overexpression** has a **sensitivity and a specificity close to 100%** to identify HPV positive tumors of the head and neck area and may thus be used as a **biomarker of HPV infection**



P16 (+)

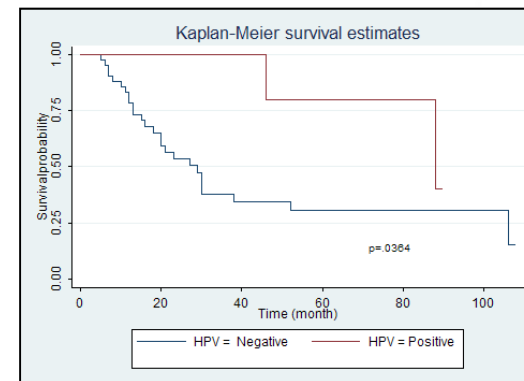
P53 (-)

P16 (-)

P53 (+)

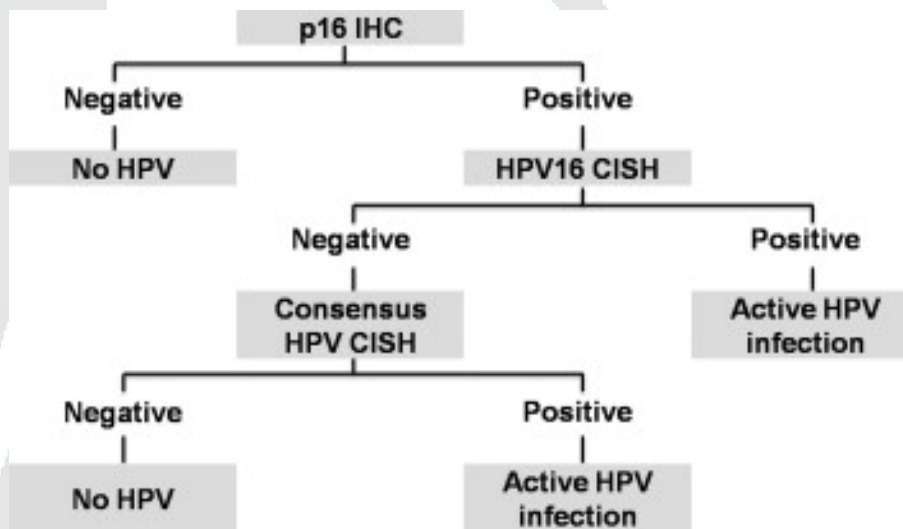
Conclusions

- Although HPV+ and HPV- do not differ in stage at diagnosis, **HPV+ squamous cell carcinomas of the head and neck have a significantly better prognosis than HPV- tumors, probably due to a better response to chemo-radiotherapy**



Conclusions

- P16 and/or HPV testing should be included in the evaluation of head and neck carcinomas (tonsillar, sinonasal) because it has a prognostic and treatment significance



Robinson M, et al. *Oral Oncology* 2010;

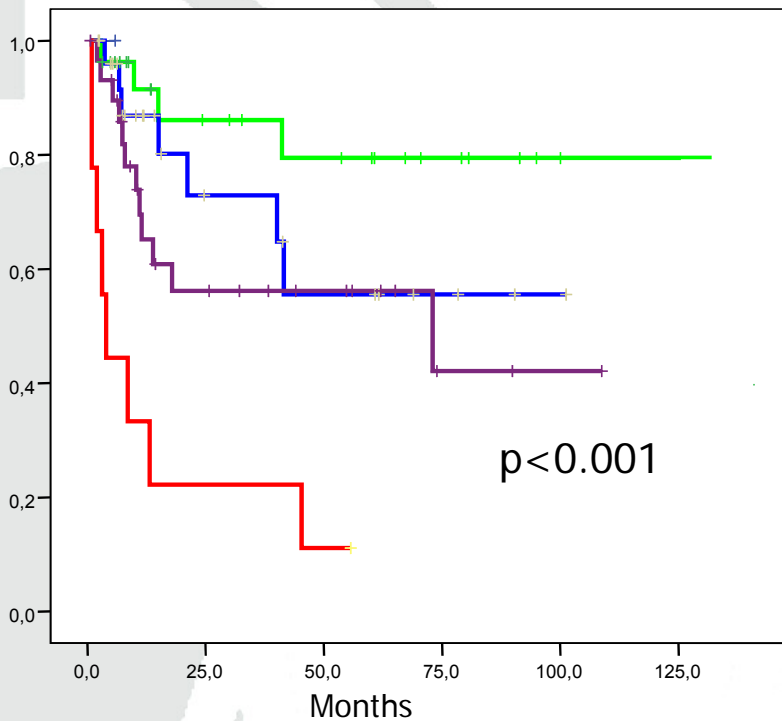
Vulvar SCC: Clinical data

	Non-HPV n = 79	HPV n = 19	p
Age (x ± SD)	77,2 ± 11,2	64,0 ± 22,1	0,003*
Tumor size (mm) (x ± SD)	33,1 ± 19,4	35,3 ± 22,8	0,595*
Ulceration			
No	23 (31,9)	6 (37,5)	0,77***
Yes	49 (68,05)	10 (62,5)	
Stage FIGO	n (%)	n (%)	0,18**
I	39 (49,4)	6 (31,6)	
II	7 (8,9)	4 (21,1)	
III	27 (34,8)	5 (26,3)	
IV	6 (7,6)	4 (21,1)	

Alonso I et al. *Cancer* 2010 (submitted)

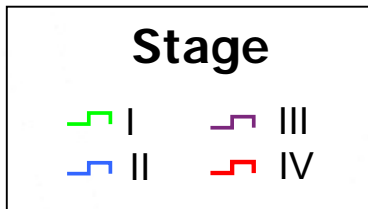
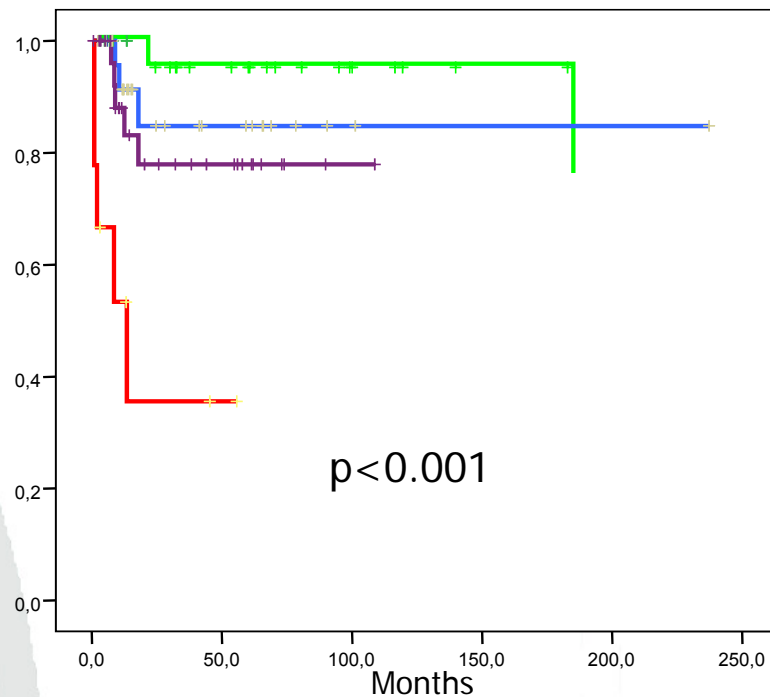
SCC of vulva: survival (stage)

Disease-free survival



Alonso I et al. *Cancer* 2010 (submitted)

Overall survival

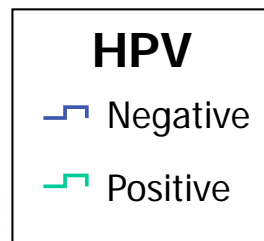
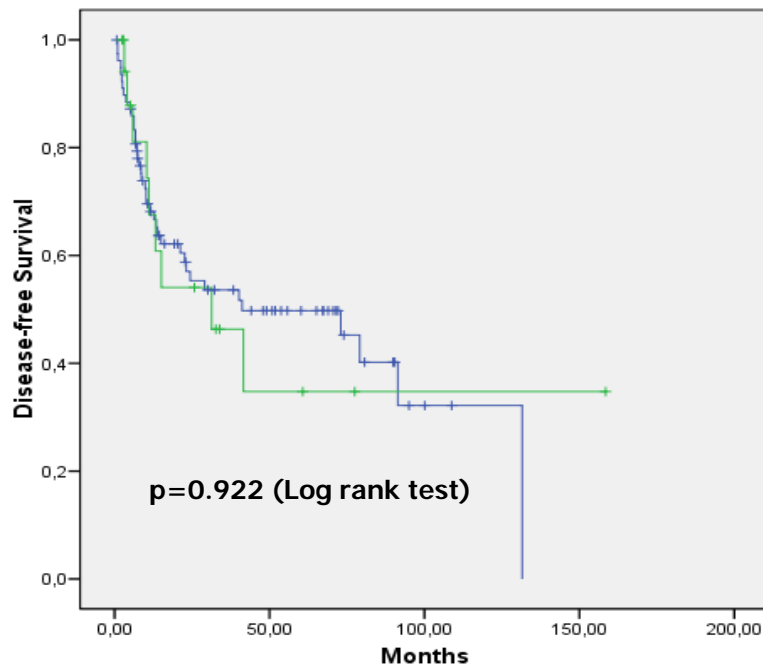




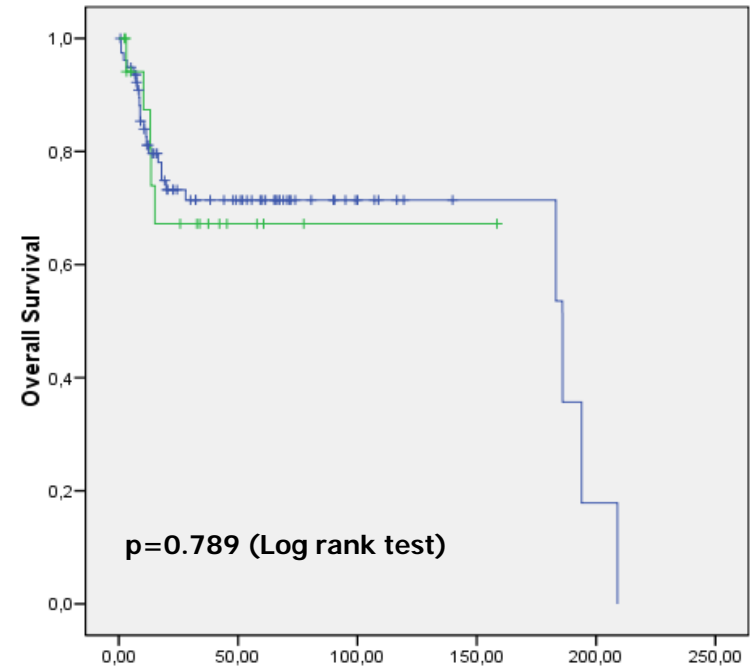
vSCC: survival (HPV status)

Disease-free survival

Alonso I et al. *Cancer* 2010 (submitted)



Overall survival

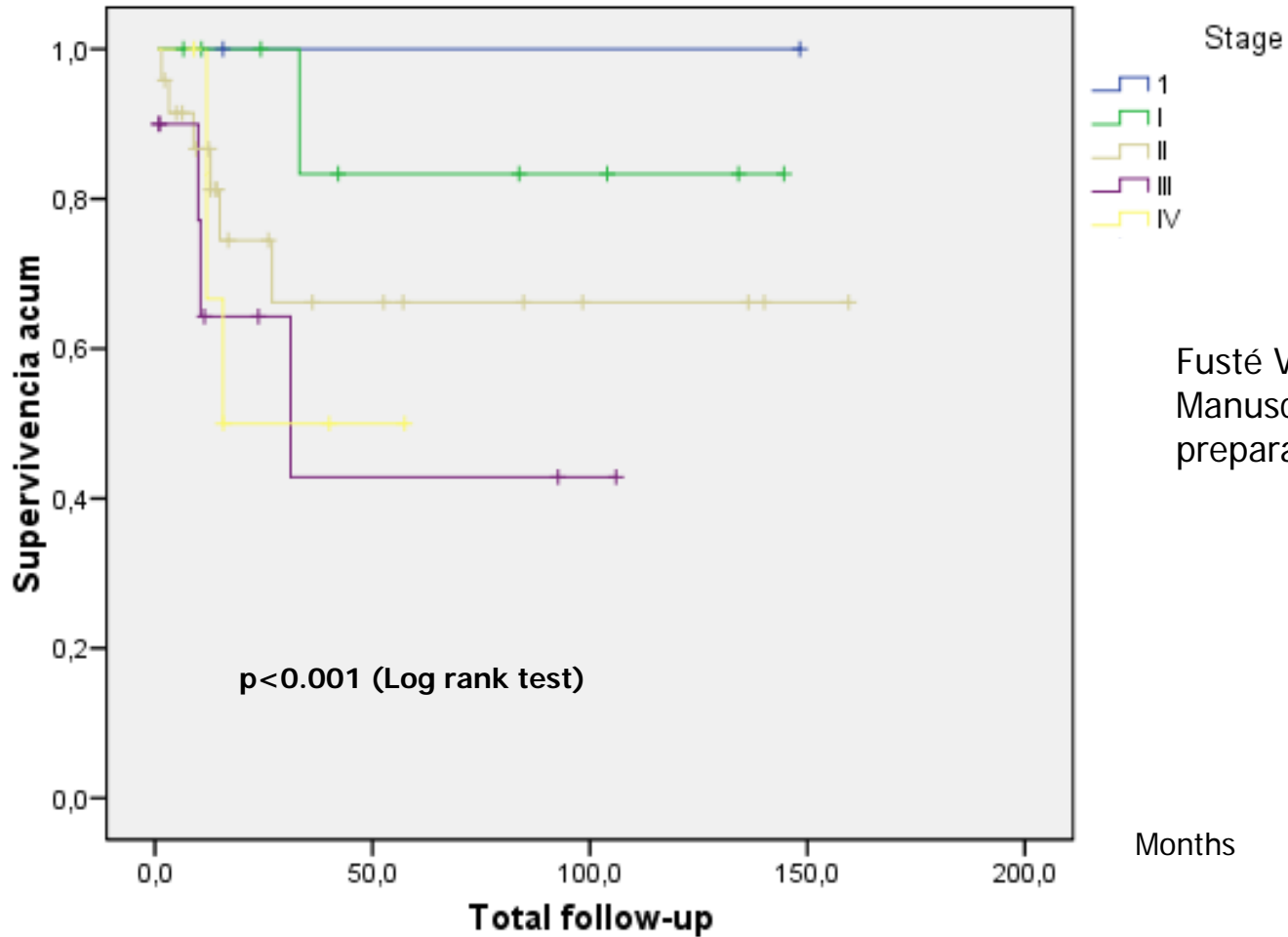


Vulvar SCC: logistic regression

	OR	95% CI	p-value
Overall Sv			
RDT (Yes vs no)	1.63	(0.58 to 4.63)	0.353
p16 (+ vs -)	1.08	(0.31 to 3.78)	0.900
HPV (+ vs -)	0.76	(0.19 to 3.01)	0.701
u-VIN vs d-VIN	0.97	(0.17 to 5.59)	0.970
Disease-free Sv			
RDT (Yes vs no)	1.63	(0.58 to 4.63)	0.353
p16 (+ vs -)	1.08	(0.31 to 3.78)	0.900
HPV (+ vs -)	0.76	(0.19 to 3.01)	0.701
u-VIN vs d-VIN	1.07	(0.28 to 4.06)	0.919

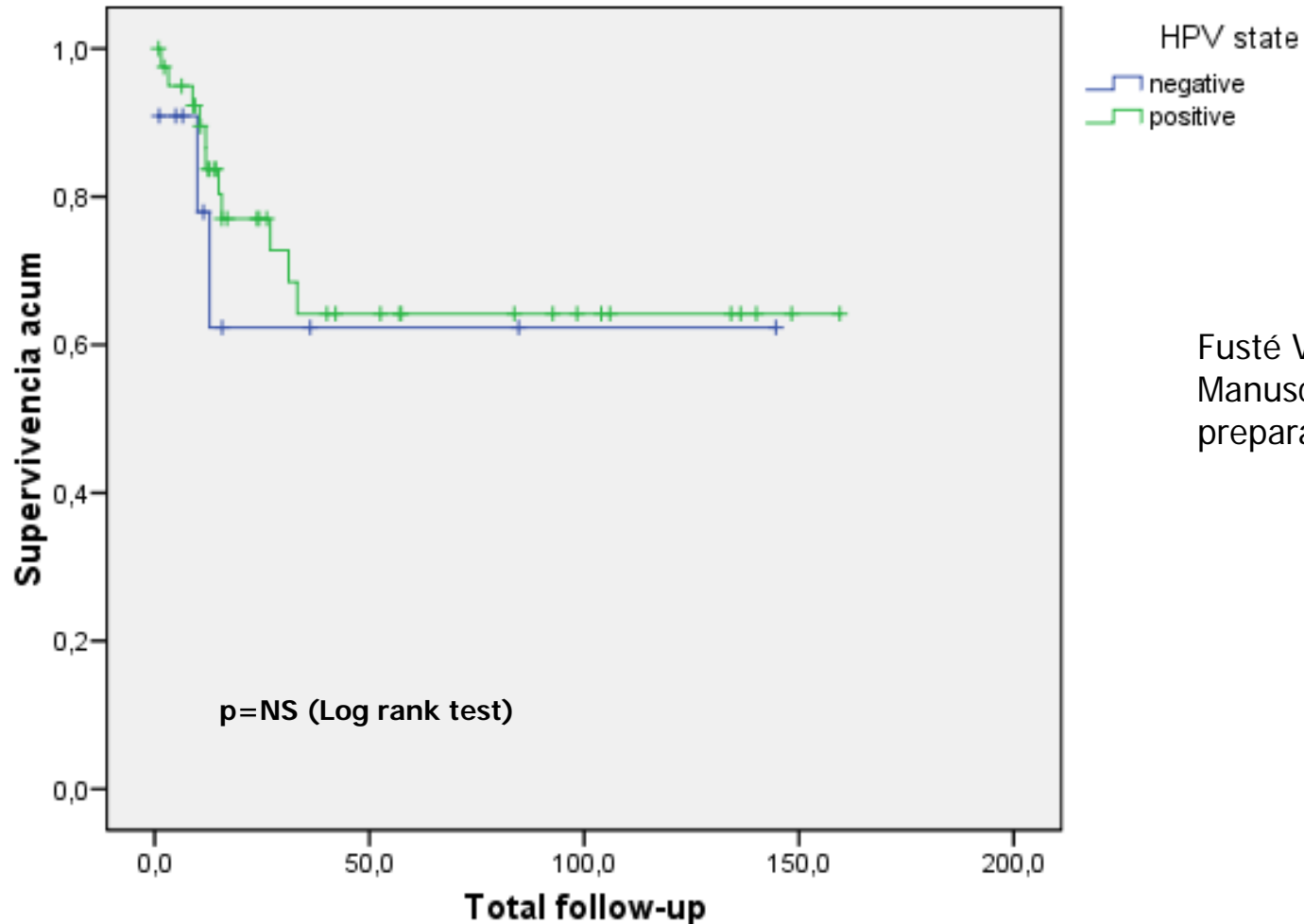
Alonso I et al. Manuscript in preparation

Vaginal SCC: survival (Stage)



Fusté V et al.
Manuscript in
preparation

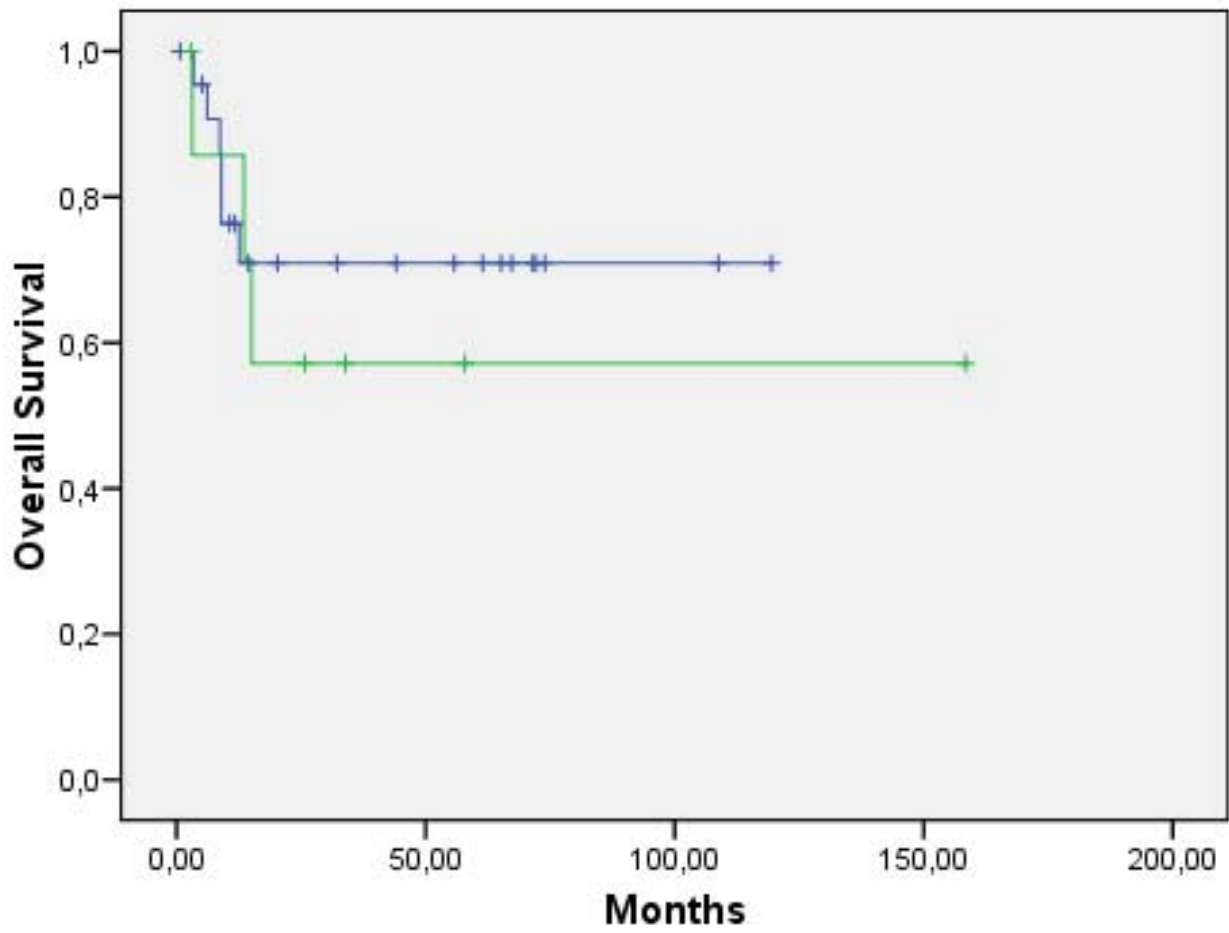
VaSCC: survival (HPV status)



Fusté V et al.
Manuscript in
preparation



VaSCC: survival (previous lesions)



Fusté V et al.
Manuscript in preparation



Conclusions

- In contrast with head and neck tumors, **HPV+ squamous cell carcinomas of the vulva and vagina DO NOT** have a **significantly better prognosis** than HPV- tumors
- **No clinical differences** are observed between vaginal carcinomas with or without multifocal low genital tract pathology
- Radiotherapy does not have a different effect in HPV+ compared to HPV- tumors

SCC in vulva, vagina, H&N: WHO

• Vulva

- Keratinizing
- Non keratinizing
- Basaloid
- Warty

- Verrucous
- Keratoacanthoma-like
- With tumor giant cells
- Others

• Vagina

- Keratinizing
- Non keratinizing
- Basaloid

- Verrucous
- Warty

• Head and neck

- Keratinizing
- Non keratinizing
- Papillary
- Basaloid

- Spindle cell
- Acantholytic
- Verrucous



Evaluation of p16^{INK4a} immunostaining: problems and pitfalls

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p16^{INK4a}: utilidad clínica

- Permite identificar de forma rápida aquellas neoplasias relacionadas con HPV en algunas localizaciones
- Reduce la variación inter- e intra-observador en el diagnóstico de CIN2-3
- Mejora de la sensibilidad del patólogo en la identificación de lesiones de CIN2-3
- Identificación de lesiones de CIN1 con mayor riesgo de progresión

Lesión cervical - p16^{INK4a}

Biopsy final evaluation	N (326)	P16 ^{INK4a} (%)		
		Negative (n=182)	Focal (n=38)	Diffuse (n=106)
No lesion	161	153 (95%)	8 (5%)	0 (0%)
CIN 1	85	29 (34%)	29 (34%)	27 (32%)
CIN 2/3	80	0 (0%)	1 (1%)	79 (99 %)

Ordi J, et al. *Int J Gynecol Pathol* 2009; 28:90-97



Inter-Observer Agreement

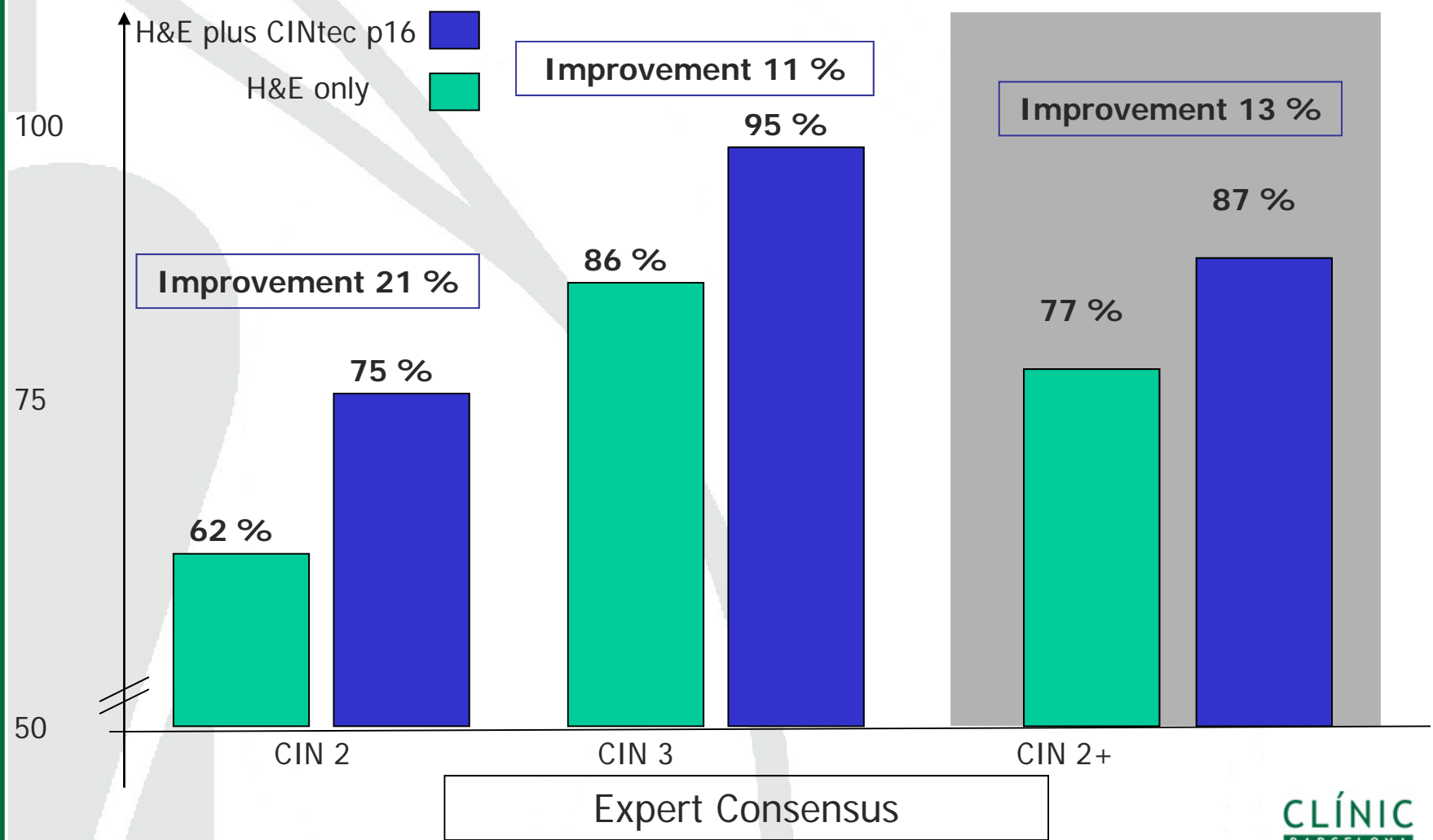
Diagnostic Category	Kappa H&E	Kappa H&E plus CINtec® Histology	Statistical significance
CIN2+, all cases	0,580	0,756	p<0,0001
CIN2+, punch biopsies only	0,598	0,748	p<0,0001
CIN2+, conization biopsies only	0,548	0,765	p<0,0001

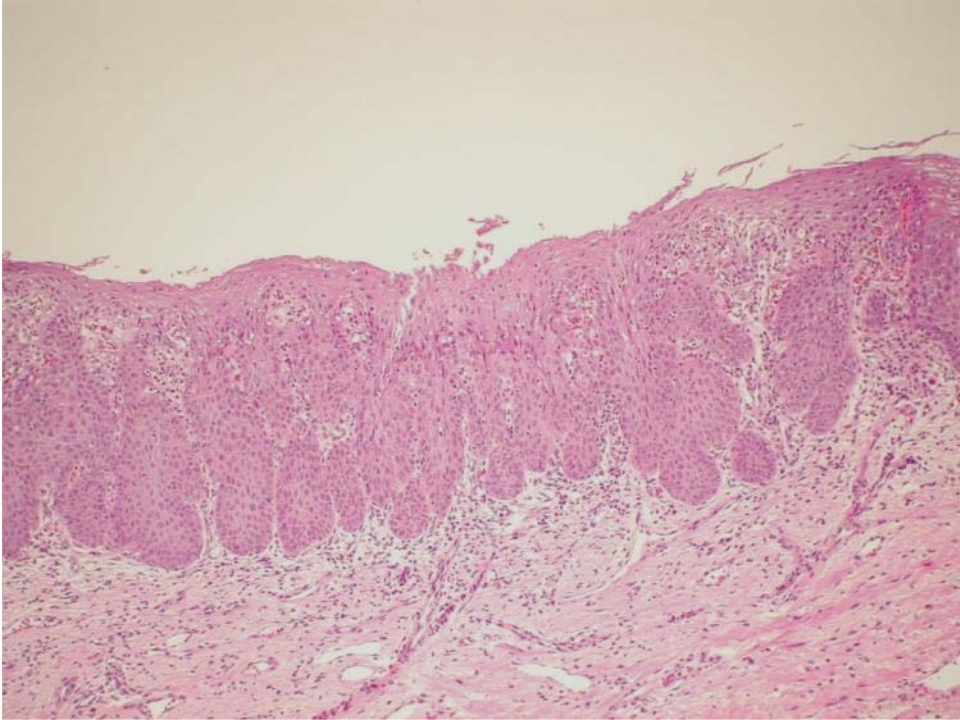
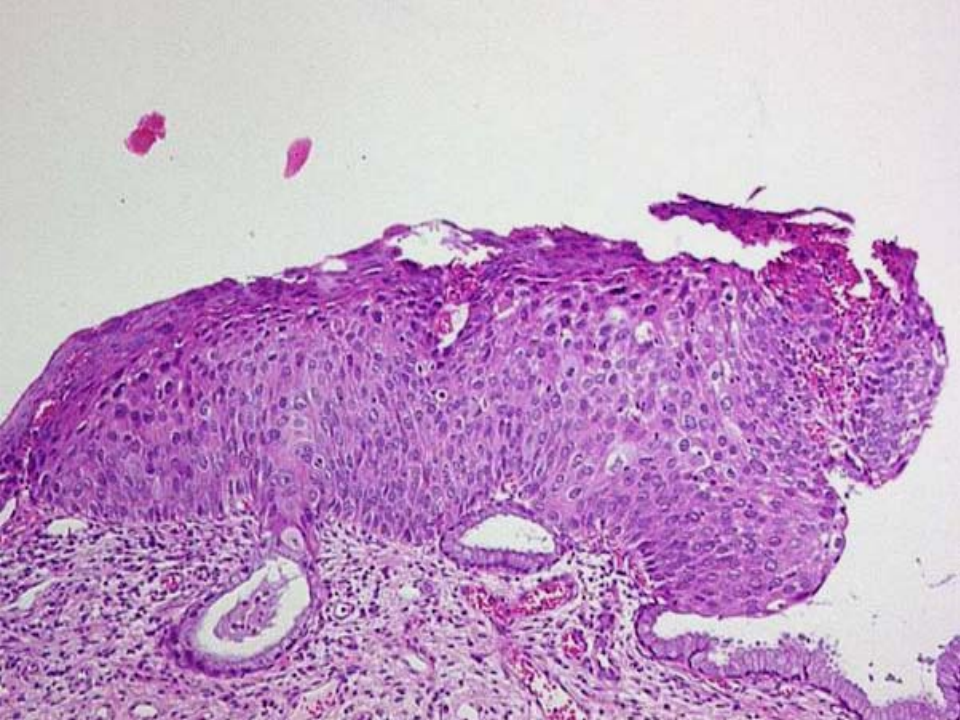
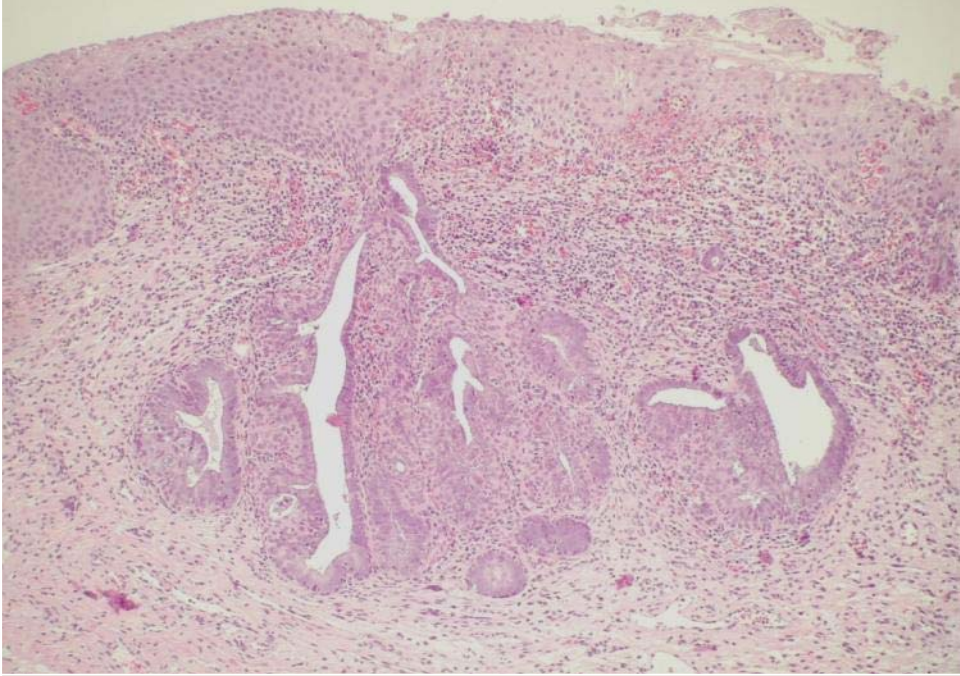
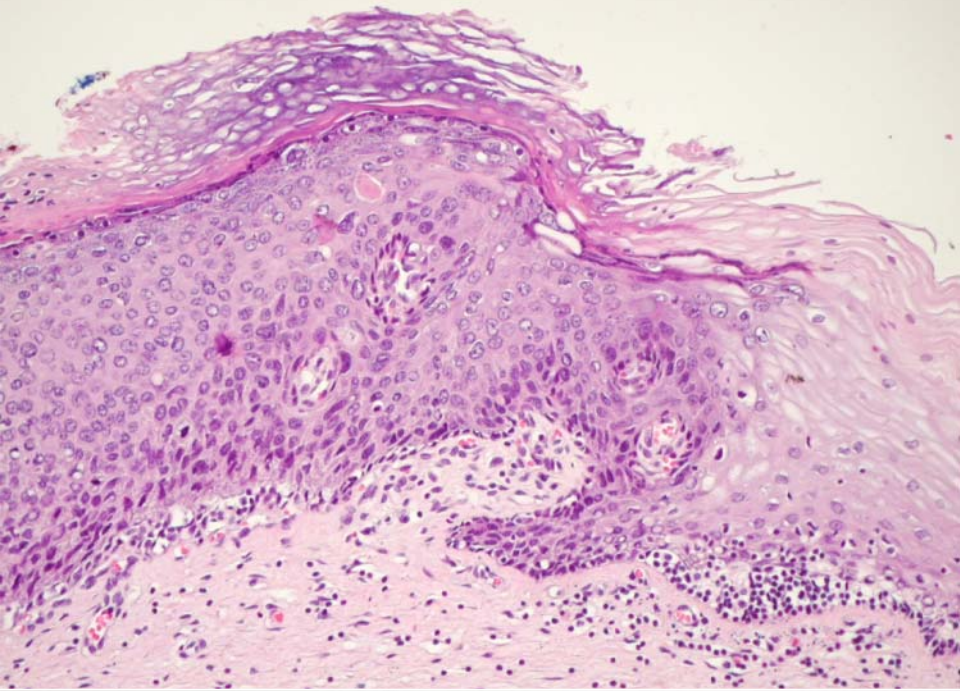
Bergeron C, Ordi J, et al. *Am J Clin Pathol* 2010; 133:395-406

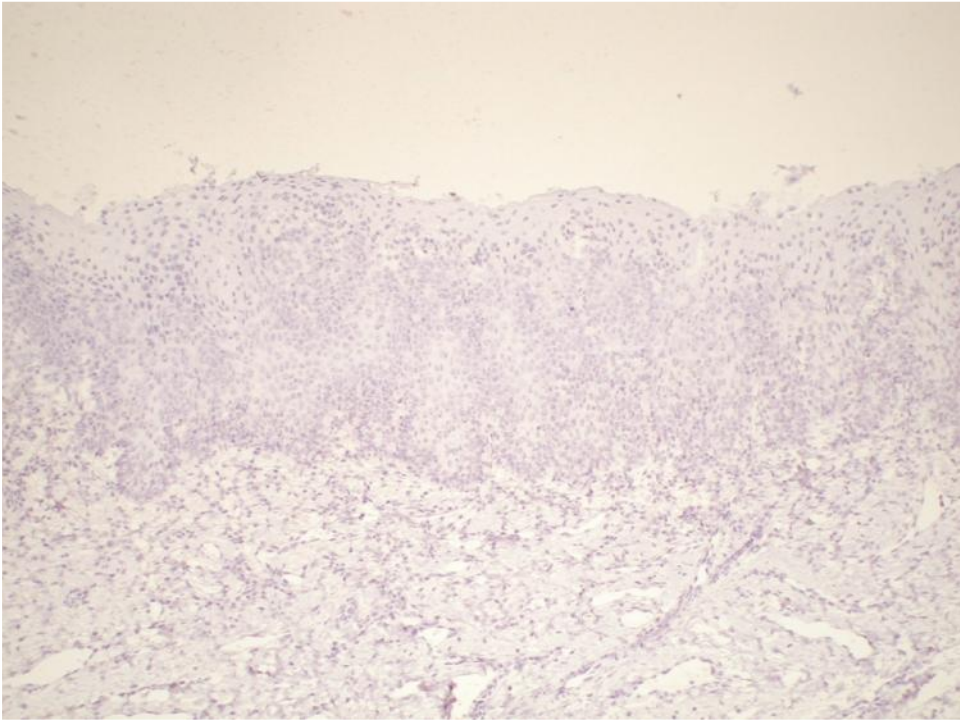
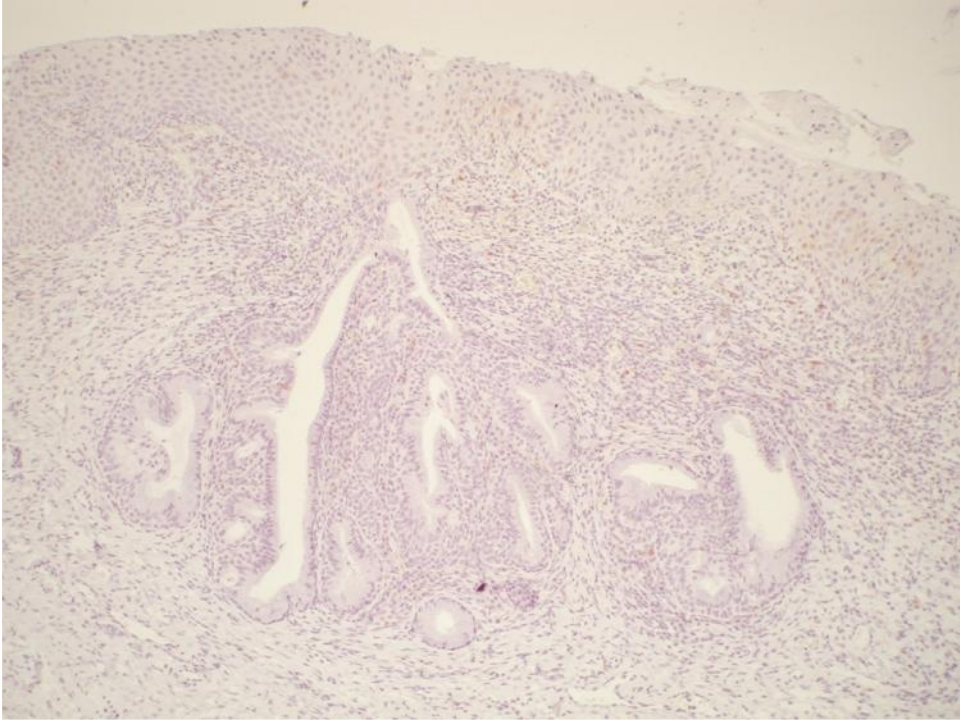
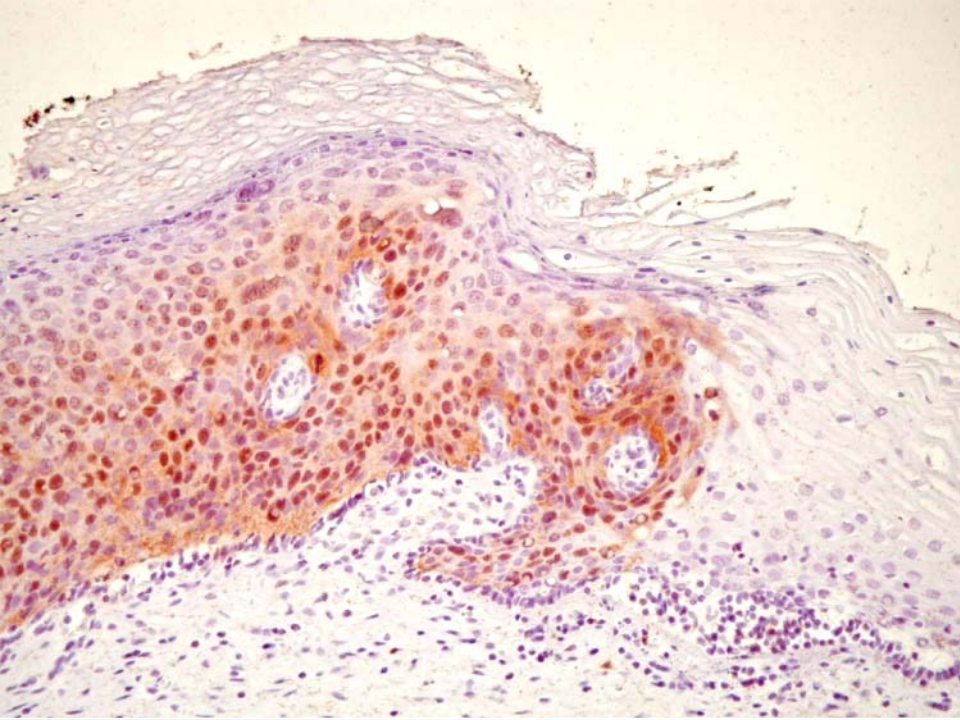


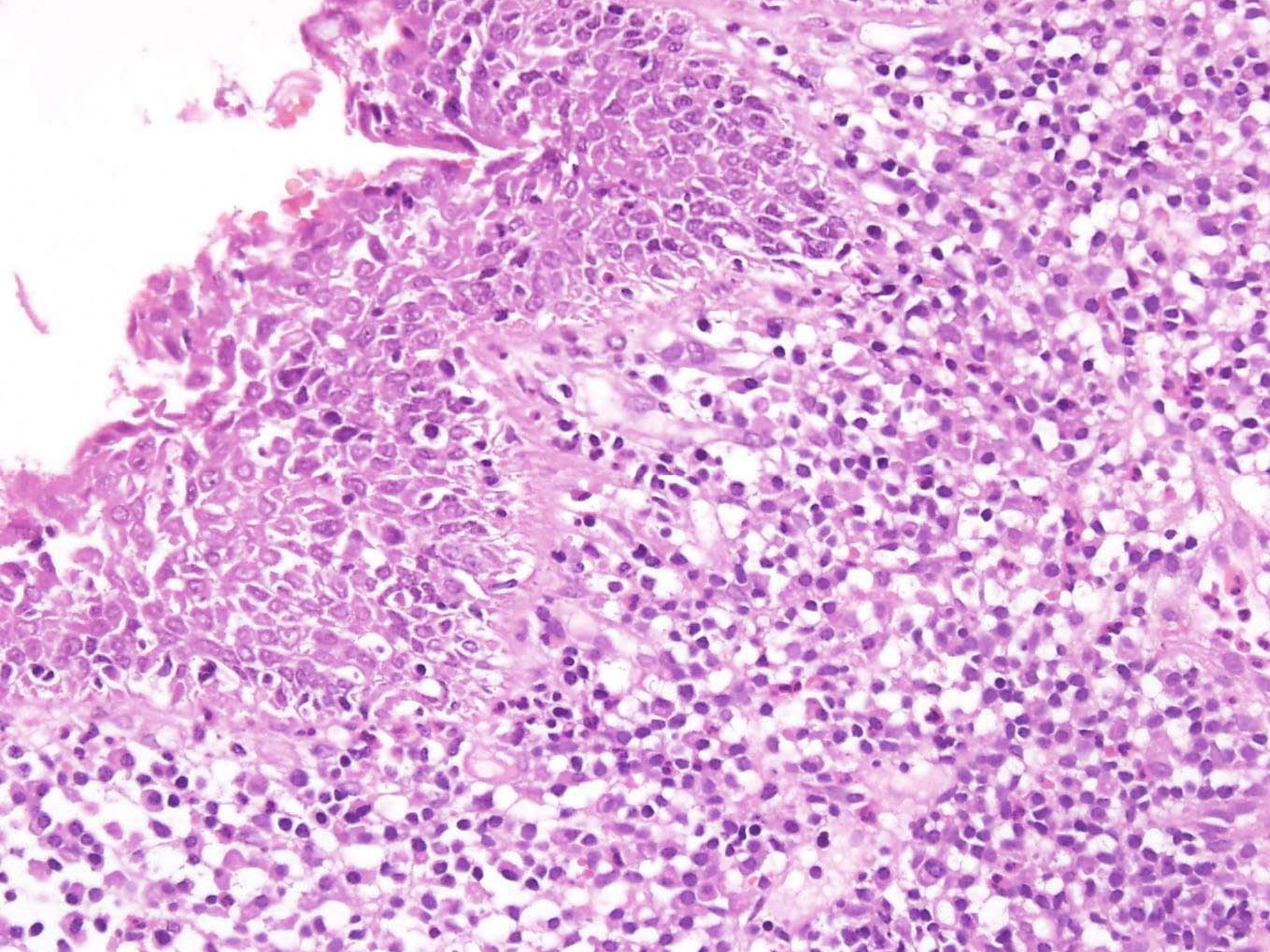
p16^{INK4a}: Gain in Sensitivity

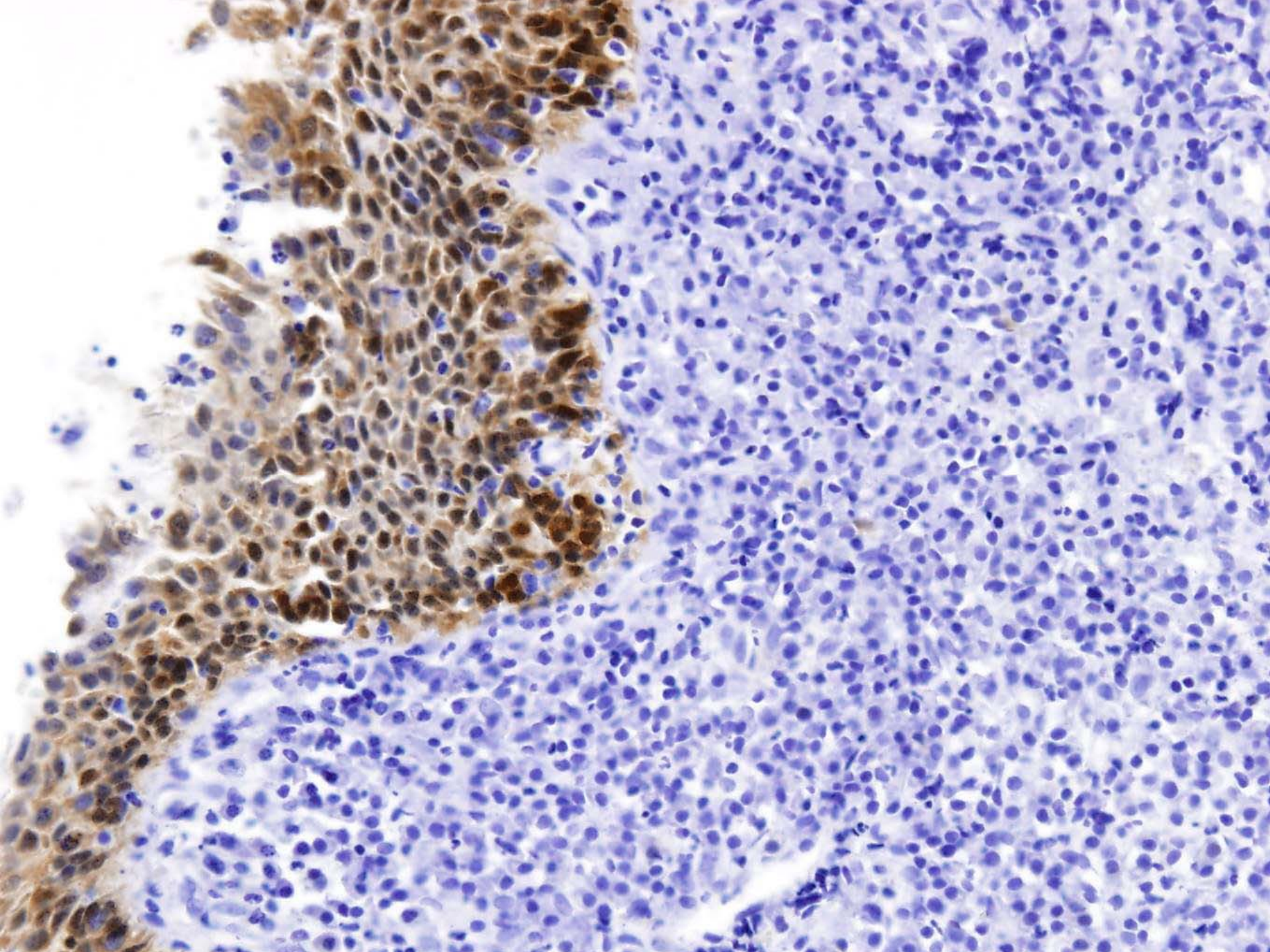
Sensitivity (%) Bergeron C, Ordi J, et al. *Am J Clin Pathol* 2010; 133:395-406

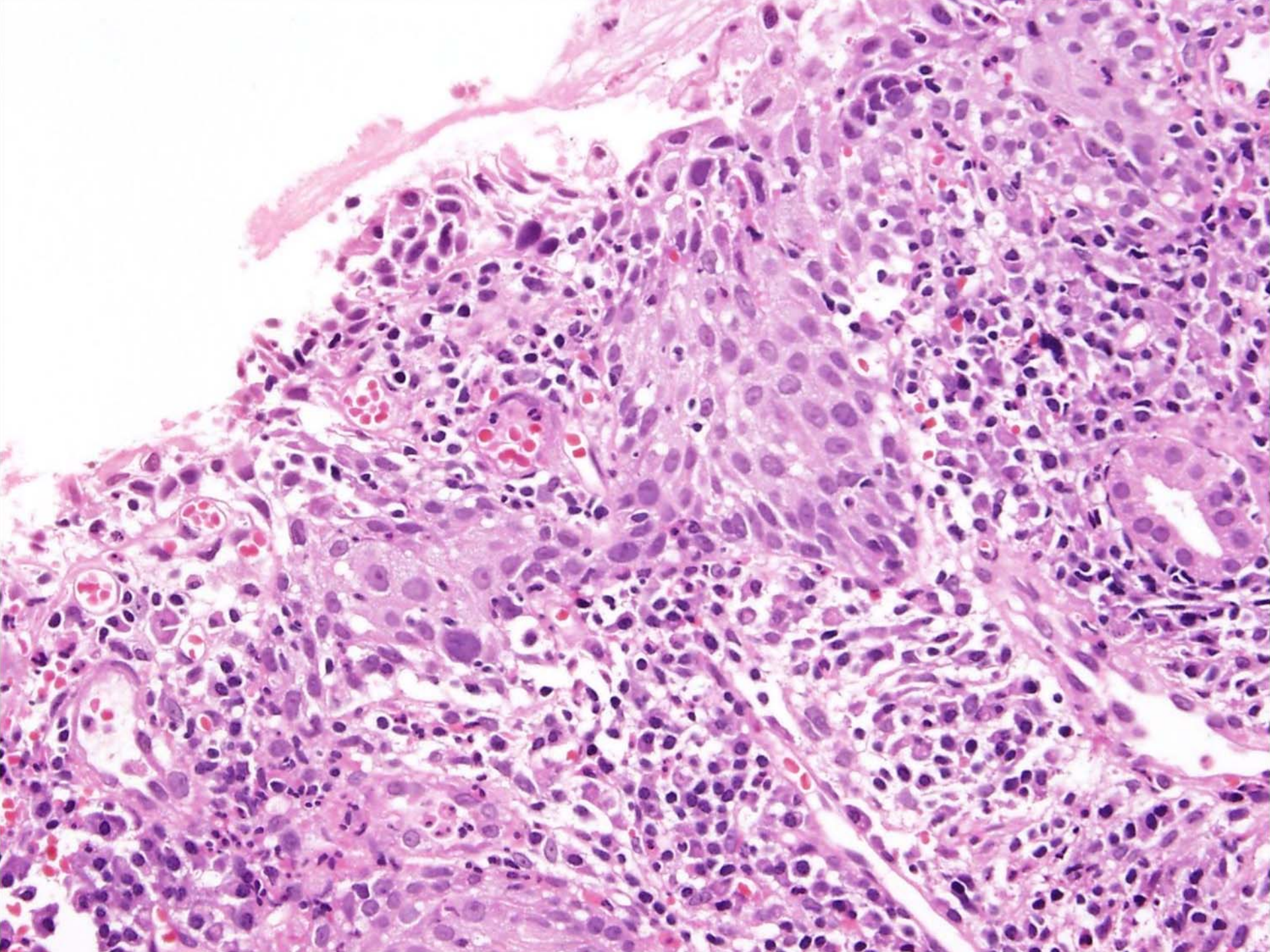


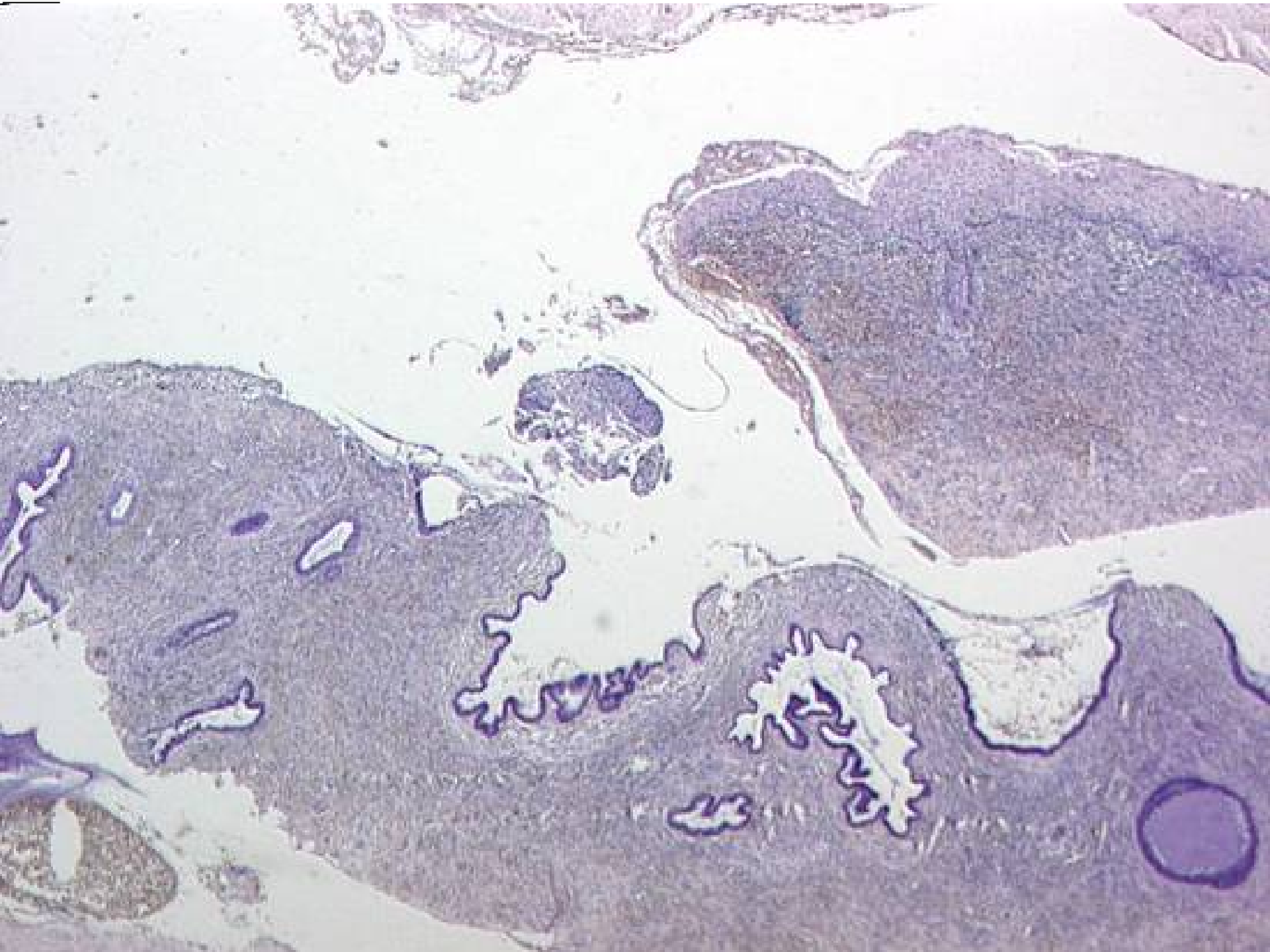


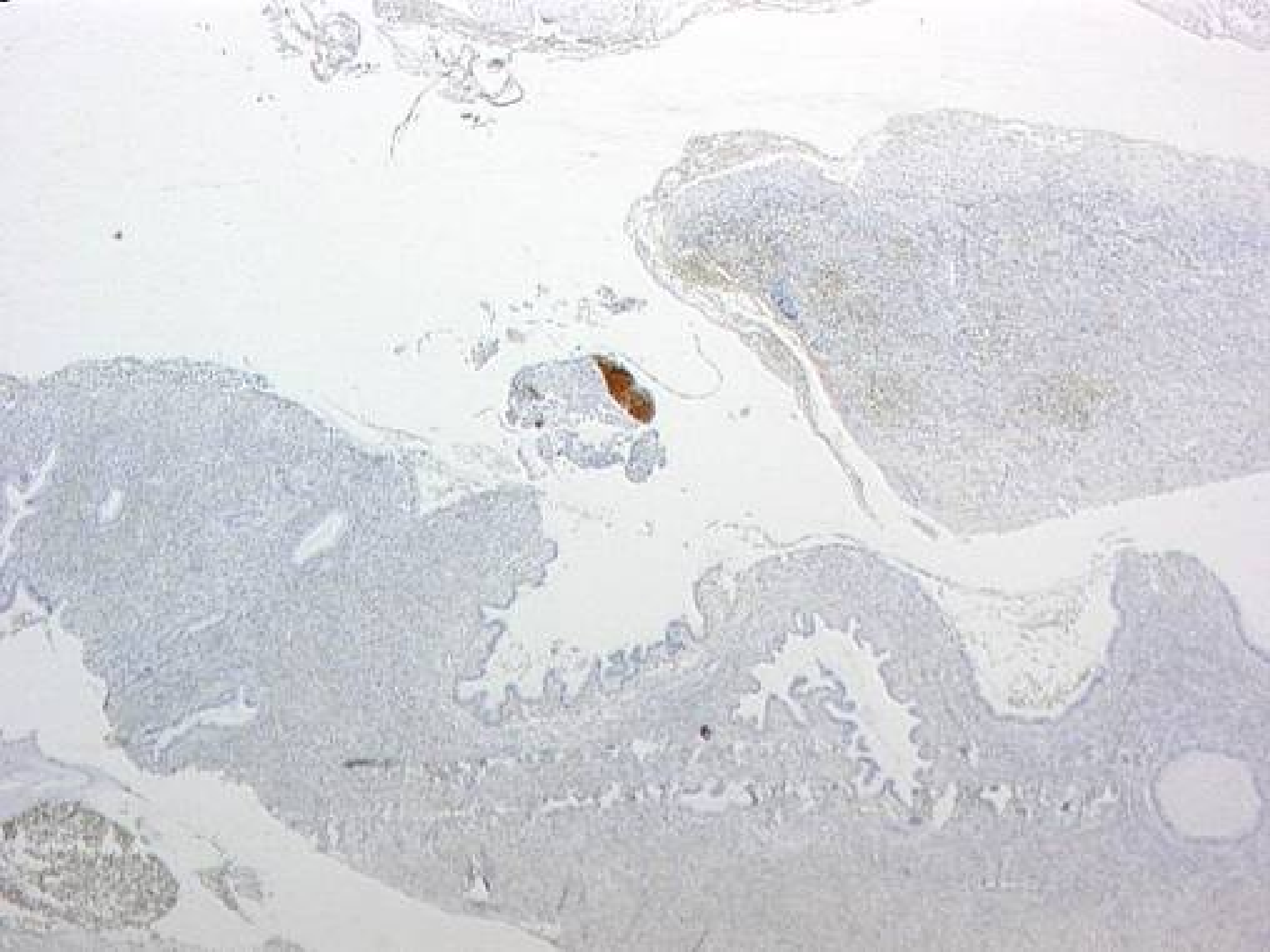


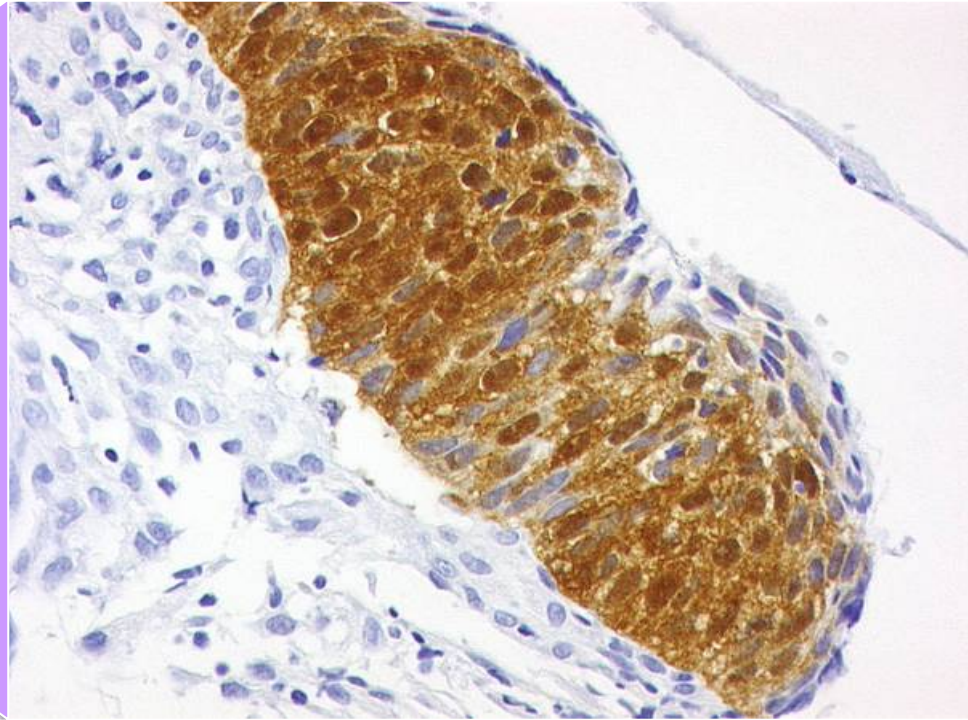
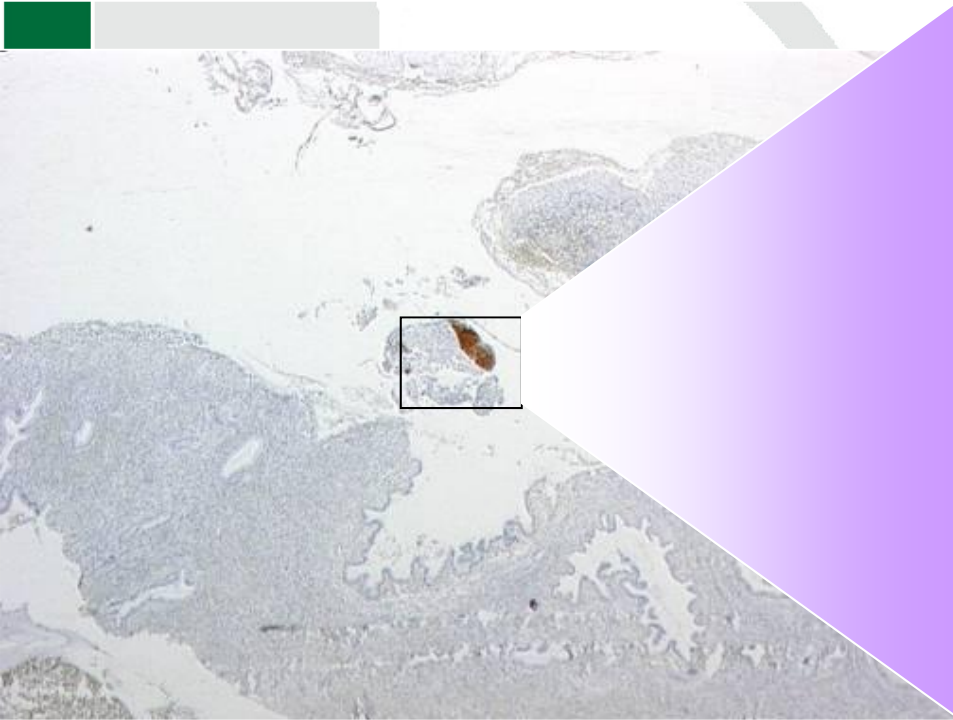
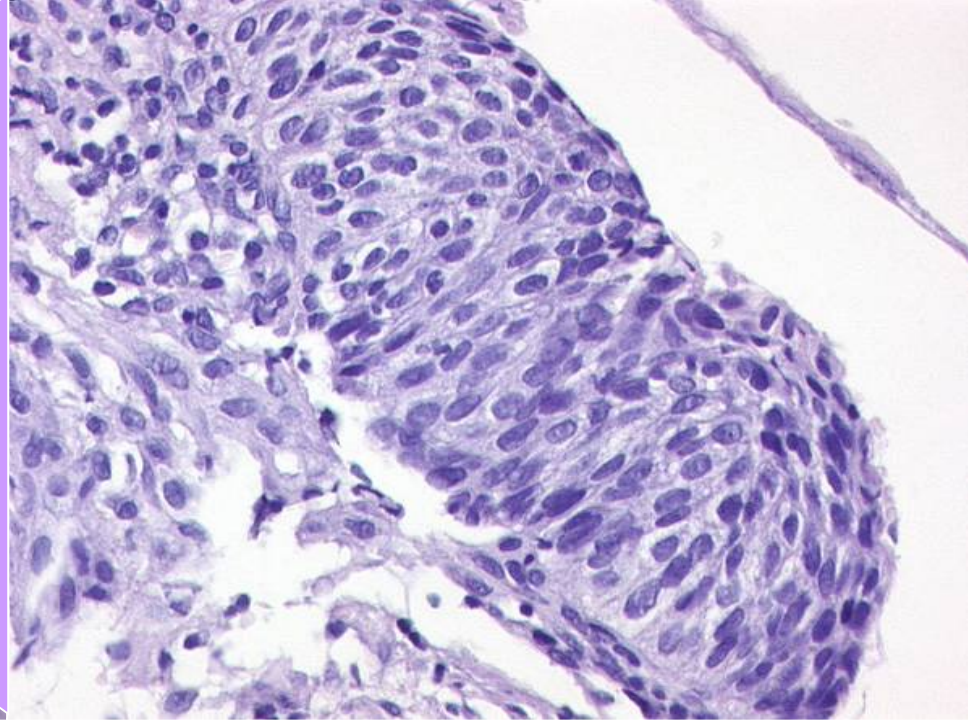
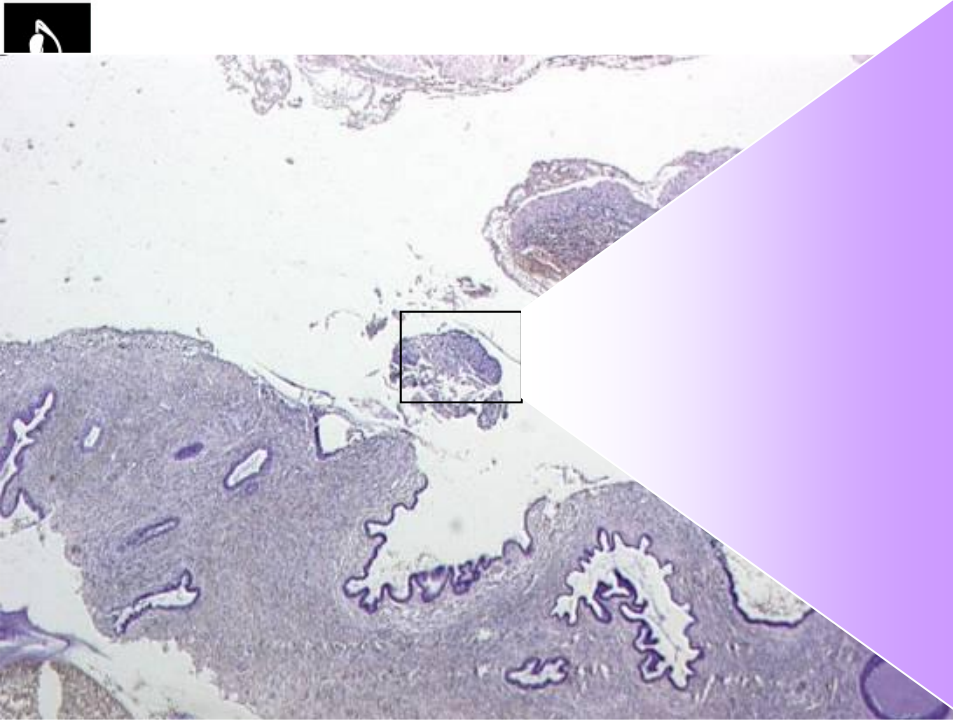


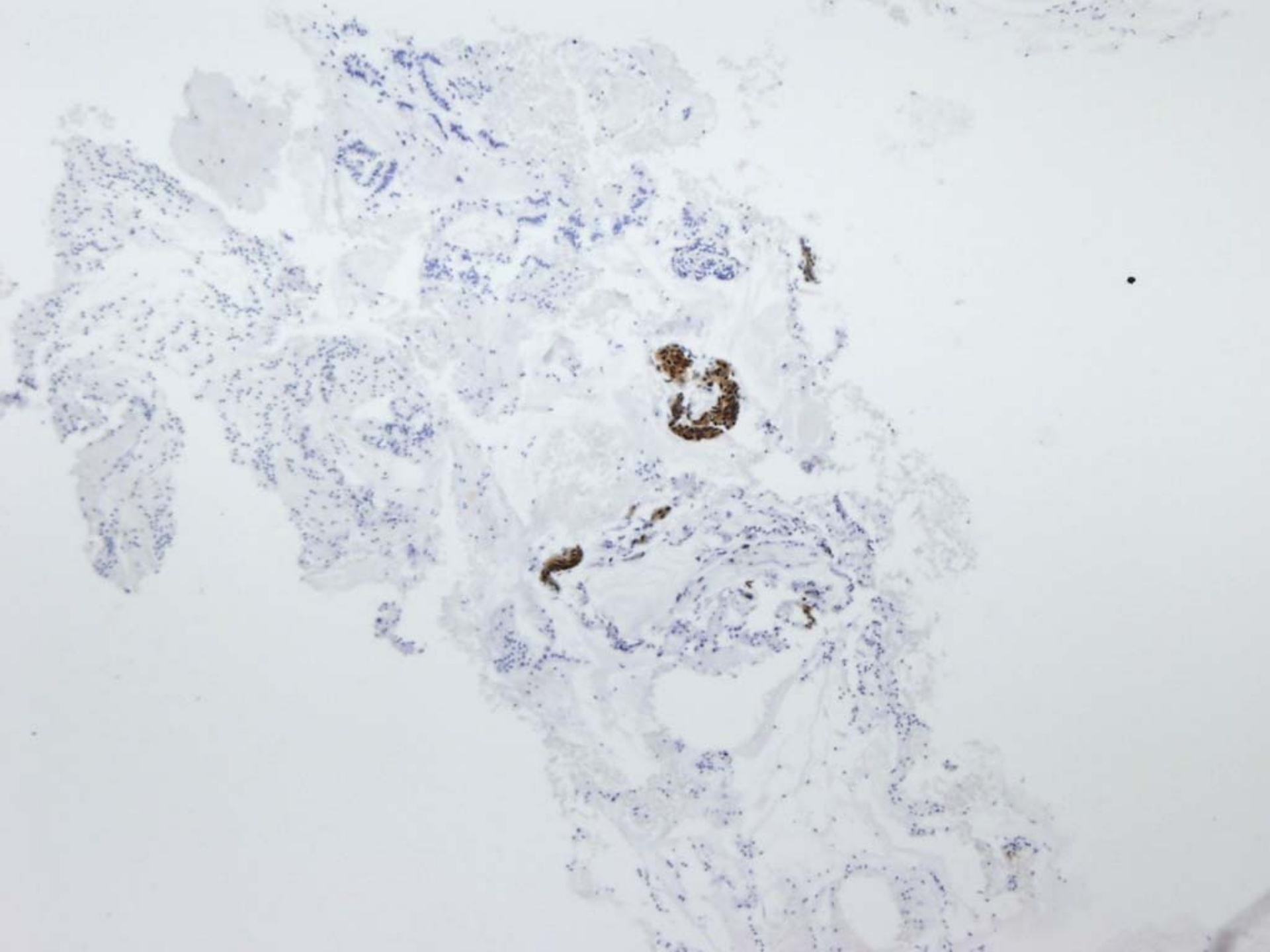








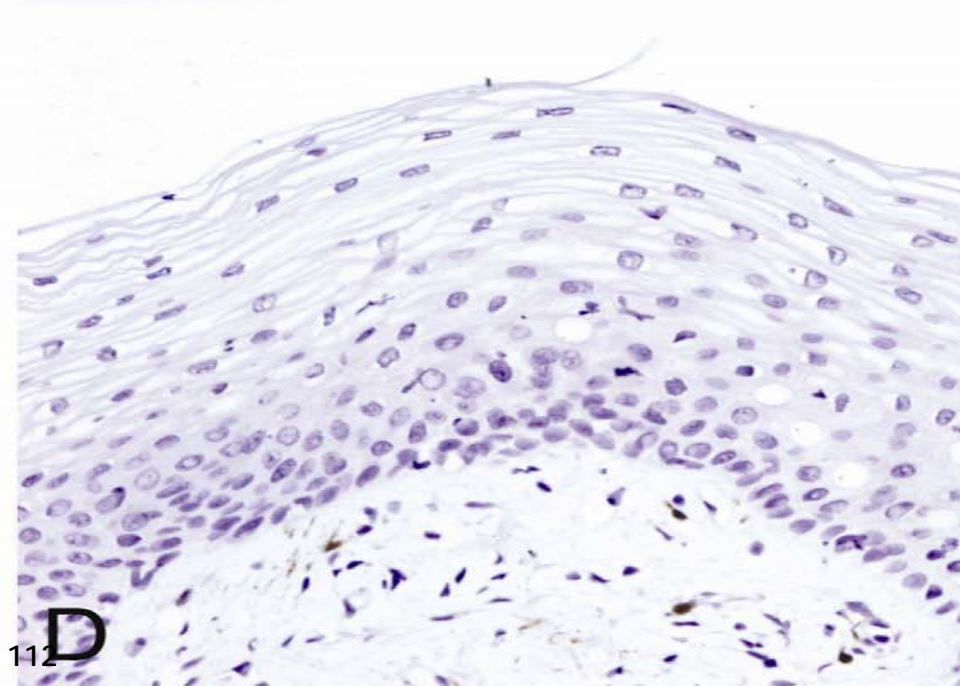
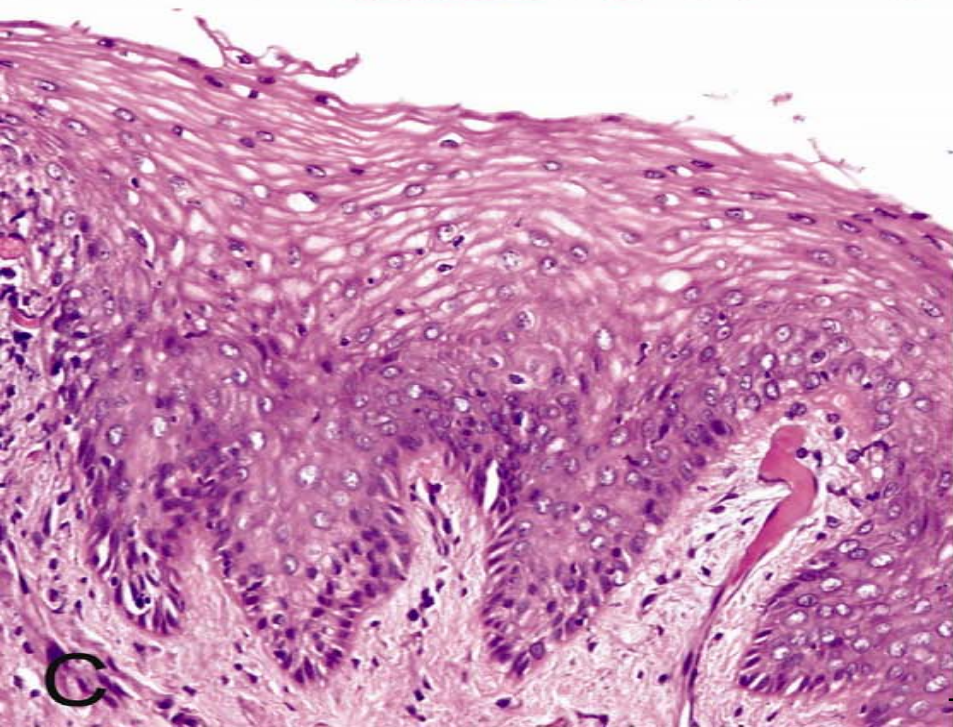
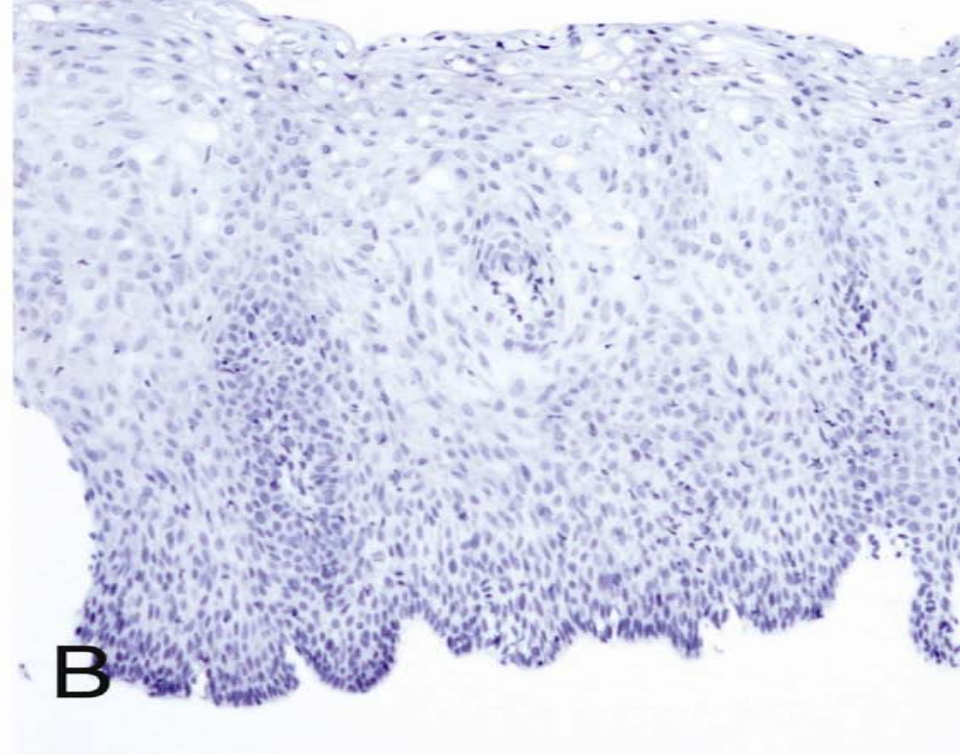
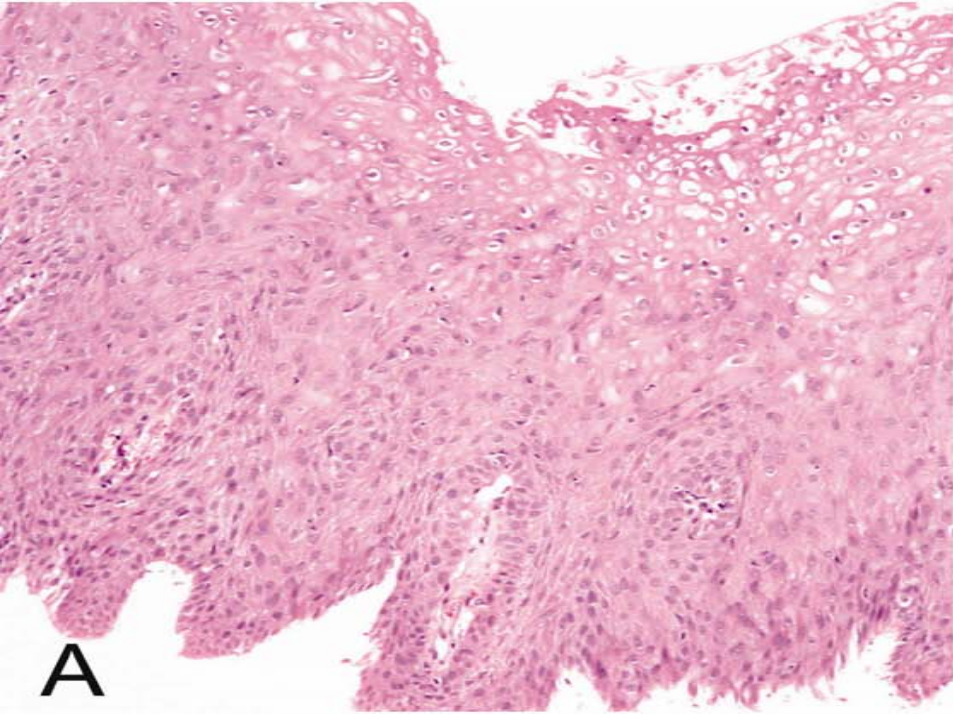


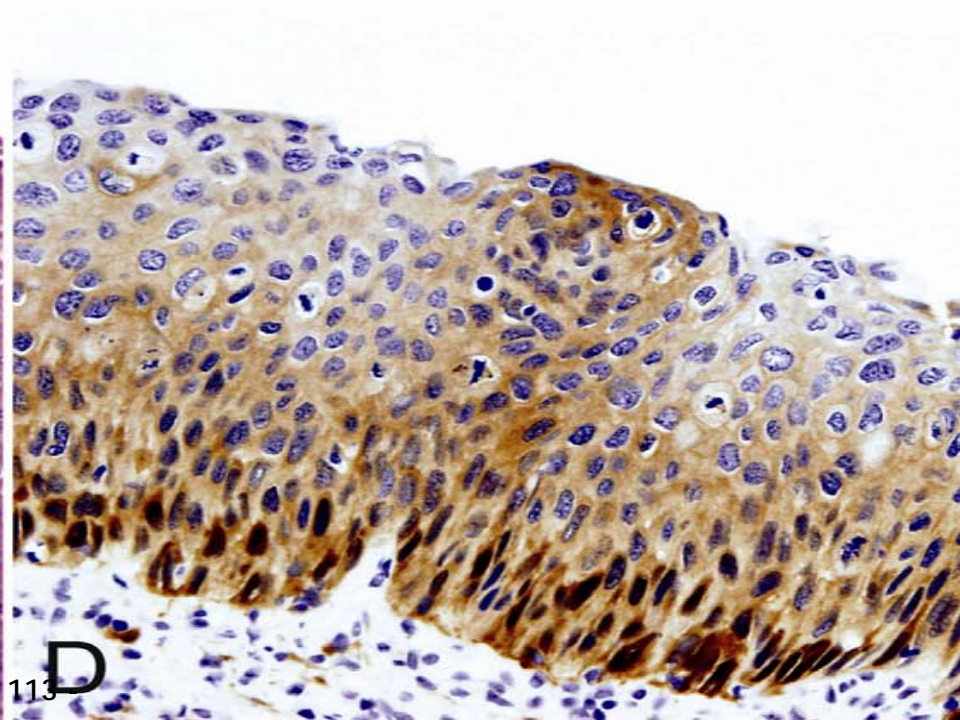
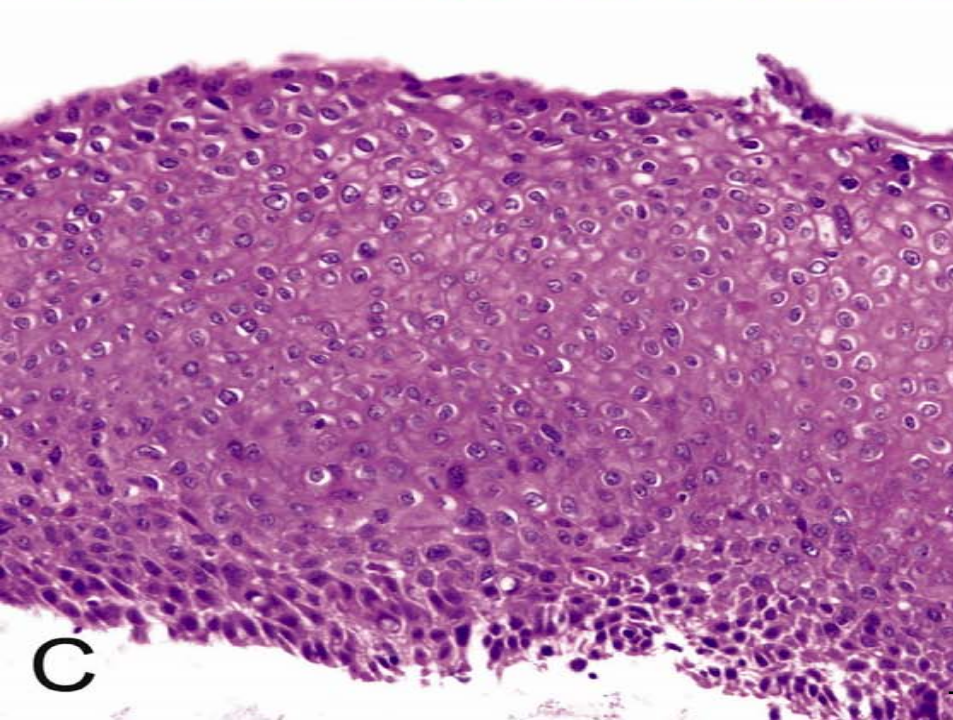
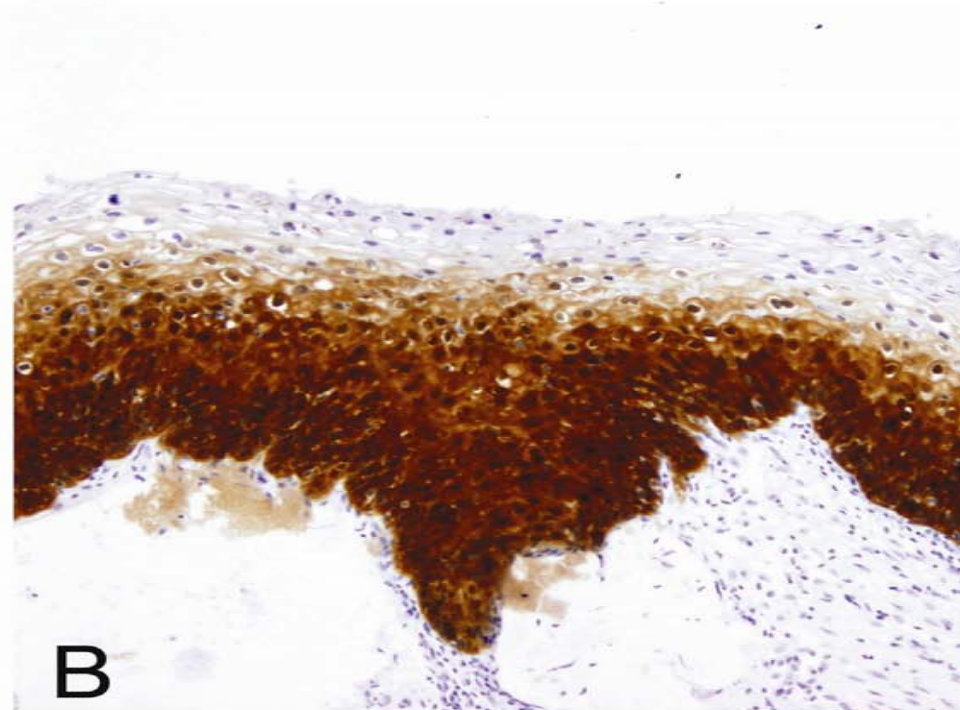
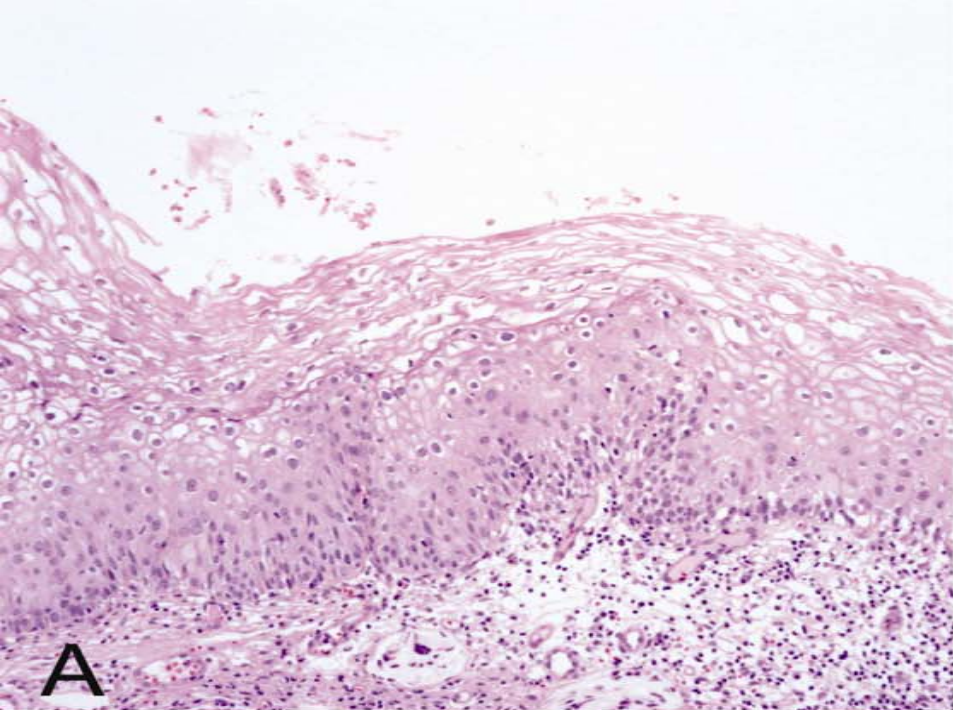


P16^{INK4a}: marcador de progresión

Evolution at follow-up	n	p16 ^{INK4a} immunostaining		
		Diffuse (%)	Focal (%)	Negative (%)
Progression	14	14 (100)	0 (0)	0 (0)
Persistence				
Cytology LSIL, HPV positive	28	12 (42.9)	4 (14.3)	12 (42.9)
Cytology negative, HPV positive	25	16 (64.0)	3 (12.0)	6 (24)
Cytology LSIL, HPV negative	5	2 (40.0)	3 (60.0)	0 (0)
Regression	66	33 (50.0)	15 (22.7)	18 (27.3)
Overall	138	77 (55.8)	25 (18.1)	36 (26.1)

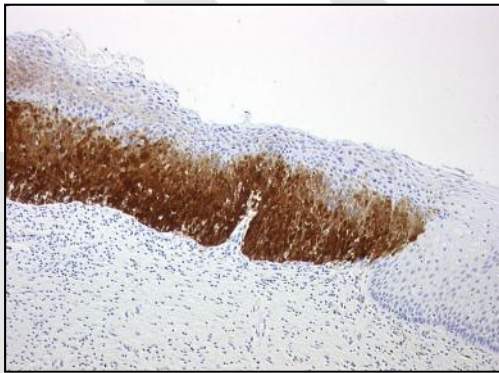
Del Pino et al. *Am J Obstet Gynecol* 2009; 201:488



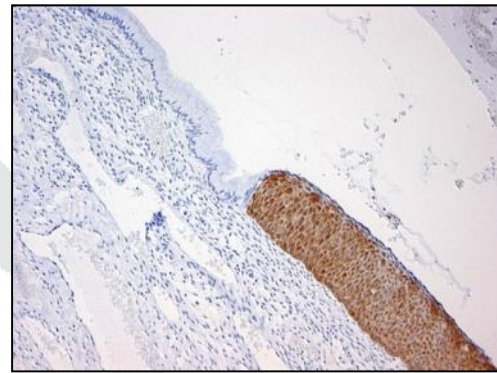


1: What is a positive reaction?

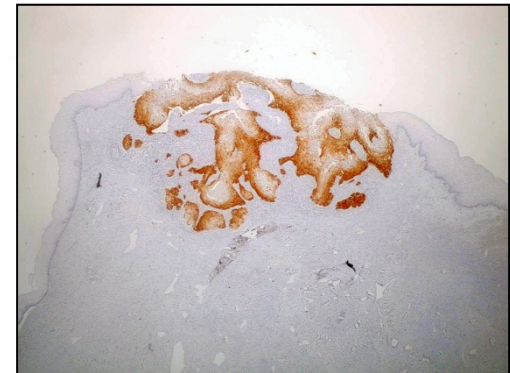
- **Positive:** basal continuous staining



CIN 2

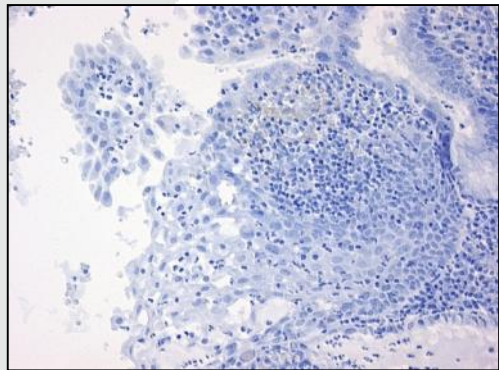


CIN 3

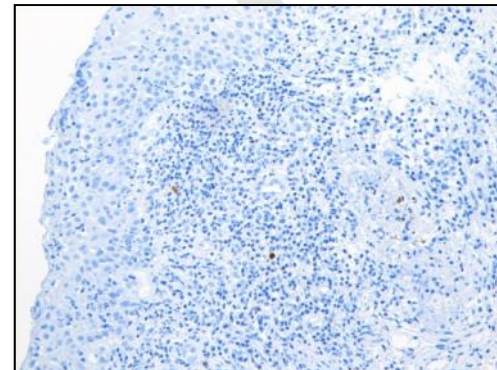


Squamous cell carcinoma

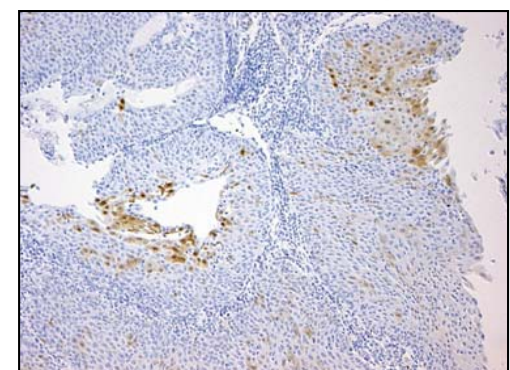
- **Negative:** absence or isolated cells



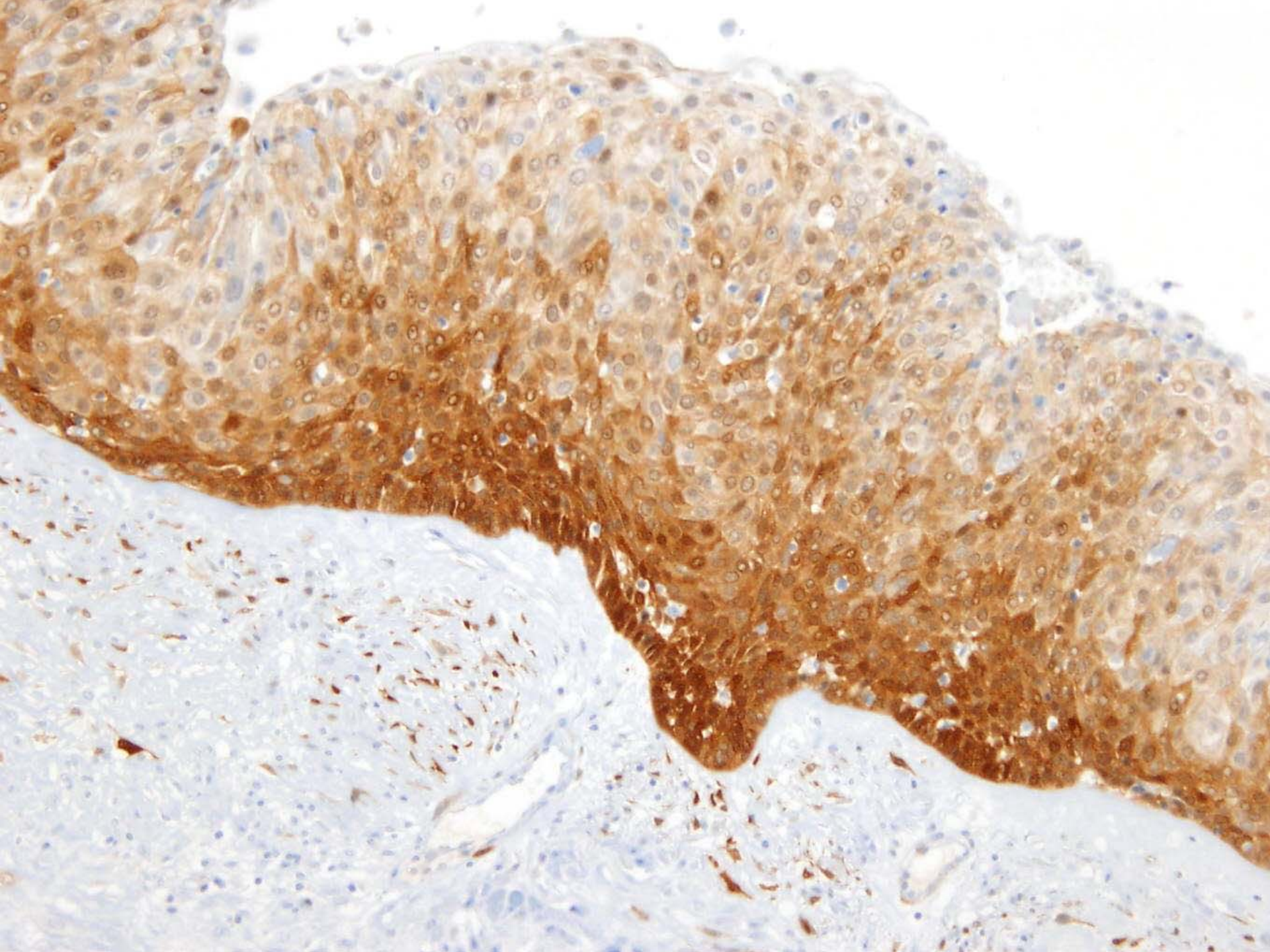
Immature metaplasia

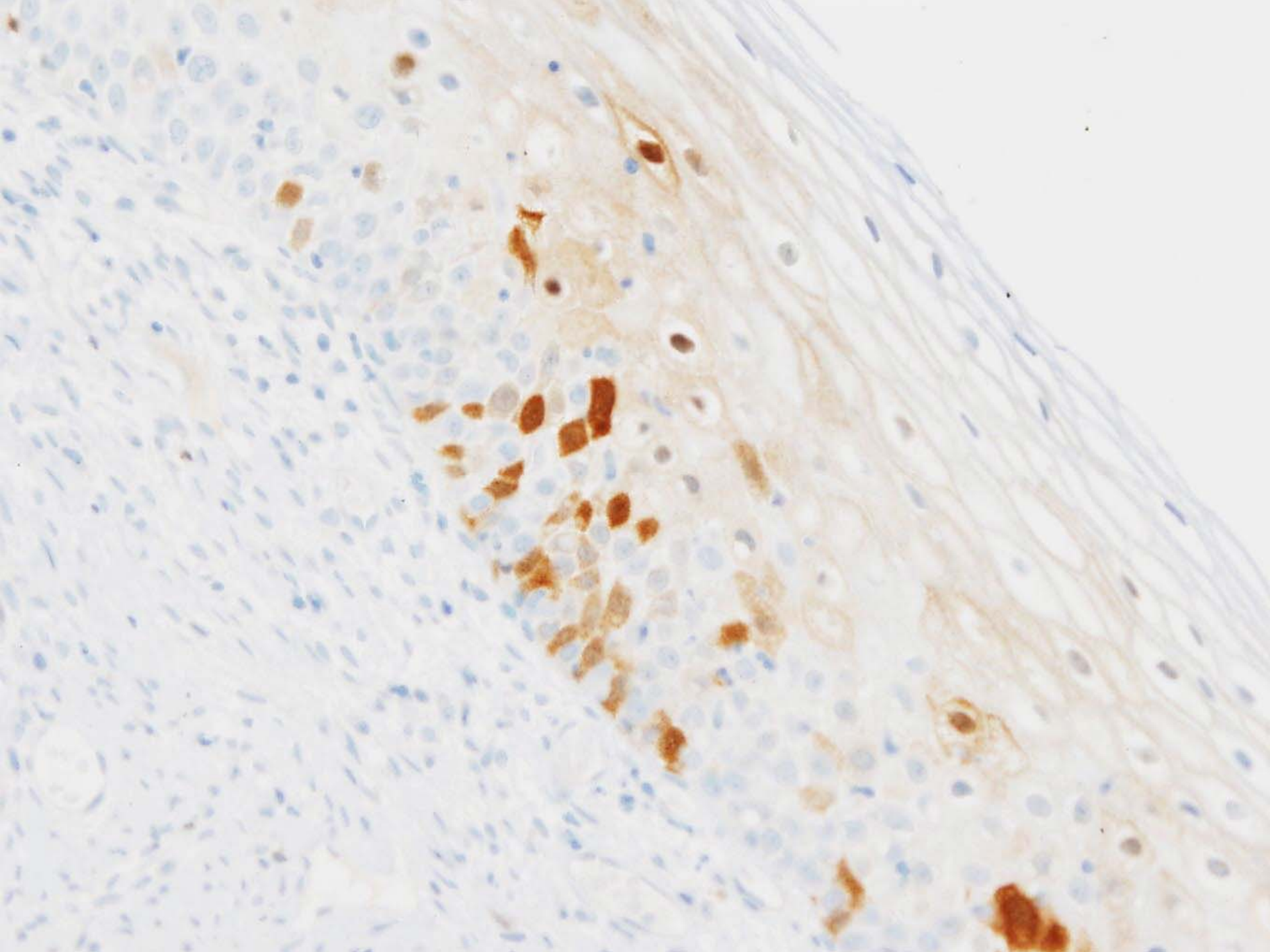


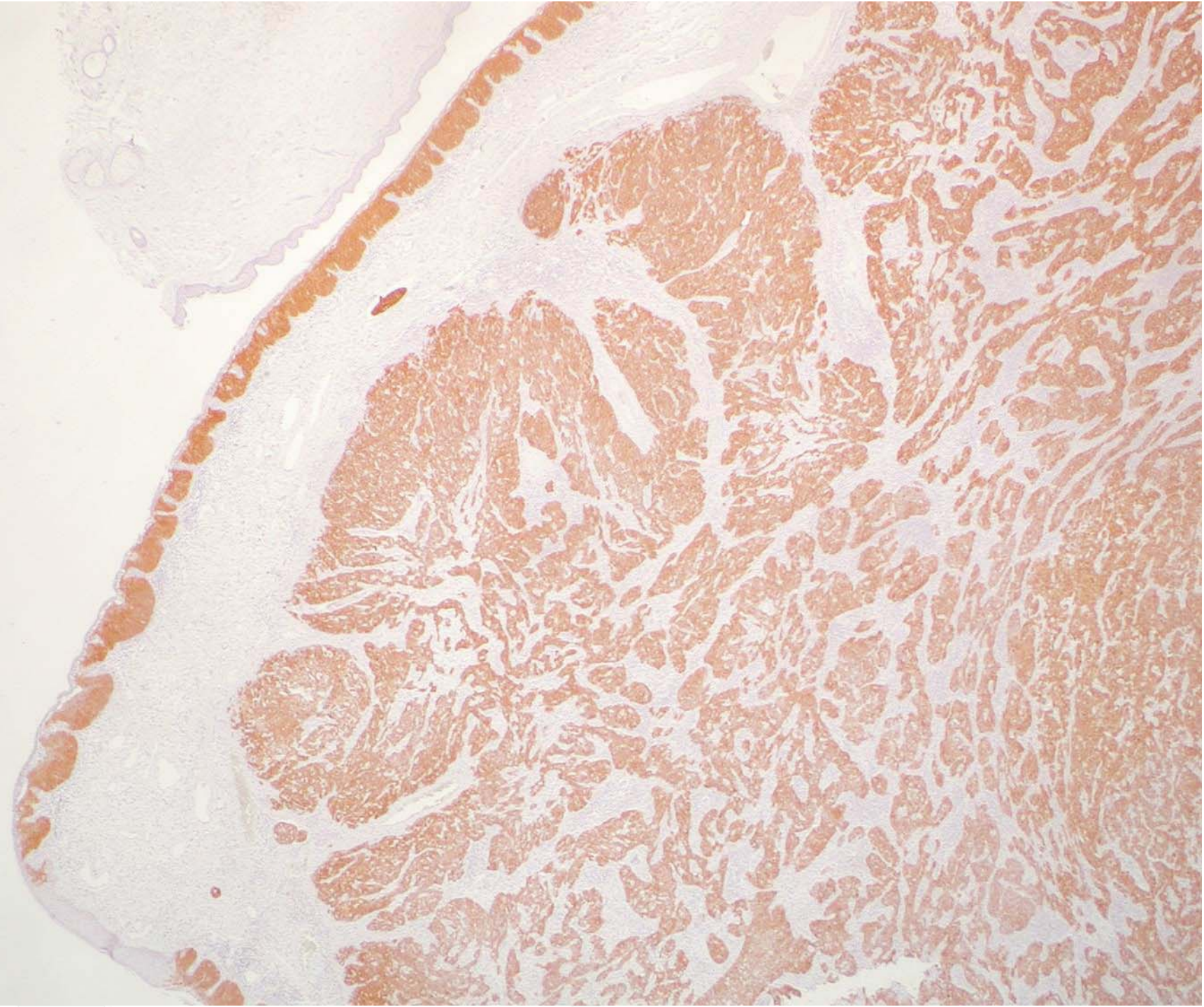
Cervicitis

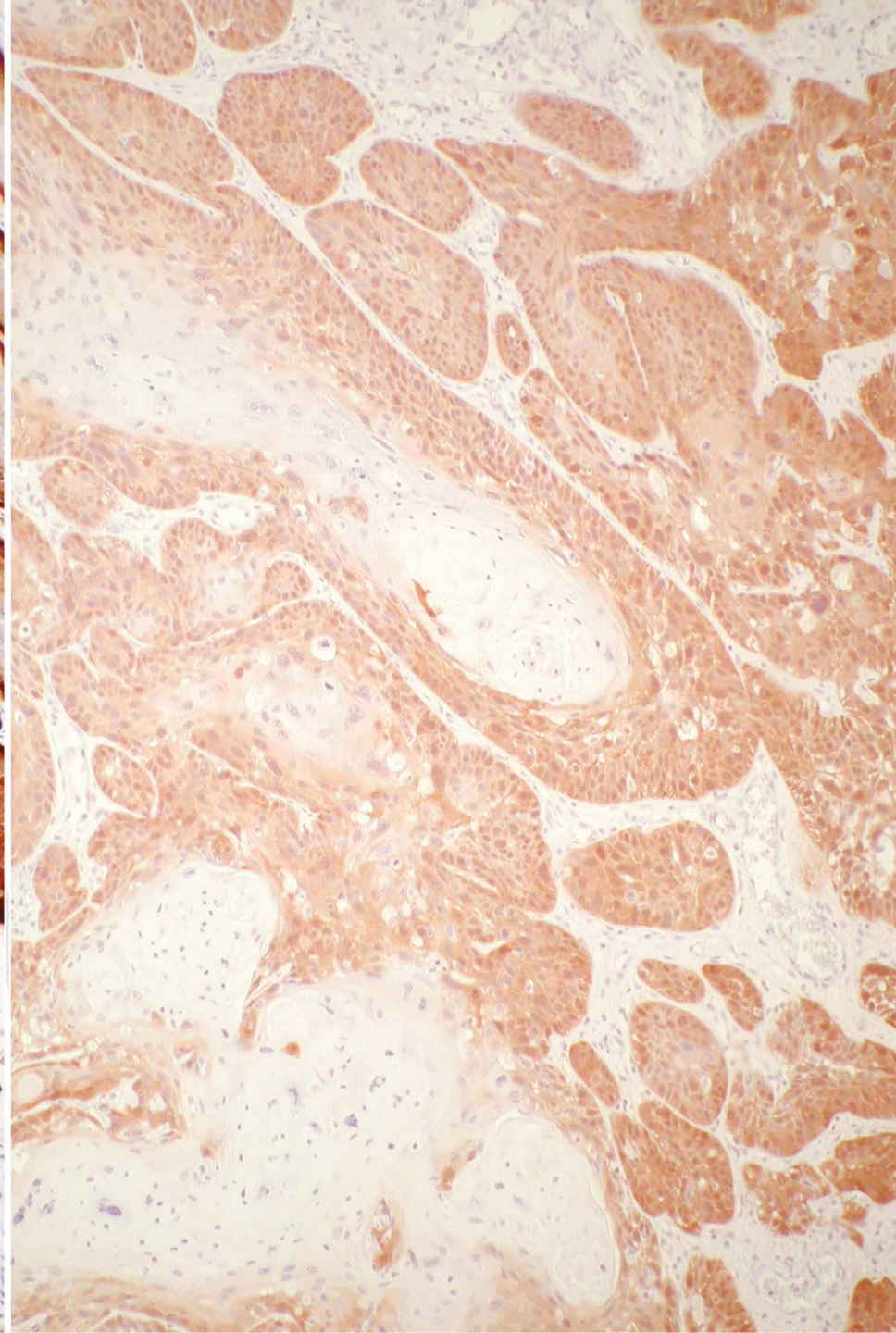
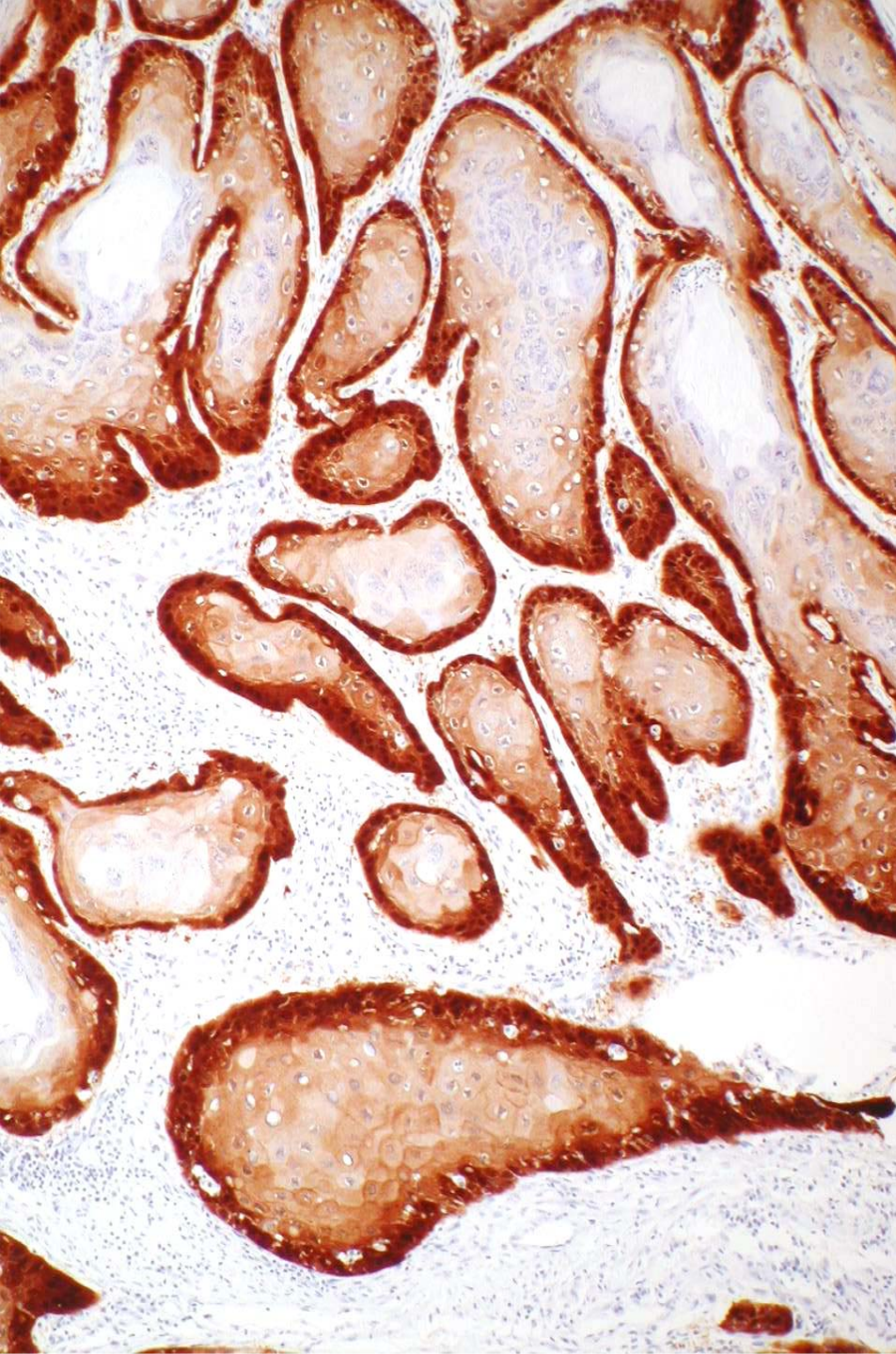


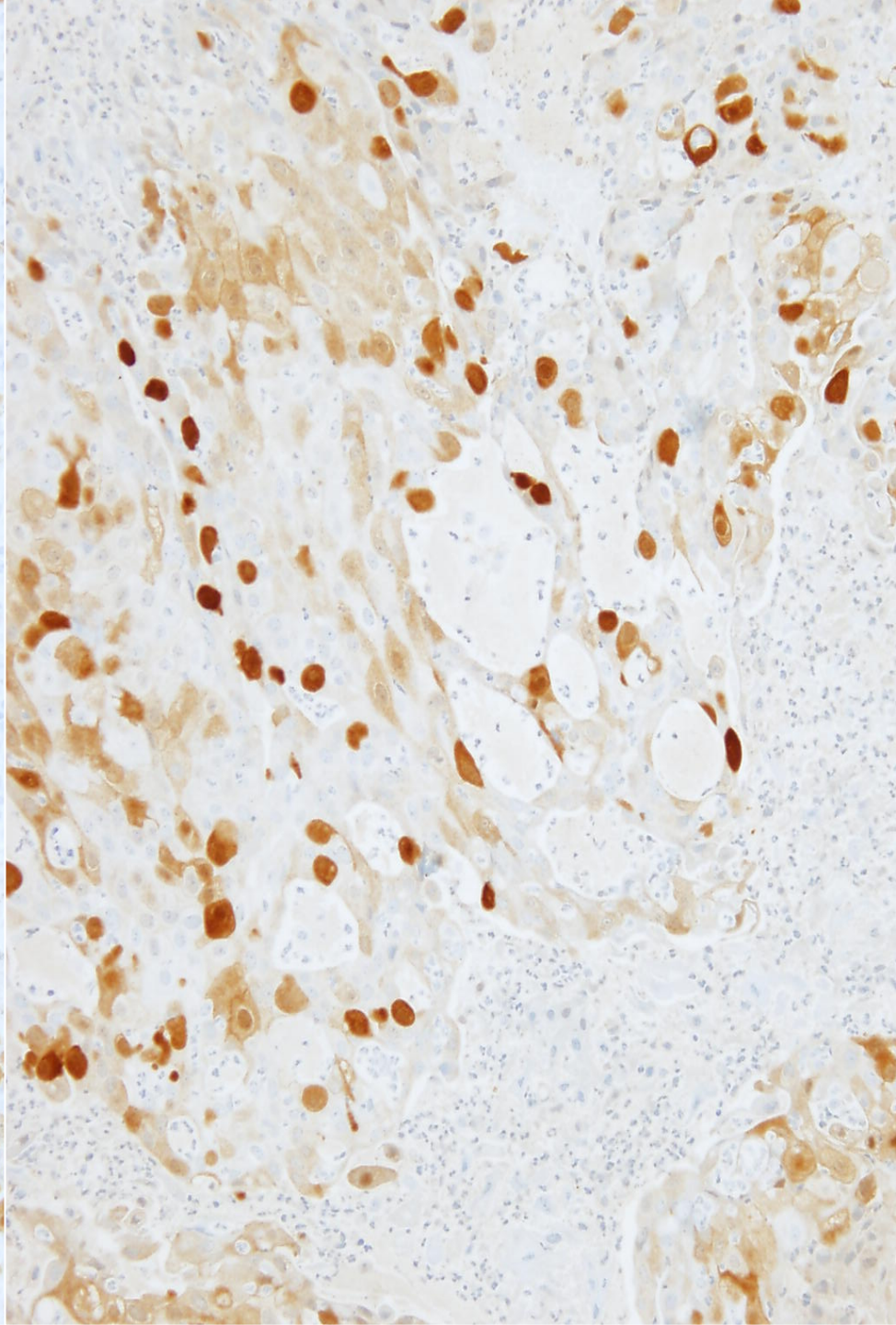
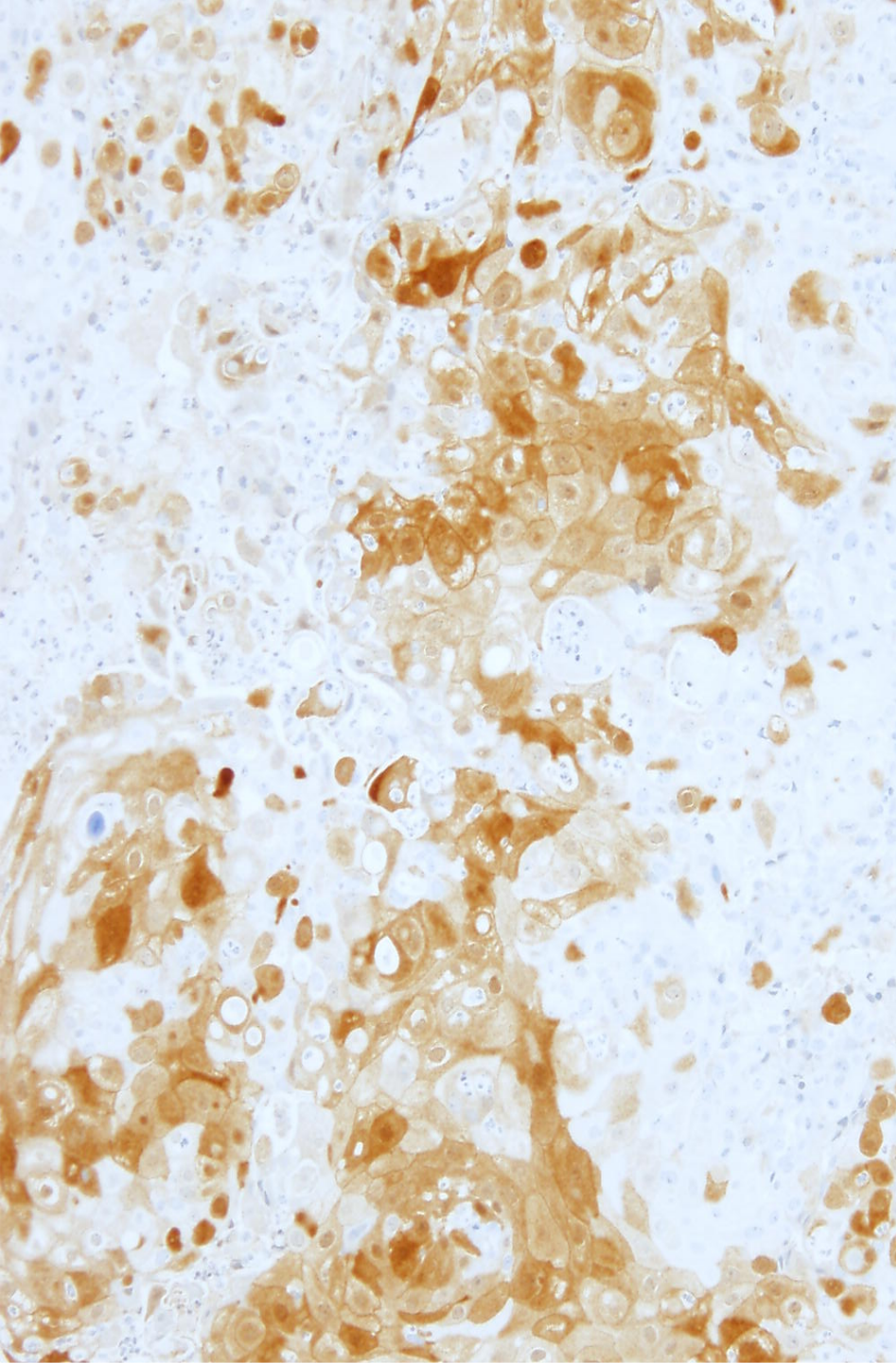
Mature metaplasia







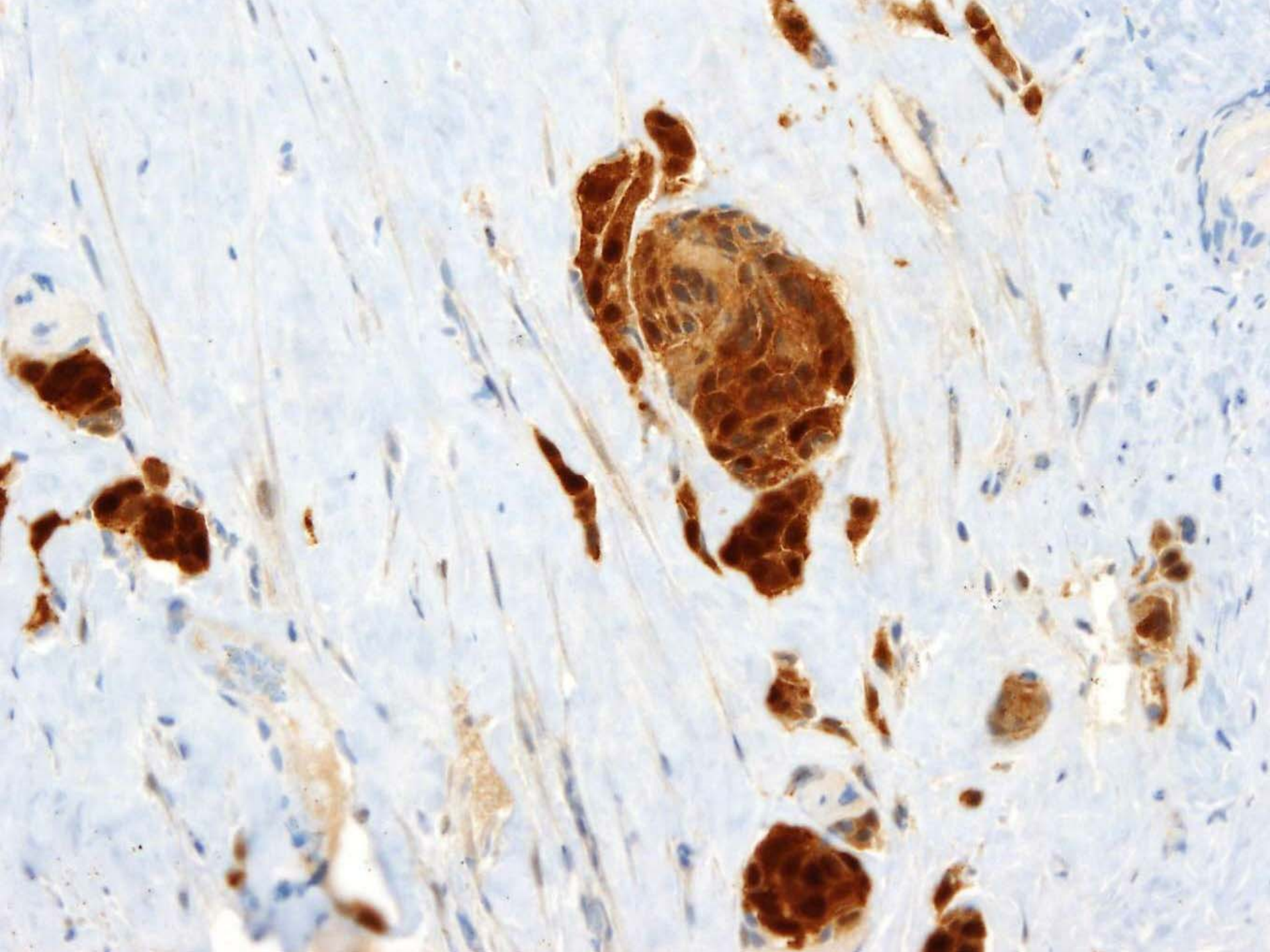


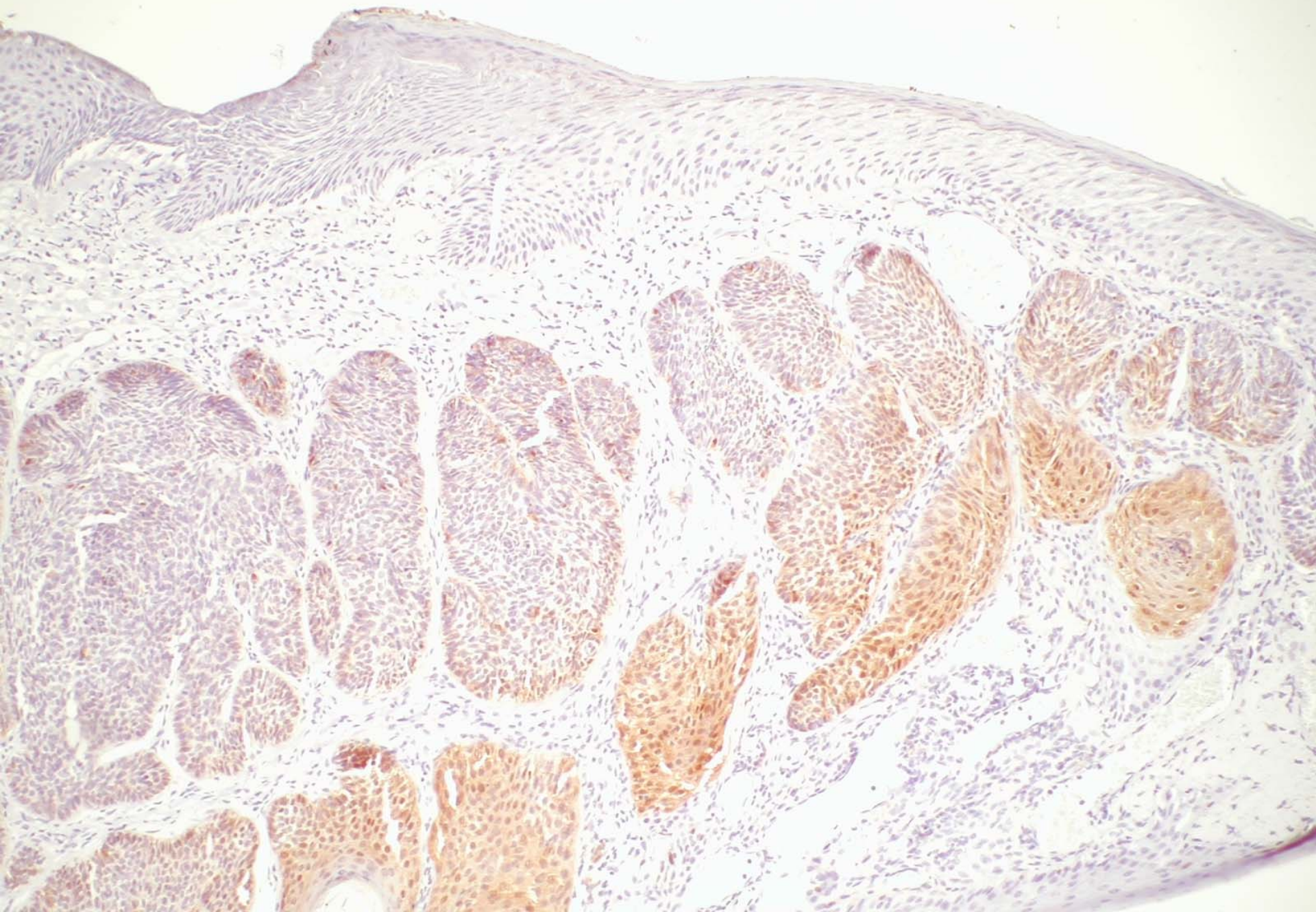




Pitfall 2: p16 en altres tumors

- Paradigma p16 = presència d'HPV genital vàlid en **neoplàsies en llocs amb possibilitat de transmissió sexual**
- Compte en l'extrapolació a altres neoplàsies

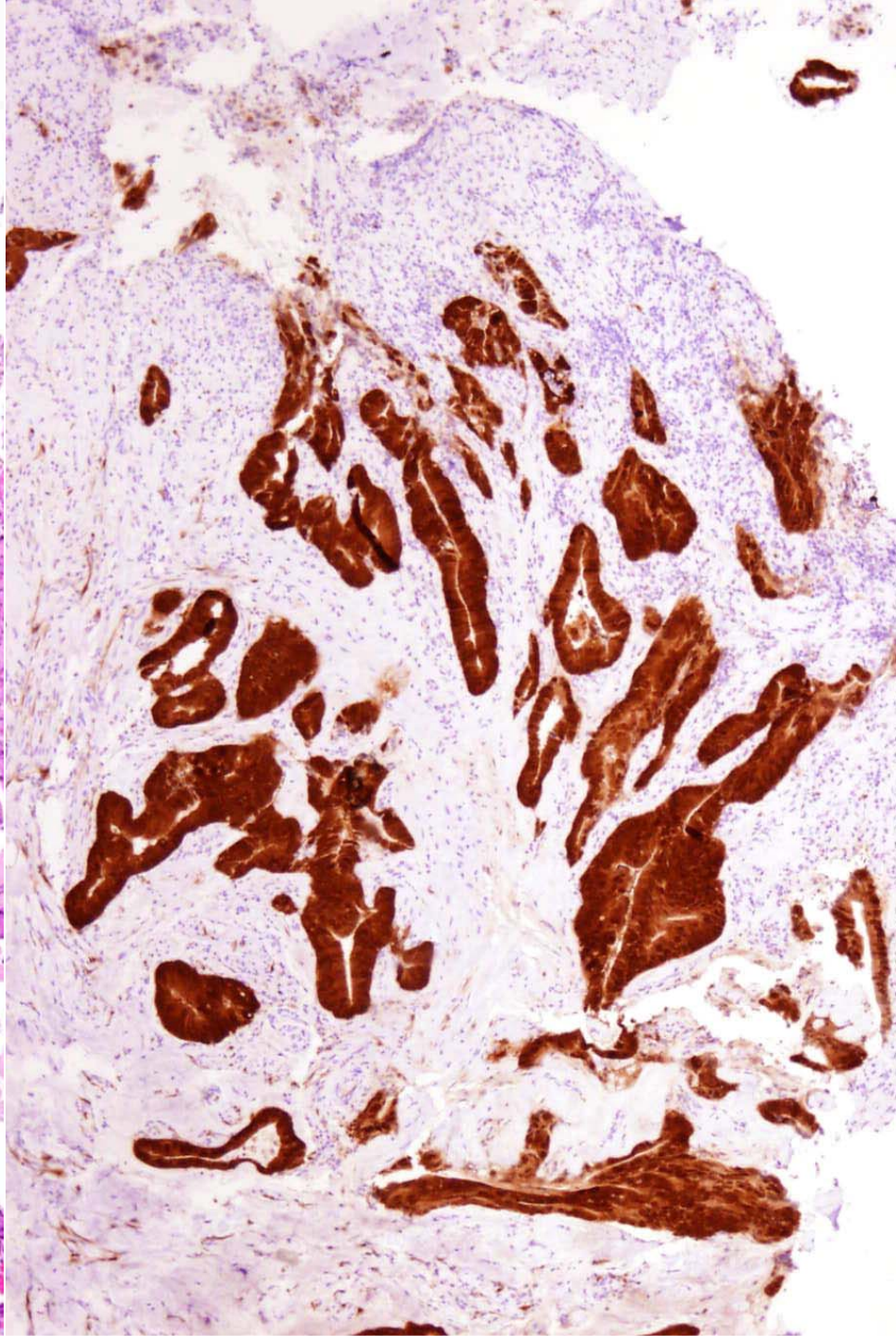
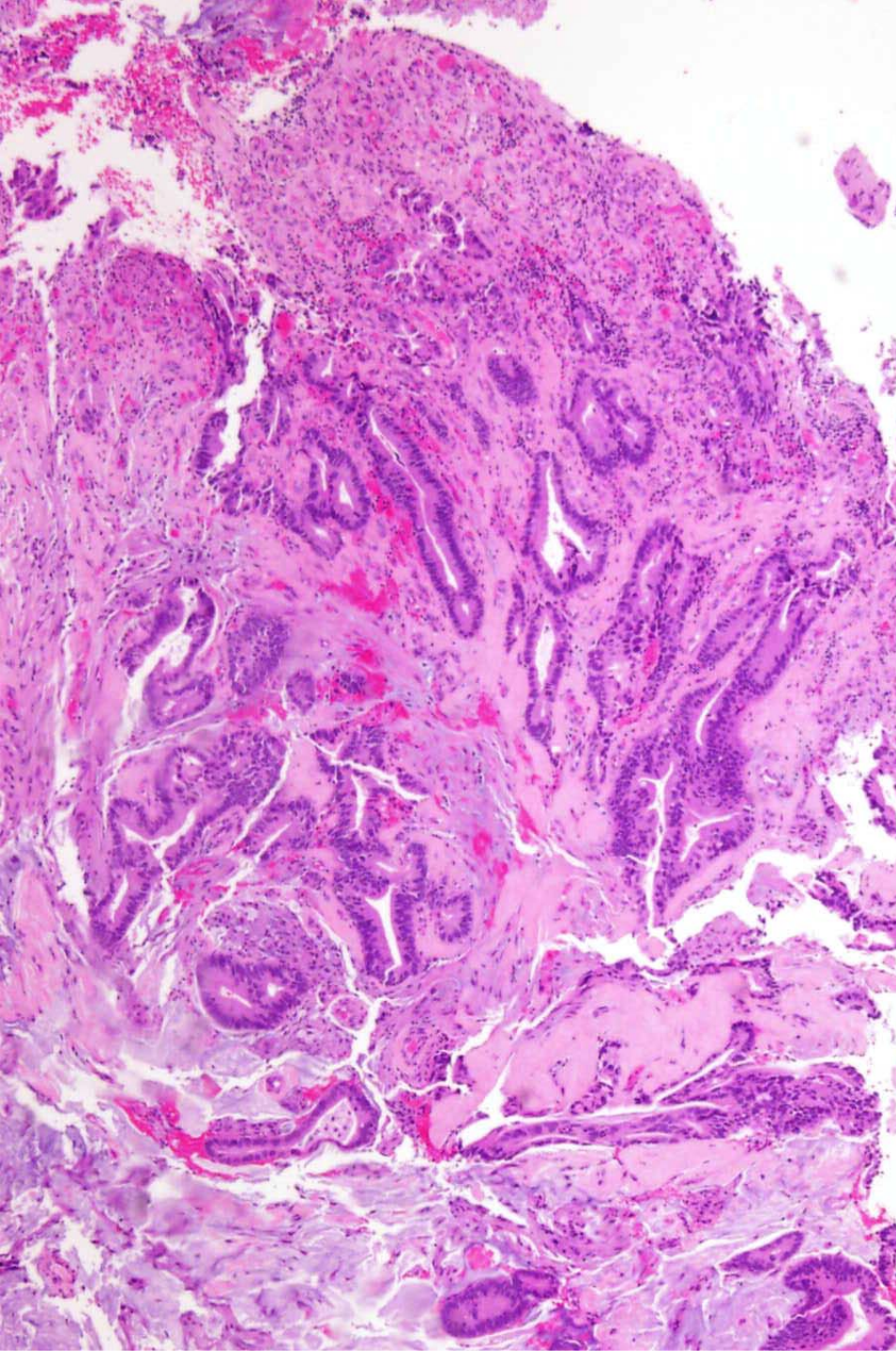


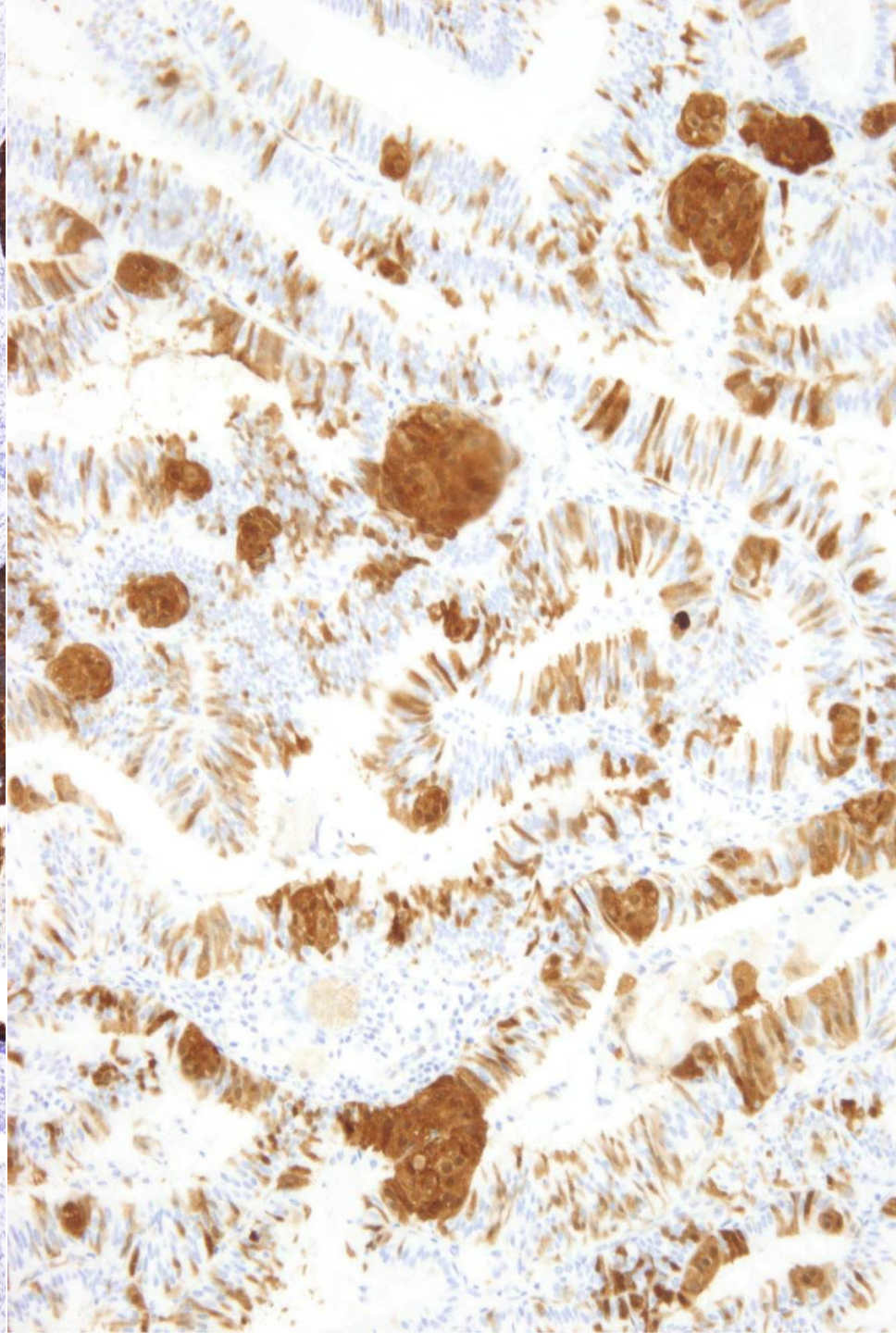
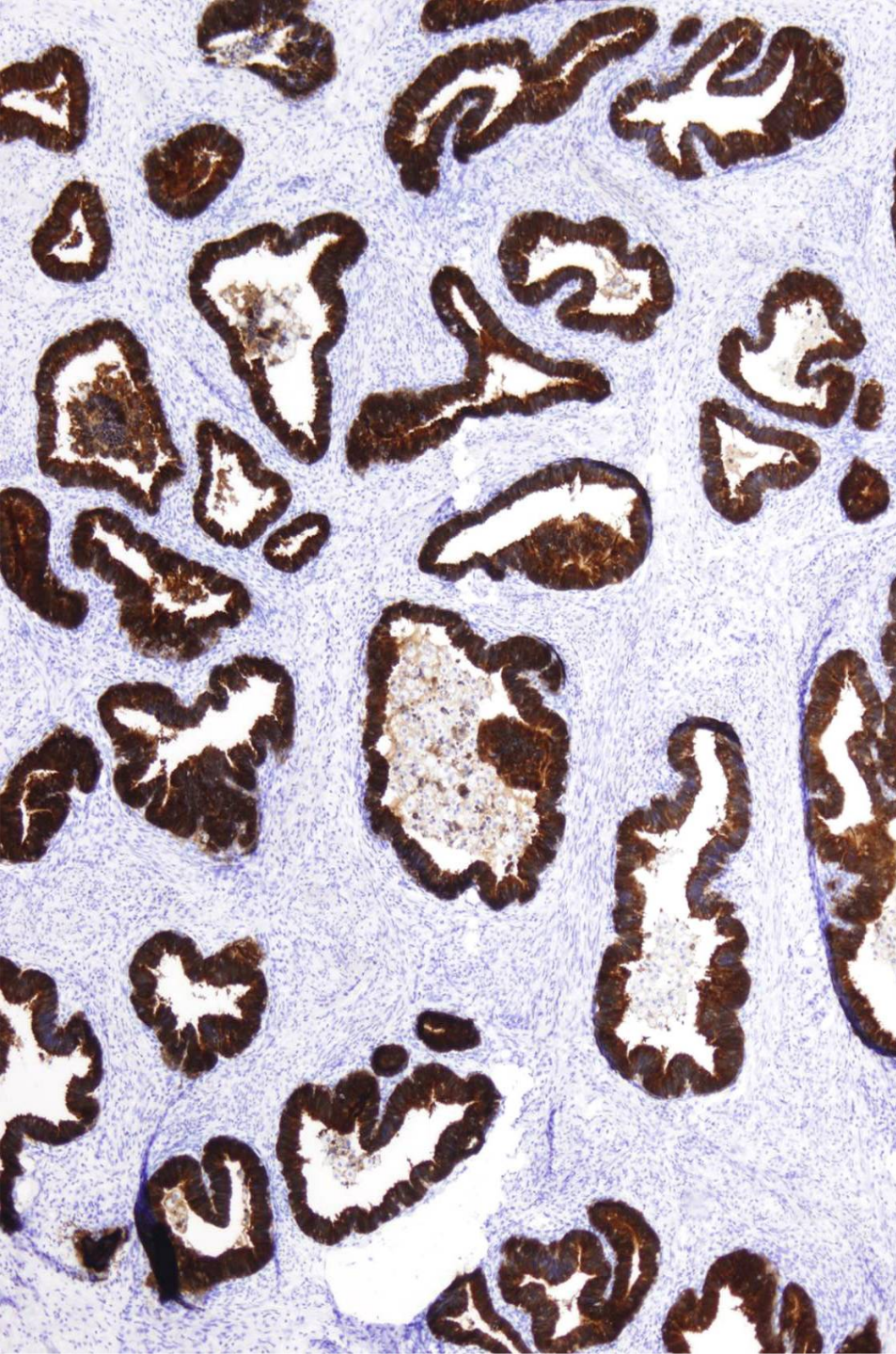




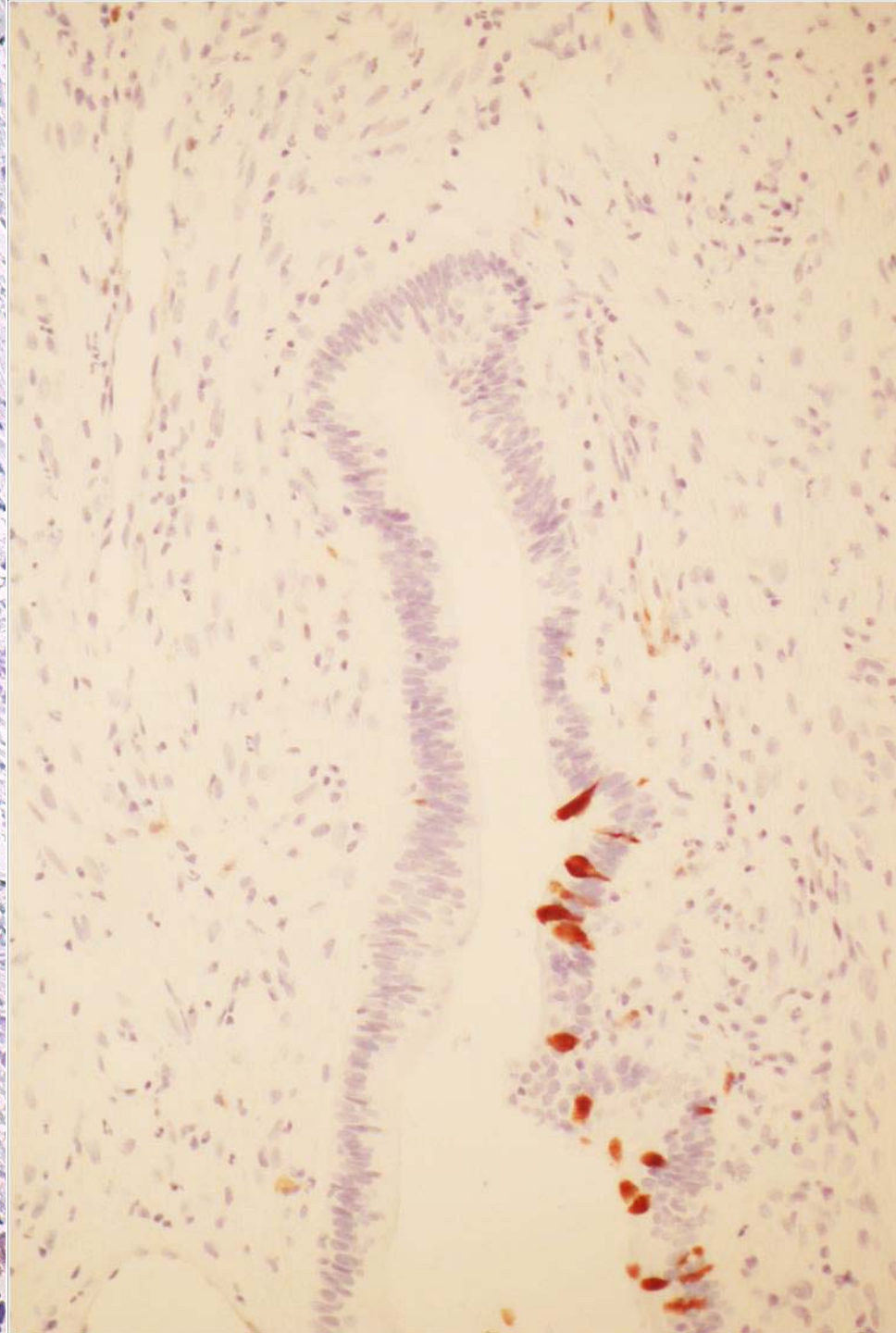
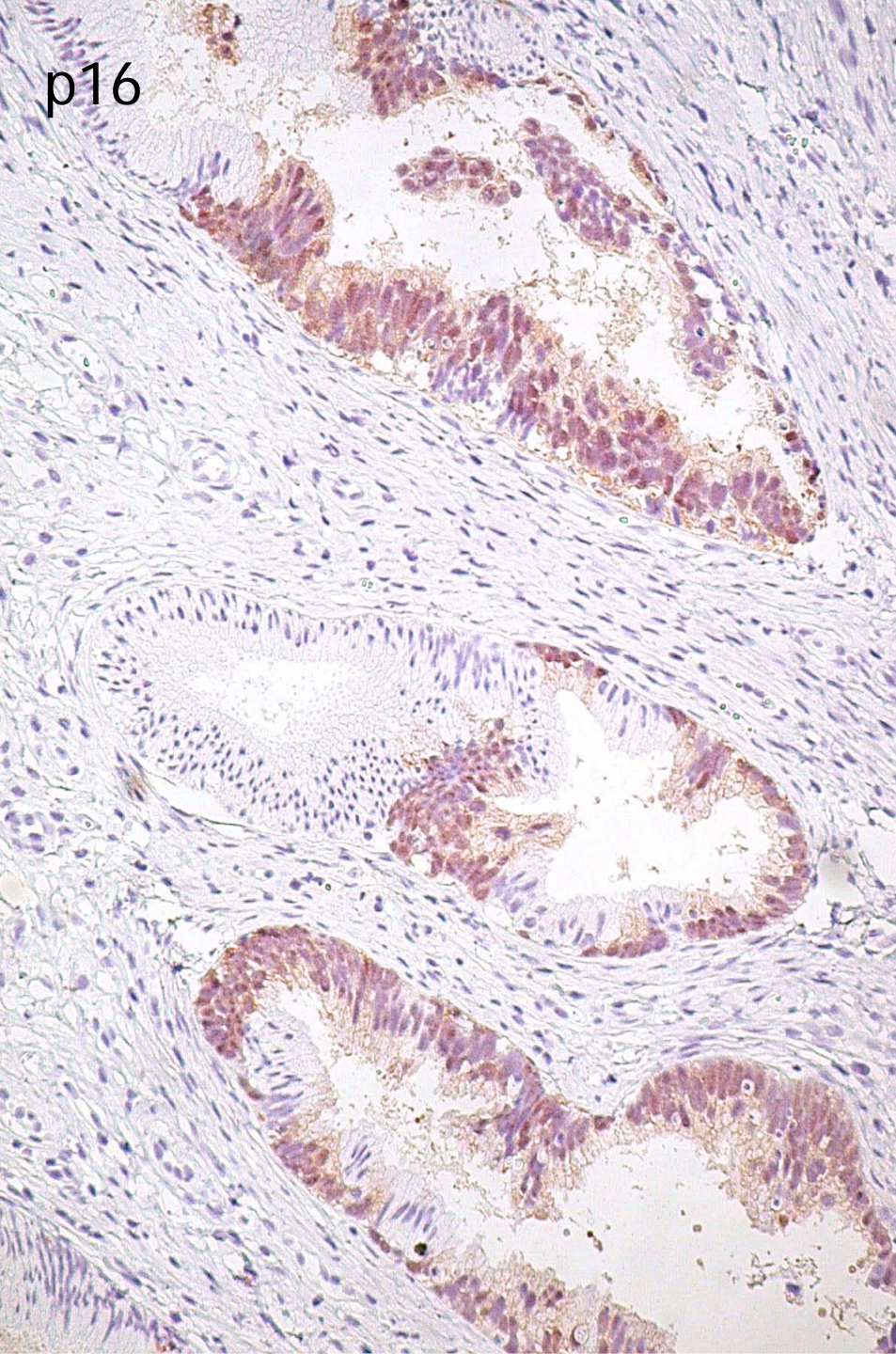
Pitfall 3: p16 en lesions glandulars

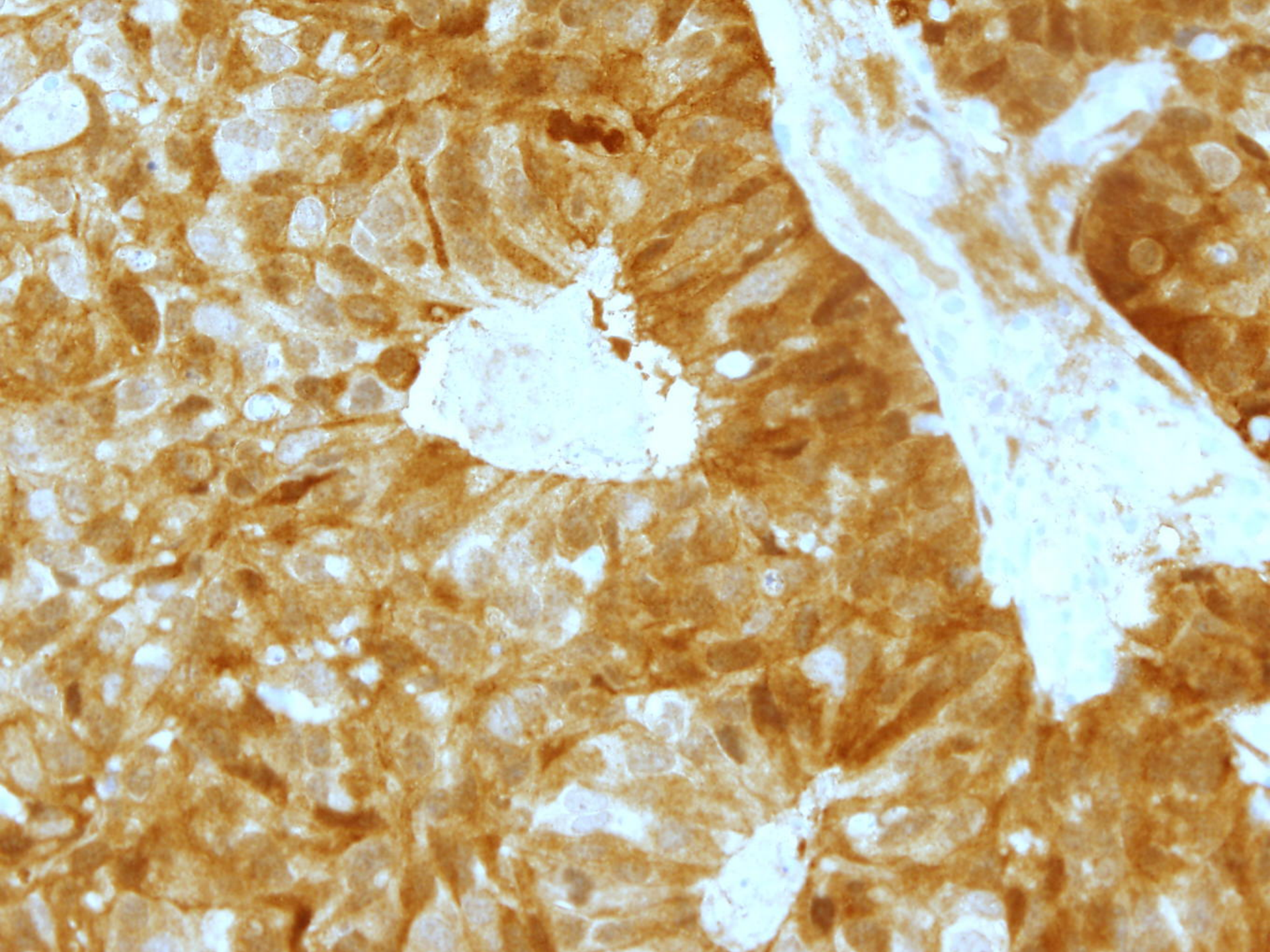
- Paradigma p16=presència d'HPV vàlid en **neoplàsies de l'epiteli escatós**
- Valor molt més limitat en neoplàsies glandulars

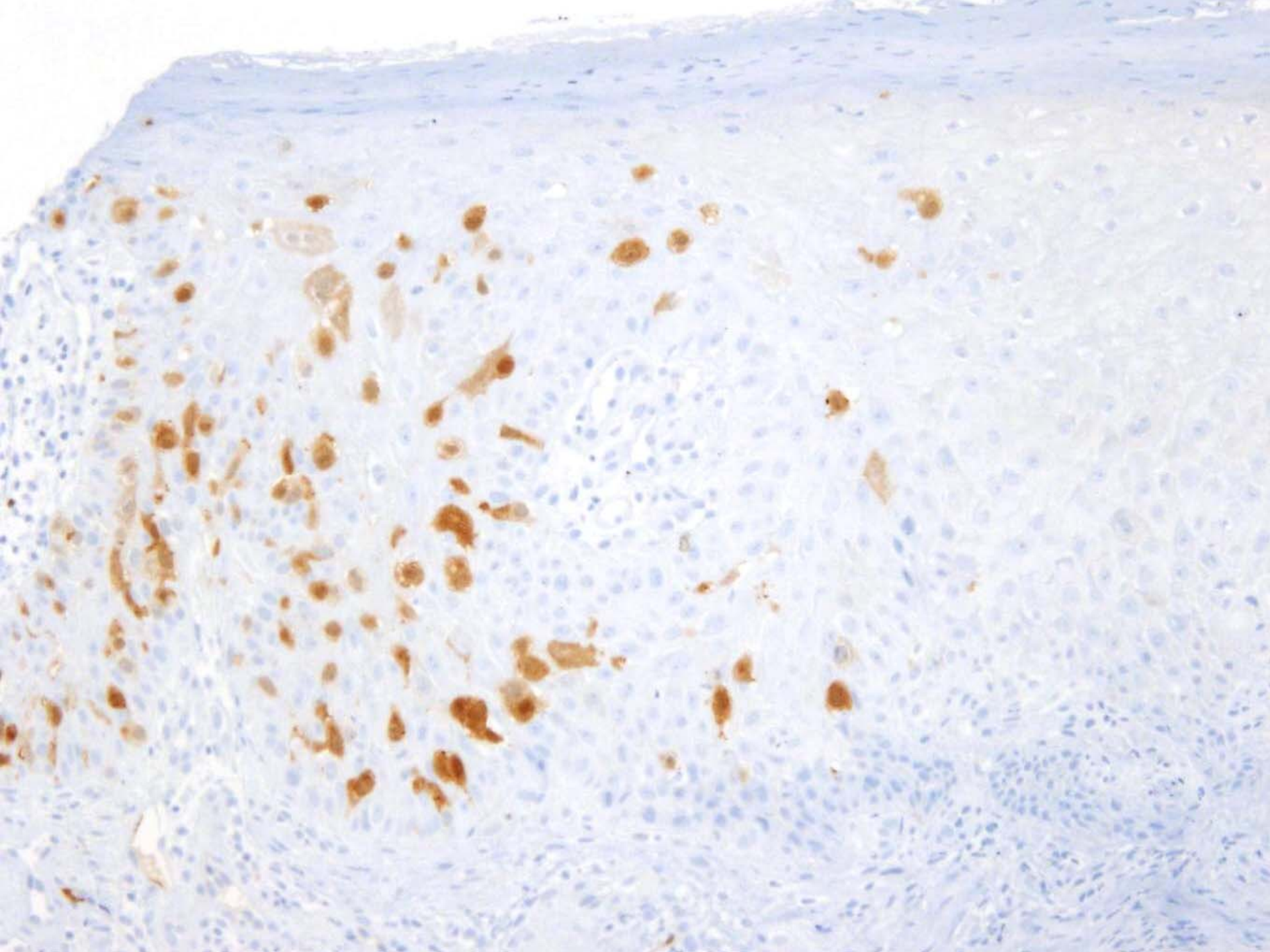




p16









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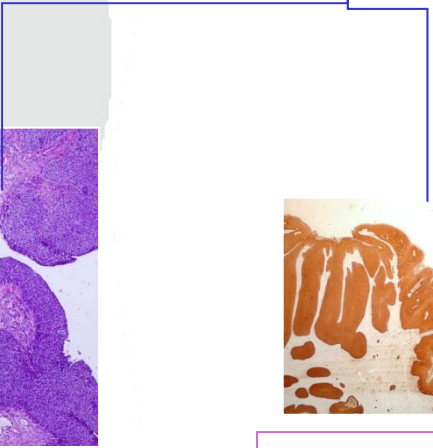
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Maria Alejo
Omar Clavero
Joellen Klaustermeier
Silvia de Sanjosé

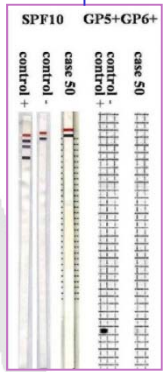
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