Cas 5 et 6

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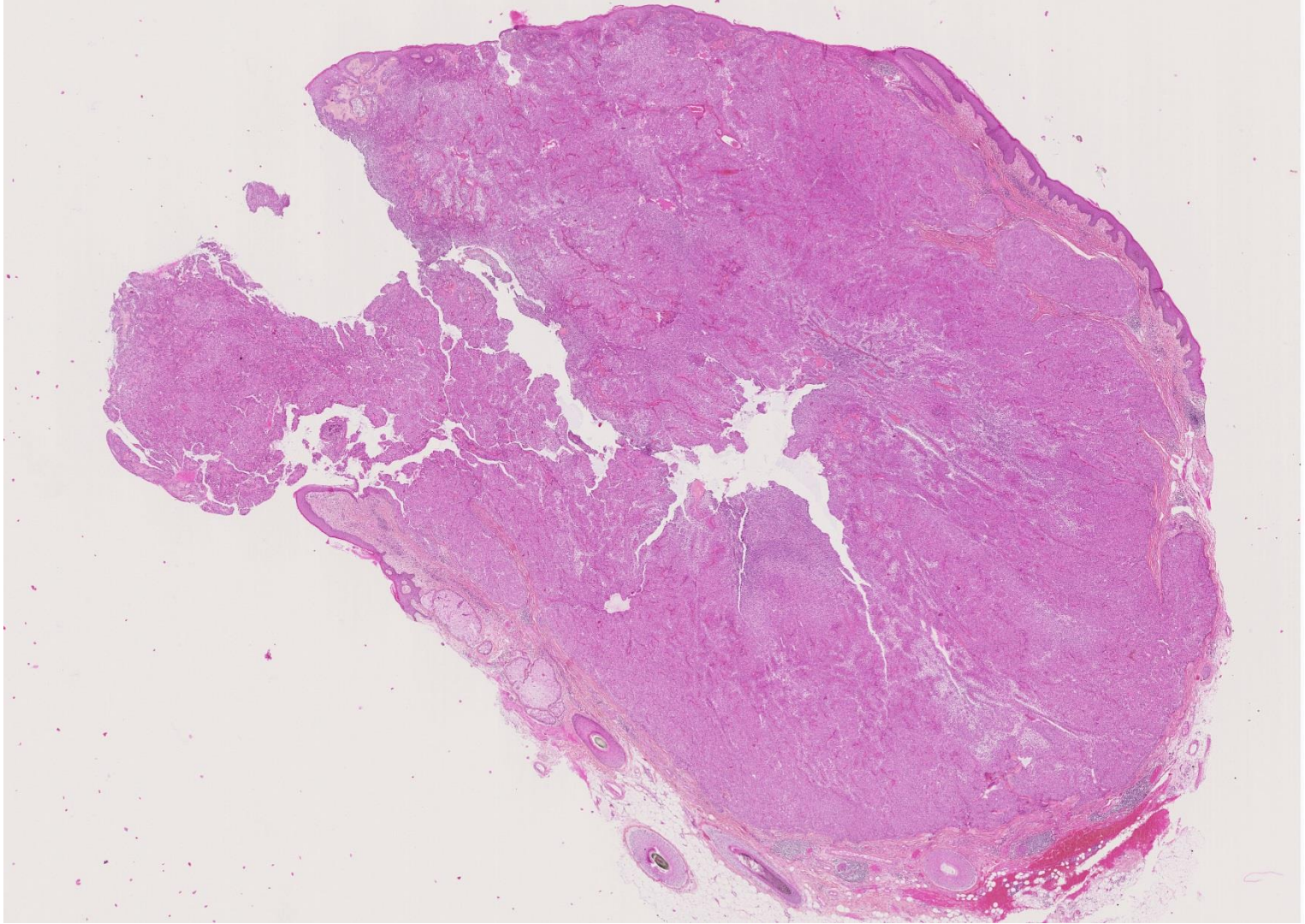
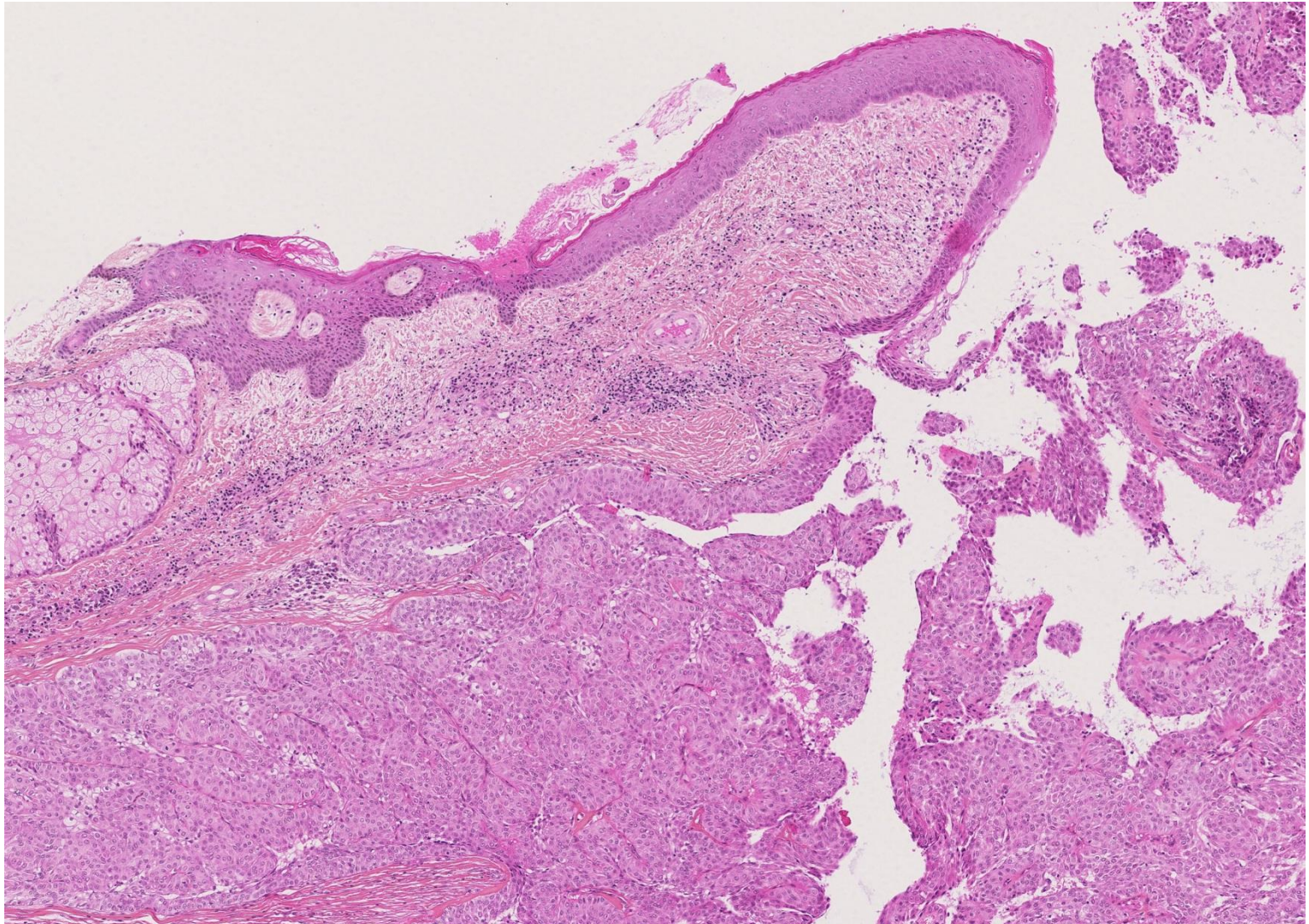
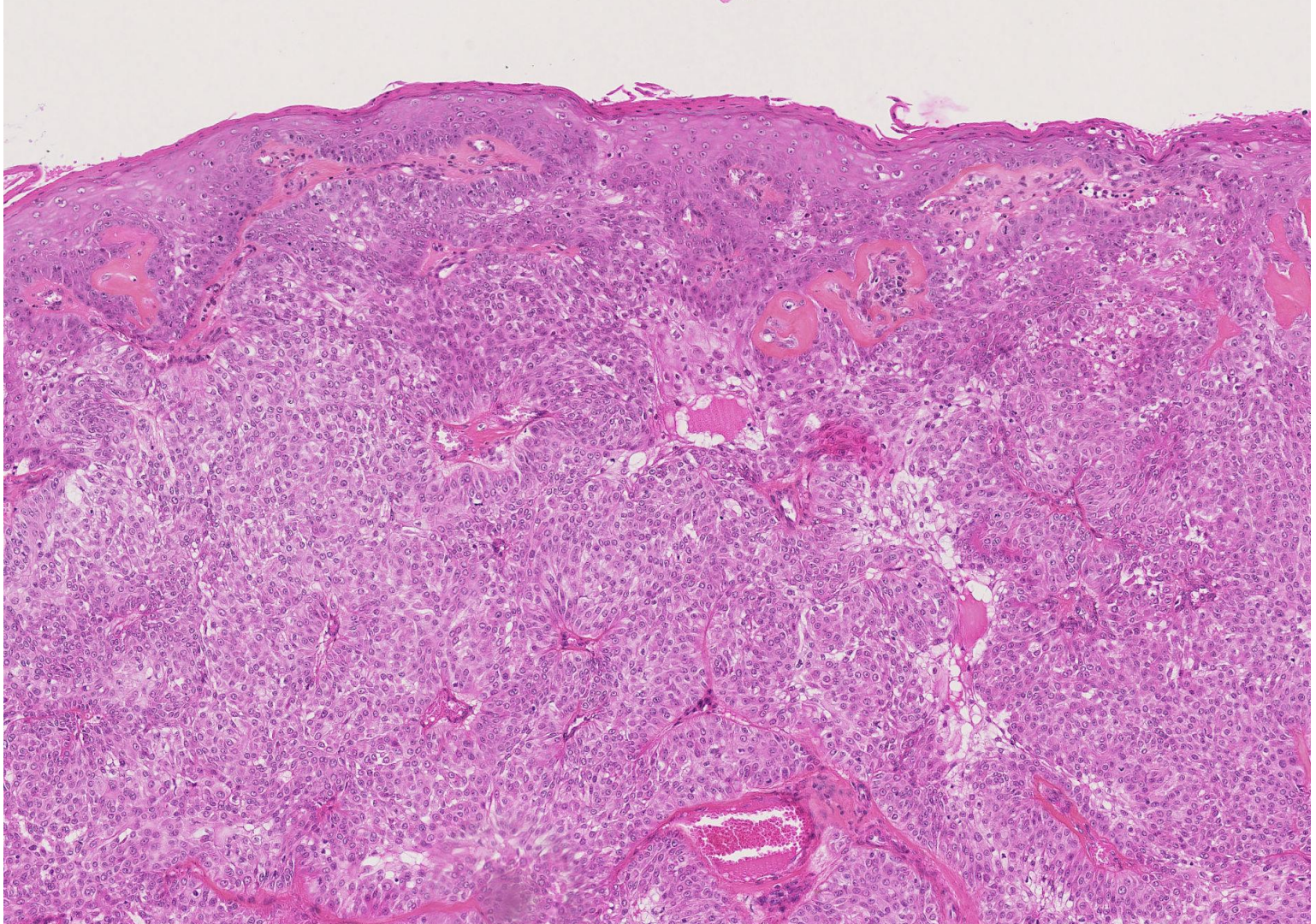
Pathologie, Hôpital Saint Louis
Université de Paris
Inserm UMR_S 976

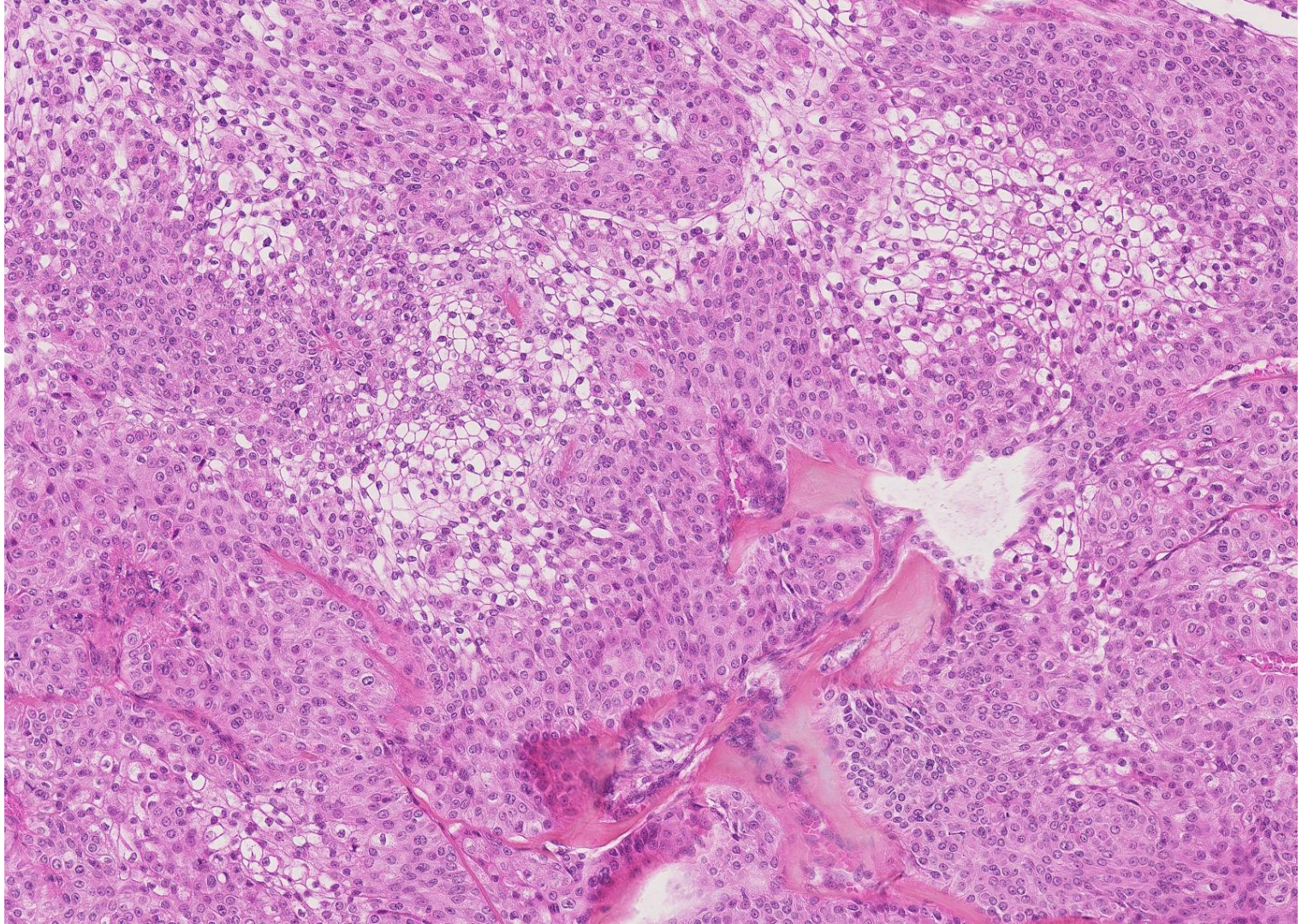
Cas 5

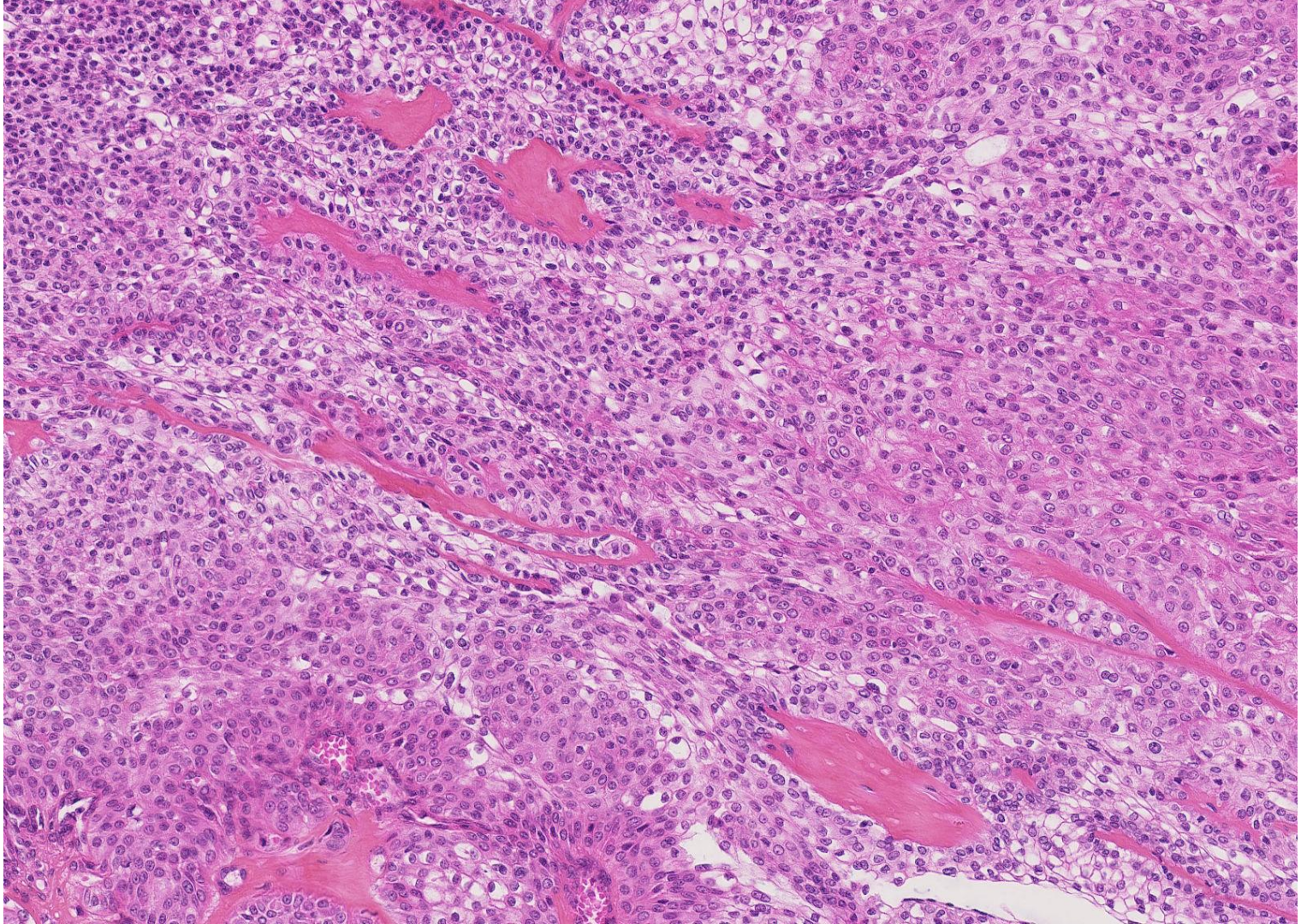
- Homme de 30 ans
- Evolution : 1 an
- Botryomycome ?

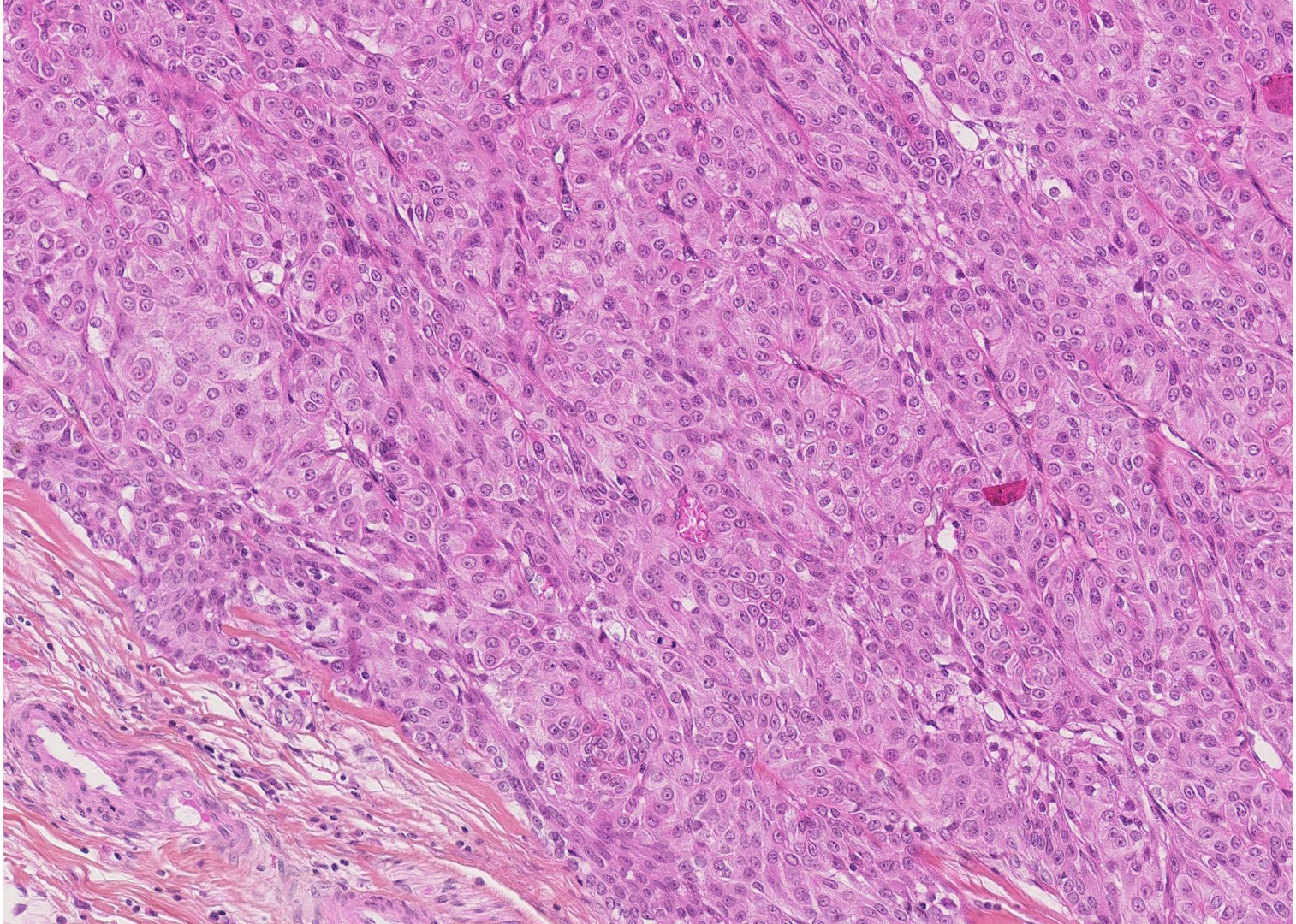












QCM (vote en ligne)

- Devant cette tumeur, quels diagnostics évoquez-vous ?

A- Carcinome épidermoïde

B- Trichilemmome géant

C- Sébacéome

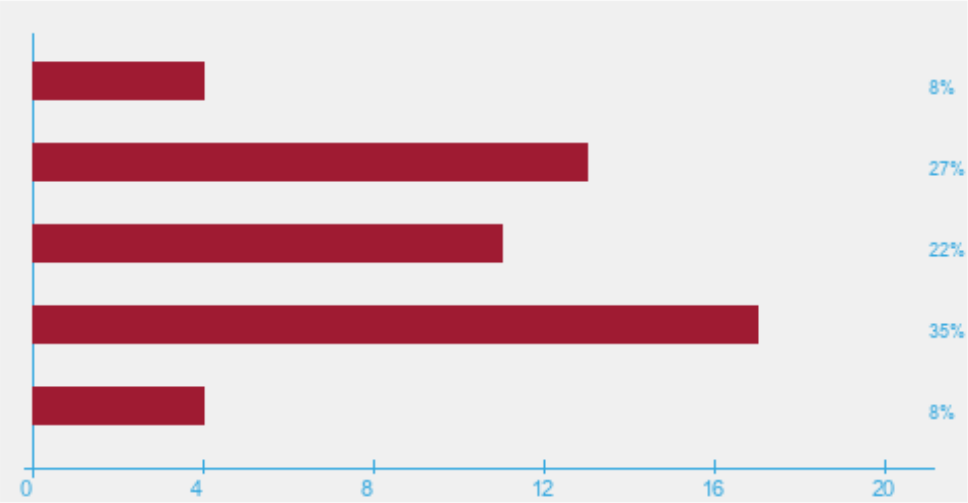
D- Hidradénome

E- Métastase de carcinome à cellules claires

Résultats des votes en ligne

TEC_05

Devant cette tumeur, quel diagnostic évoquez-vous ?
Nombre de votes: 45 - Par réponse



Total: 49

[4] A - Carcinome épidermoïde

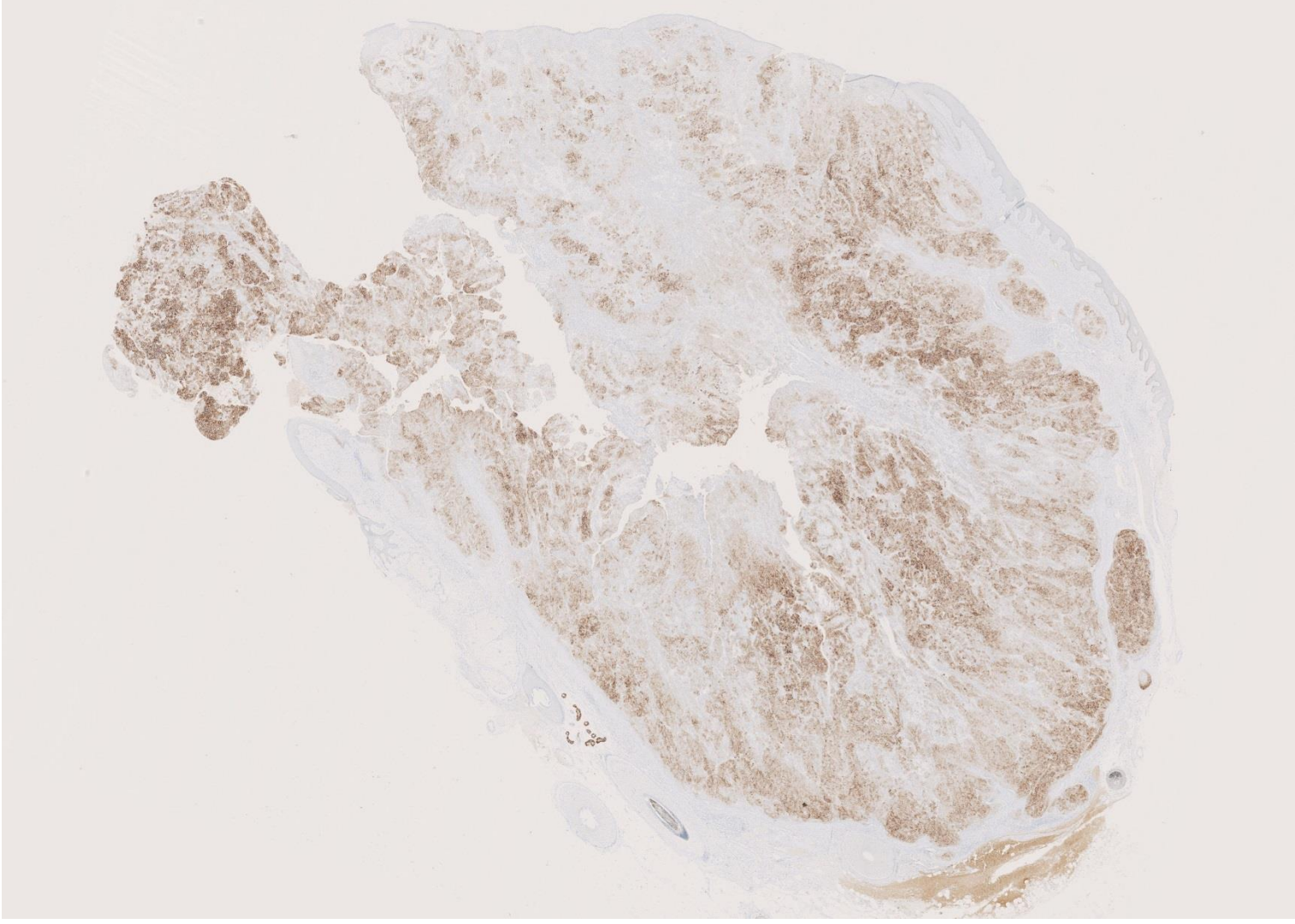
[13] B - Trichilemmome géant

[11] C - Sébacéome

[17] D - Hidradénome

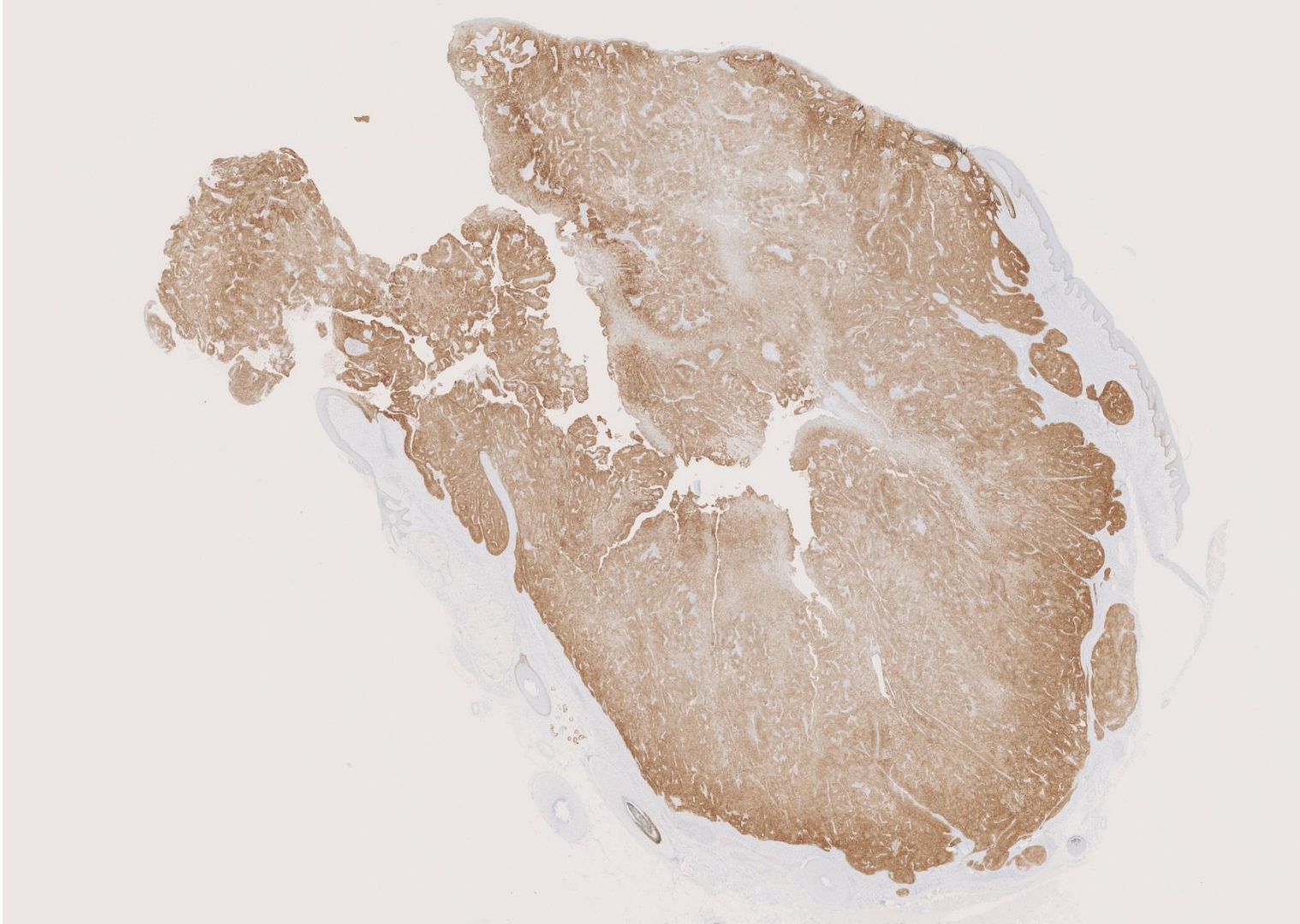
[4] E - Métastase de carcinome à cellules claires

BerEP4

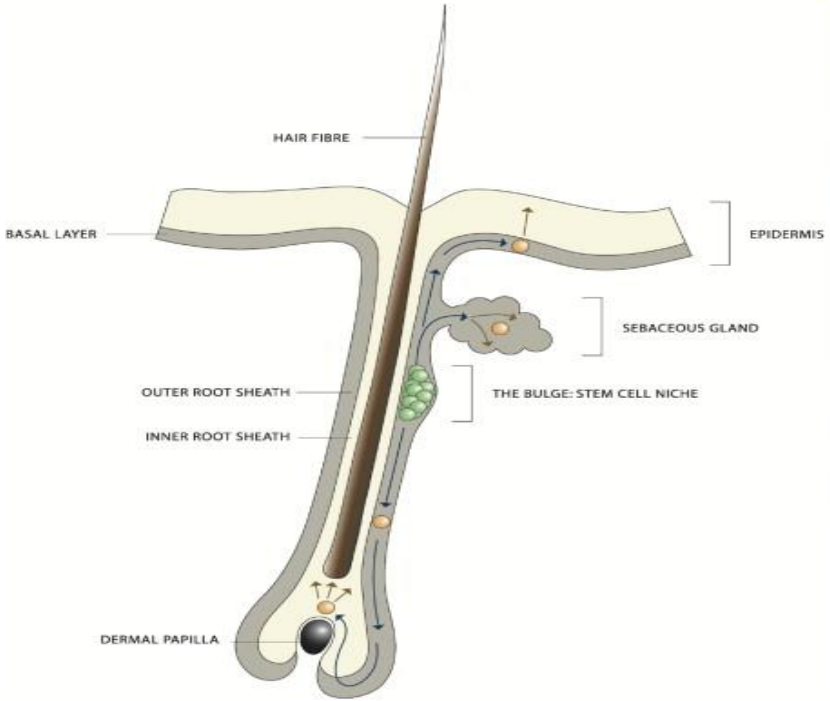


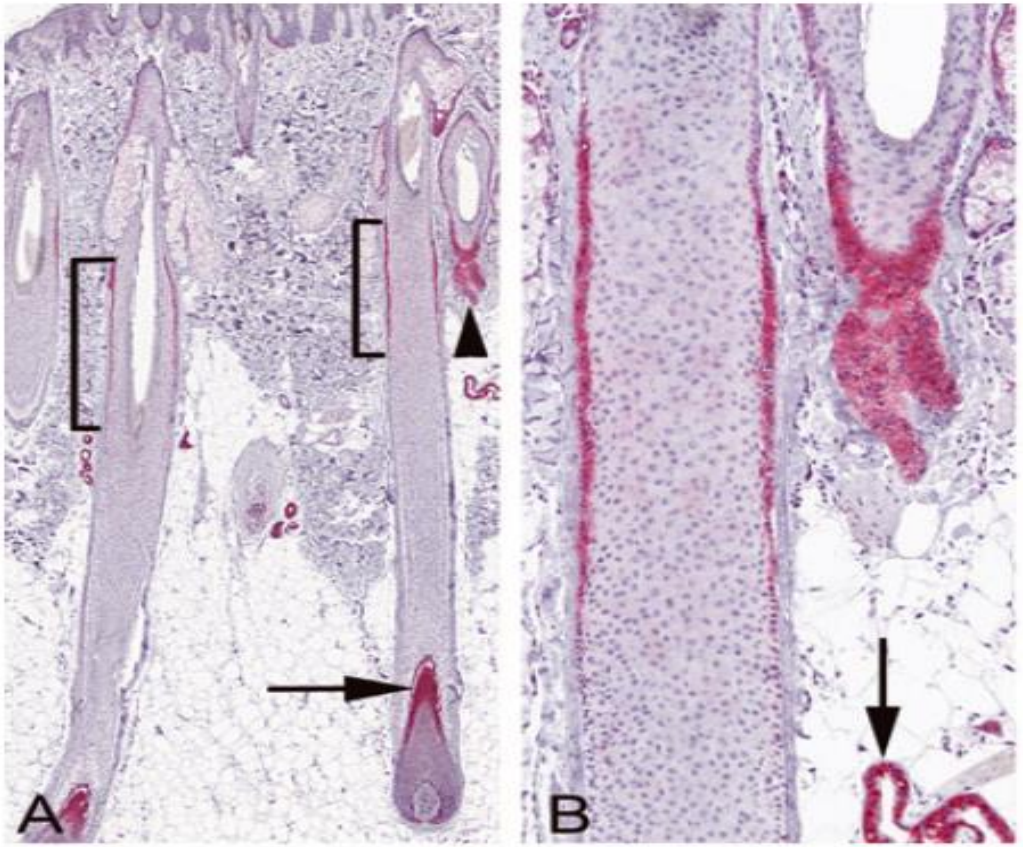
p63+ diffus
CK5/6 diffus

PHLDA1



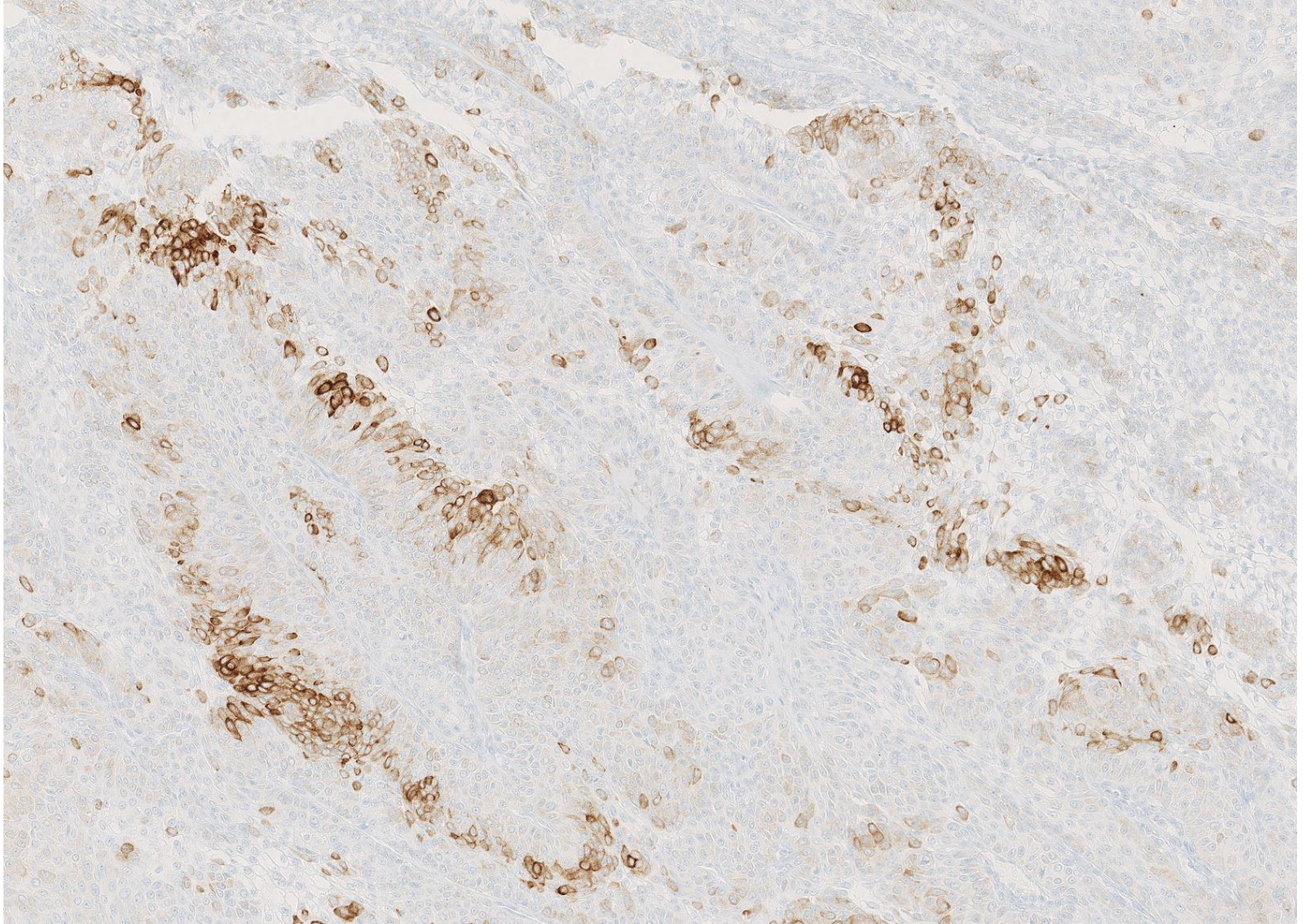
PHLDA1 (TDAG51)





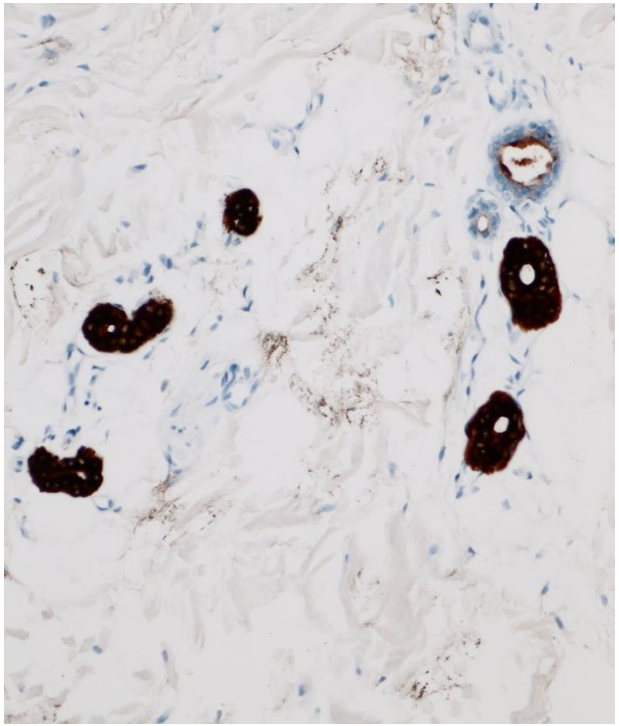
Sellheyer, Br J Dermatol 2011

CK8

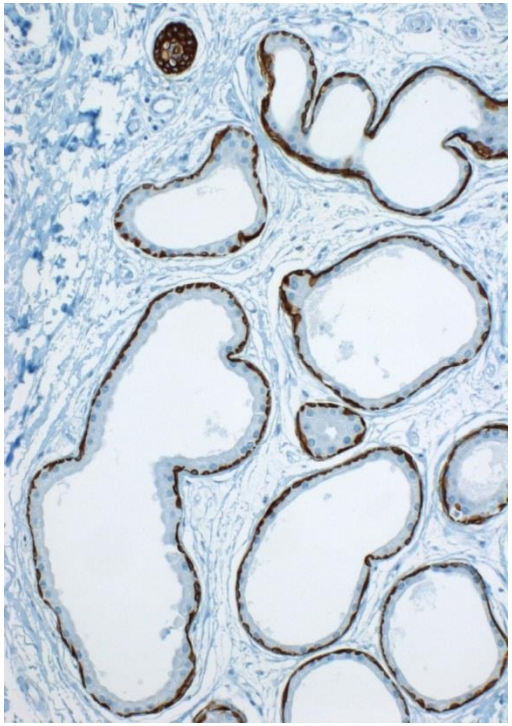


Kératines des glandes sudorales

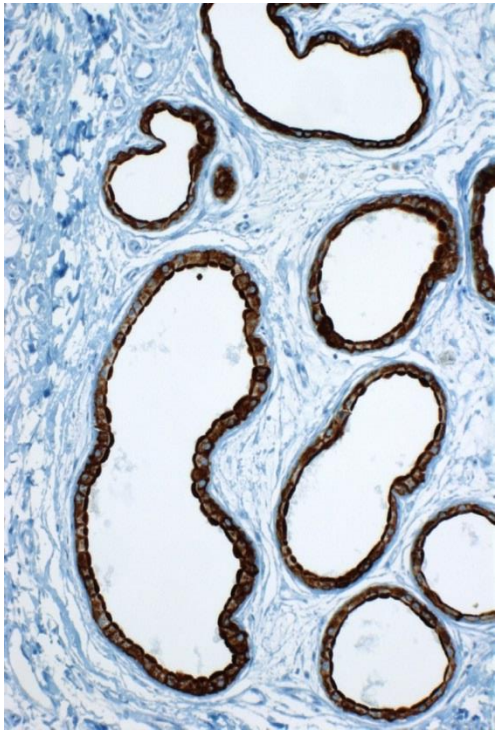
CK7



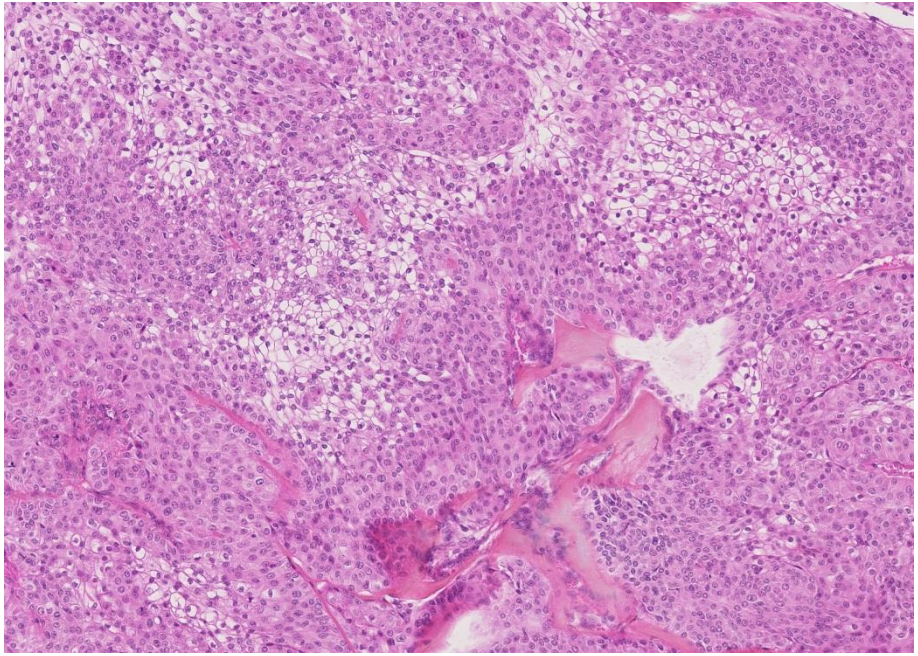
CK5/6

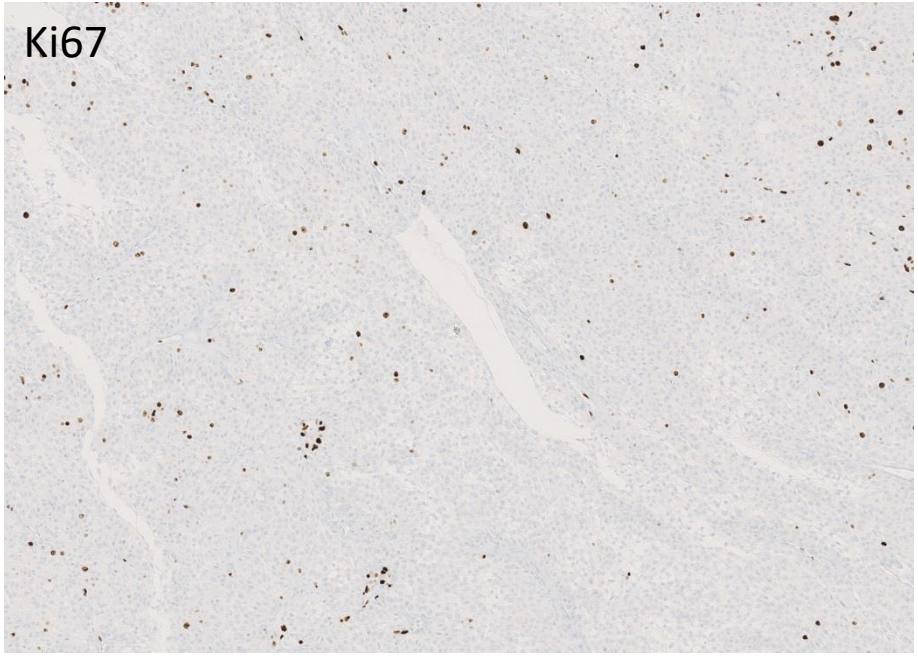


CK8

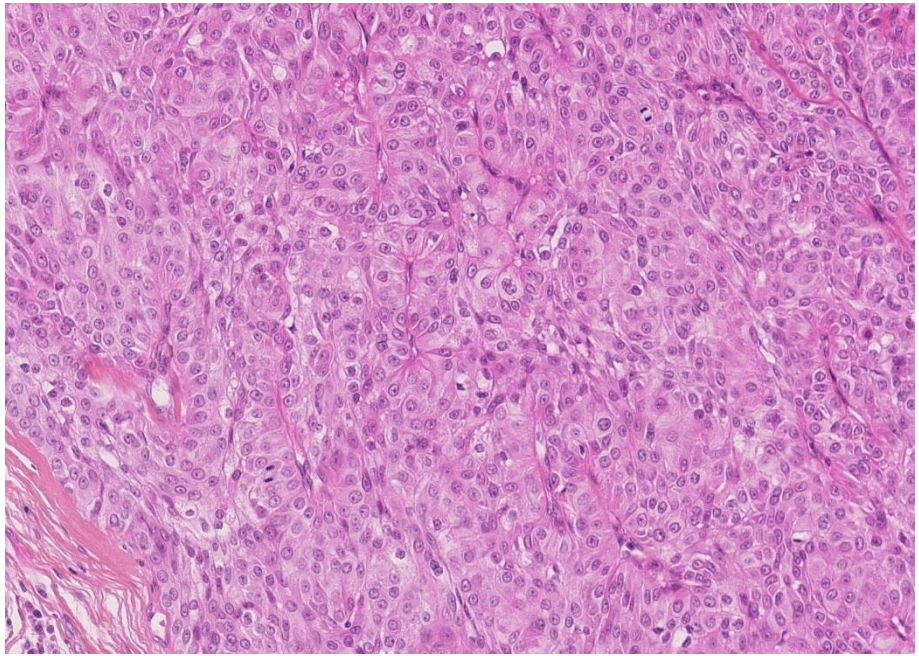


Tumeur hidradénomateuse : malignité ?

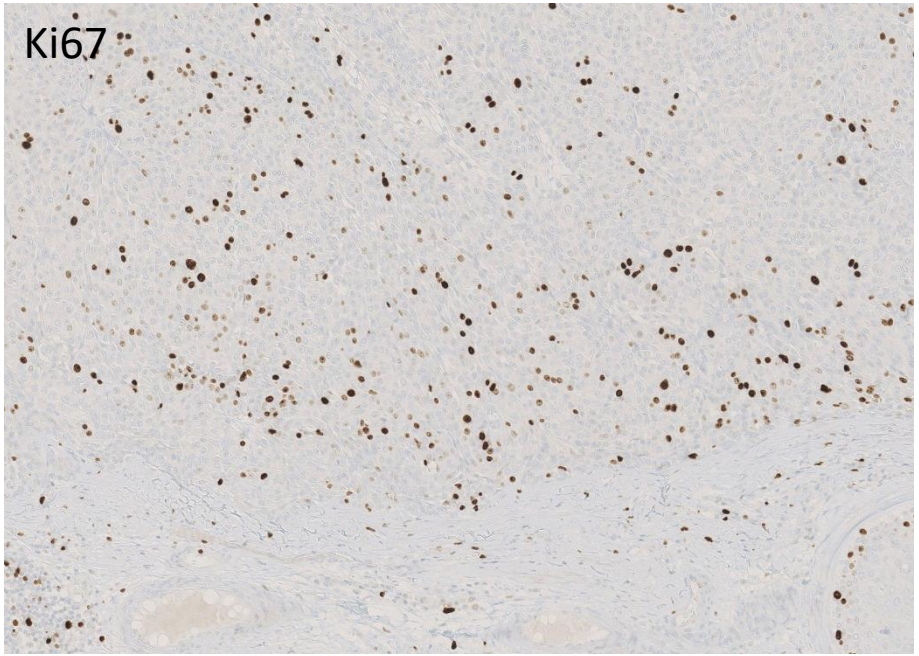


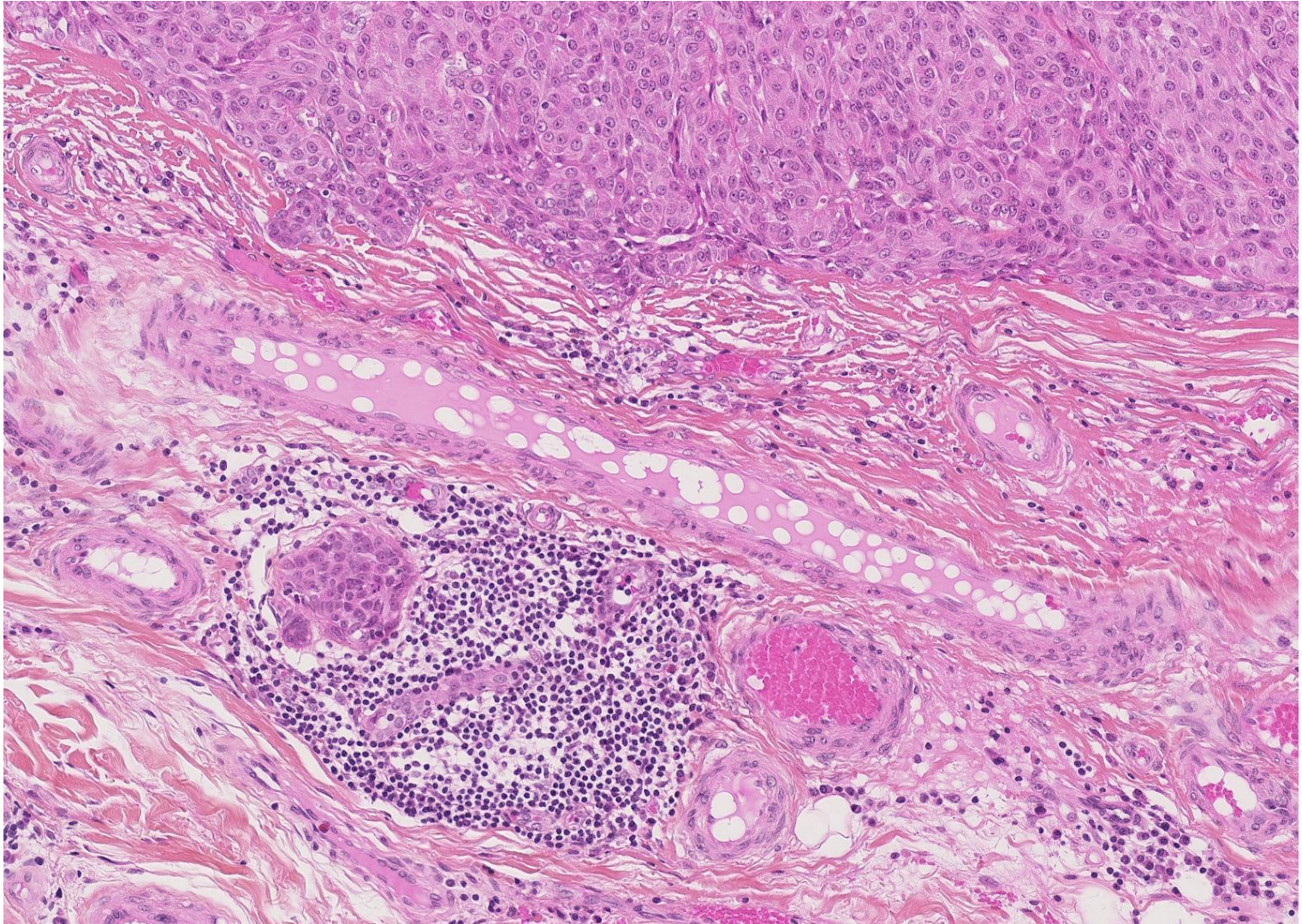


Tumeur hidradénomateuse : malignité ?



Maximum 7 mitoses / 10 hpf





QCM interactif

- Selon vous, s’agit-il :

A- d’un hidradénome bénin

B- d’un hidradénocarcinome

C- d’un hidradénome de potentiel de malignité incertain

D- d’un hidradénome atypique

E- je ne sais pas

START VOTE

QCM interactif

- Selon vous, s’agit-il :

A- d’un hidradénome bénin

B- d’un hidradénocarcinome

C- d’un hidradénome de potentiel de malignité incertain

D- d’un hidradénome atypique

E- je ne sais pas

Malignité des tumeurs annexielles

Risque de récurrence locale (après résection complète)

Carcinome annexiel microkystique (Mohs)

Porocarcinome

Risque métastatique

Carcinome annexiel microkystique

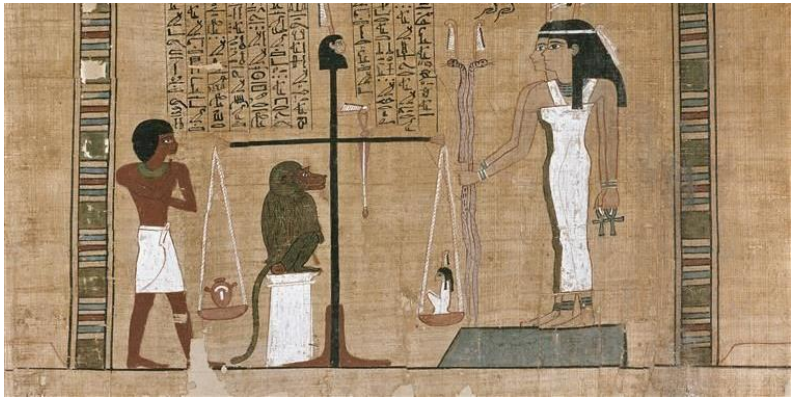
Carcinome cribriforme

Carcinome apocrine
Hidradénocarcinome
Porocarcinome

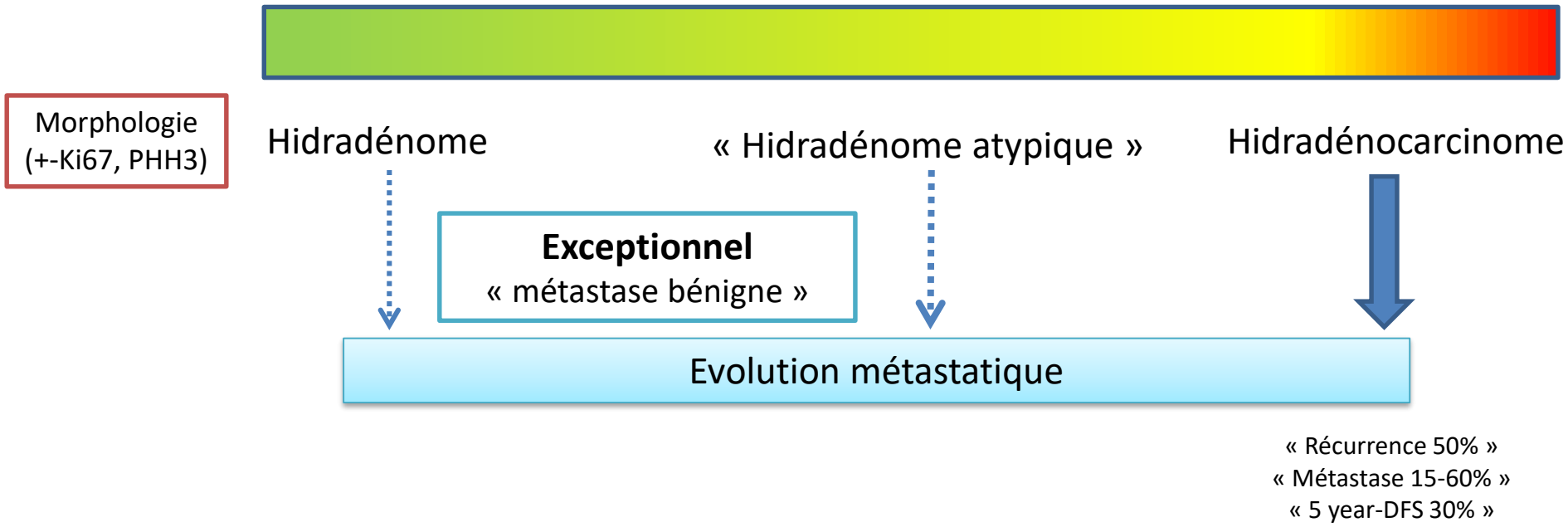
Manque de données robustes pour de nombreuses entités

Evaluation de la malignité des tumeurs annexielles

- Clinique
  - Ulcération ?
  - Cinétique ?
  - Taille (T) ?
  - Âge ?
- Pathologie
  - Silhouette / invasion profonde, destruction
  - Atypies
  - Mitoses / mitoses anormales
  - Nécrose
  - Engainement nerveux
  - Emboles vasculaires



Dyscorrélation morpho-biologique : les tumeurs hidradénomateuses



« … » , incompletely defined, lack of data, or not consensual (WHO 2018)

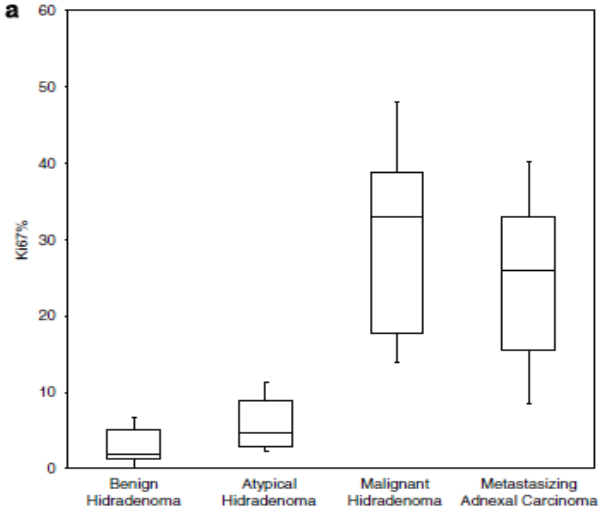
Atypical and malignant hidradenomas: a histological and immunohistochemical study

Modern Pathology (2009) 22, 600–610

Rosalynn M Nazarian*,[1], Payal Kapur*,[2], Dinesh Rakheja[2,3], Adriano Piris[1], Lyn M Duncan[1], Martin C Mihm Jr[1] and Mai P Hoang[1]

Table 2 Summary of the histological features of atypical and malignant hidradenomas

	Atypical hidradenoma	*Malignant hidradenoma*	*P-value*
Number of cases	15	15	
Loss of circumscription	13/15 (87%)	15/15 (100%)	0.49
Infiltrative growth	4/15 (27%)	13/15 (87%)	<0.001*
Deep extension	0/15 (0%)	9/15 (60%)	0.001*
Necrosis	3/15 (20%)	10/15 (67%)	0.023*
Perineural invasion	0/15 (0%)	3/15 (20%)	0.24
Vascular invasion	0/15 (0%)	2/15 (13%)	0.43
Nuclear pleomorphism	2/15 (13%)	15/15 (100%)	<0.001*
Four mitoses or greater per 10 HPFs	0/15 (0%)	13/15 (87%)	<0.001*
Cystic areas	14/15 (93%)	4/15 (27%)	<0.001*
Clear cell morphology	13/15 (87%)	14/15 (93%)	0.99
Epidermoid morphology	12/15 (80%)	13/15 (87%)	0.99
Mucinous metaplasia	1/15 (6.7%)	2/15 (13%)	0.99
Dystrophic calcification	2/15 (13%)	4/15 (27%)	0.36
Hyalinized stroma	15/15 (100%)	12/15 (80%)	0.99
Duct formation	15/15 (100%)	13/15 (87%)	0.27
Nuclear pseudoinclusion	8/15 (53%)	6/15 (40%)	0.69
Nuclear groove	11/15 (73%)	9/15 (60%)	0.42



In the case of CCNH a lesion is to be considered benign if it lacks an infiltrative growth pattern, deep extension, necrosis, nuclear pleomorphism, and ≥ 4 mitoses/10 HPF.

Tumeurs annexielles de potentiel de malignité incertain (ATUMP)

- Terme descriptif (proposé dans l'OMS 2018)
- Seuils bénignité/malignité non consensuels

  - Hidradénome atypique / hidradénocarcinome
  - Porome atypique / porocarcinome
  - Tumeur mixte atypique / tumeur mixte maligne
  - Sébaceome ou adénome sébacé atypique / carcinome sébacé

« Give a recommendation for complete excision and consideration of follow-up » (OMS, 2018)

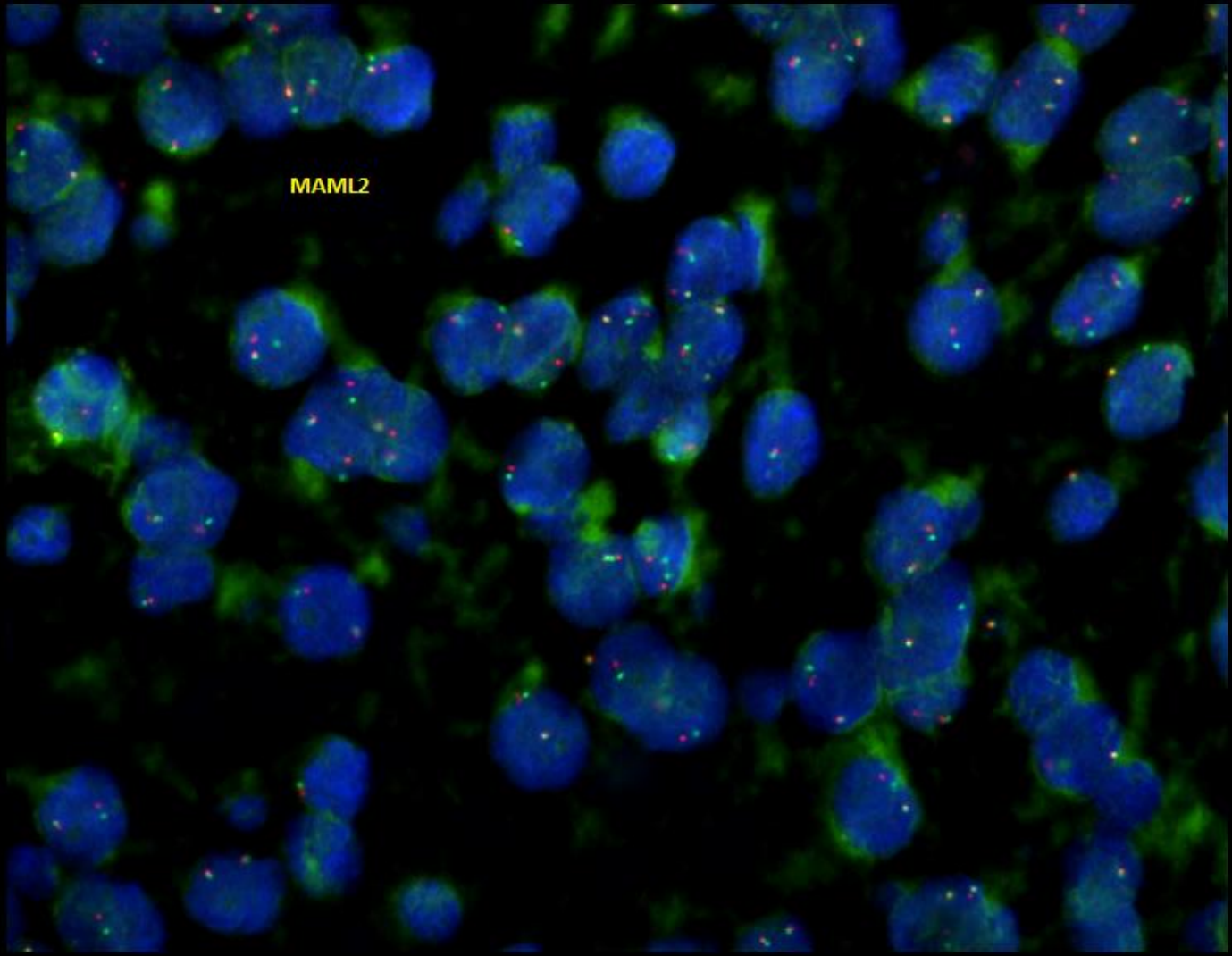
Caractérisation moléculaire des tumeurs annexielles

Tumeur	Principales altérations identifiées
Carcinome adénoïde kystique	*MYB-NFIB* ou autre altération de *MYB* (60%)
Hidradénome/hidradénocarcinome	*CRTC1-MAML2* (<50%) *CRTC3-MAML2* (<5%)
Carcinome secrétoire	*ETV6-NTRK3* (<100%) NFIX-PKN1
Spiradénome, cylindrome, spiradénocylindrome Carcinome ex-spiradénome/cylindrome	*Mutation de CYLD* (Brooke-Spiegler syndrome)
Tumeur mixte (syringome chondroïde)	*PLAG1* rearrangement (<100%)
Myoepithéliome (syncytial)	*EWSR1*-PBX3 (100% ?)
Pilomatricome / carcinome pilomatriciel	*CTNNB1* mutation (<100%)
Tumeurs sébacées du syndrome de Muir-Torre	MSI

Tumeurs annexielles et salivaires : parenté moléculaire

TABLE 1. Key Molecular Alterations in Selected Salivary Gland Carcinomas

Tumor Type		Chromosomal Alteration	Gene Fusion/ Rearrangement	Prevalence (%)
MAMMARY ANALOG SECRETORY CARCINOMA	MASC	t(12;15)(p13;q25)	*ETV6-NTRK3*	95-98
		t(12;X)	*ETV6-RET*	2-5
MUCOEPIDERMOID CARCINOMA	MEC	t(11;19)(q21;p13)	*CRTC1-MAML2*	40-80
		t(11;15)(q21;q26)	*CRTC3-MAML2*	5
HYALINIZING CLEAR CELL CARCINOMA	HCCC	t(12;22)(q21;q12)	*EWSR1-ATF1*	80-90
ADENOID CYSTIC CARCINOMA	AdCC	t(6;9)(q22-23;p23-24)	*MYB-NFIB*	25-80
		t(8;9)	*MYBL1-NFIB*	10-20
POLYMORPHOUS (LOW-GRADE) ADENOCARCINOMA AND CRIBRIFORM ADENOCARCINOMA OF (MINOR) SALIVARY GLAND ORIGIN	PLGA	14q12	Hotspot activating *PRKD1* somatic point mutation (E710D)	20
	CAS-Gs	t(1;14)(p36.11;q12)	*ARID1A-PRKD1*	24
		t(X;14)(p11.4;q12)	*DDX3X-PRKD1*	13
			PRKD2 and *PRKD3* rearrangements	16
SALIVARY DUCT CARCINOMA	SDC	17q21.1	*HER2* amplification	20-40
		3q26.32	*PIK3CA* mutation	20
		inv(10)(q11.21q11.22)	*NCOA4-RET*	<5
PLEOMORPHIC ADENOMA			PLAG1 rearrangement	


MAML2

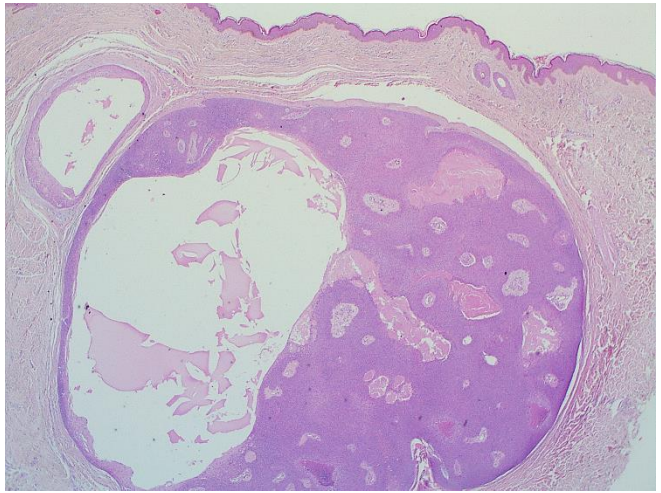
Human Pathology (2017) **70**, 55–61

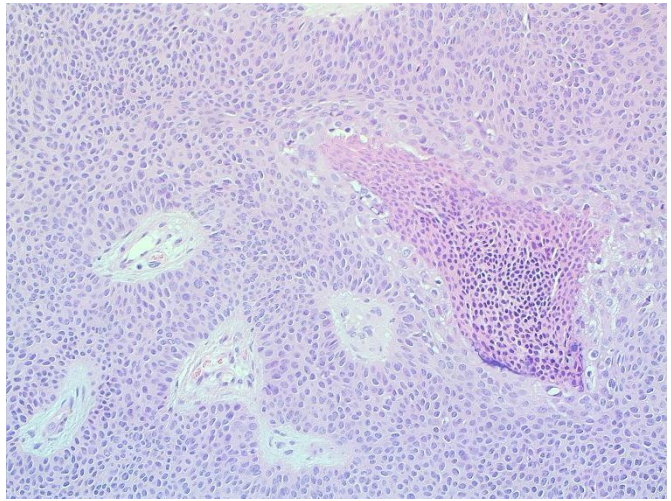
A novel fusion gene *CRTC3-MAML2* in hidradenoma: histopathological significance☆,☆☆

Yuki Kuma MD[a,b], Yuichi Yamada MD, PhD[a], Hidetaka Yamamoto MD, PhD[a], Kenichi Kohashi MD, PhD[a], Takamichi Ito MD[a,b], Masutaka Furue MD, PhD[b], Yoshinao Oda MD, PhD[a,*]

Table 3 Factors associated with CRTC1/3-MAML2 expression

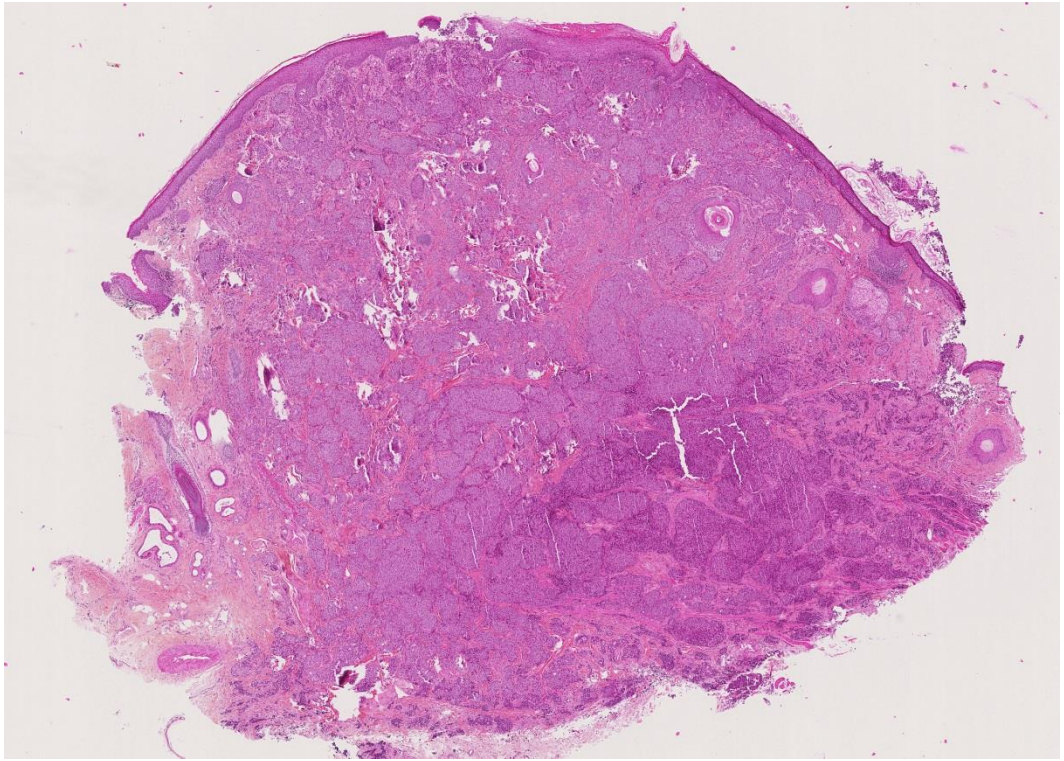
Parameters	CRTC1-MAML2	CRTC3-MAML2	*MAML2* rearrangement	Positive	Negative	Total
Component cell						
C > P	2	1	4	7	2	9
C = P	2	0	3	5	4	9
P > C	6	1	4	11	10	21
Total	10	2	11	23	16	39
Average of major diameter (mm)				21.5	24.7	
Pathological diagnosis						
Clear cell hidradenoma	10	2	11	23	13	36
Poroid hidradenoma	0	0	0	0	3	3
Total	10	2	11	23	16	39

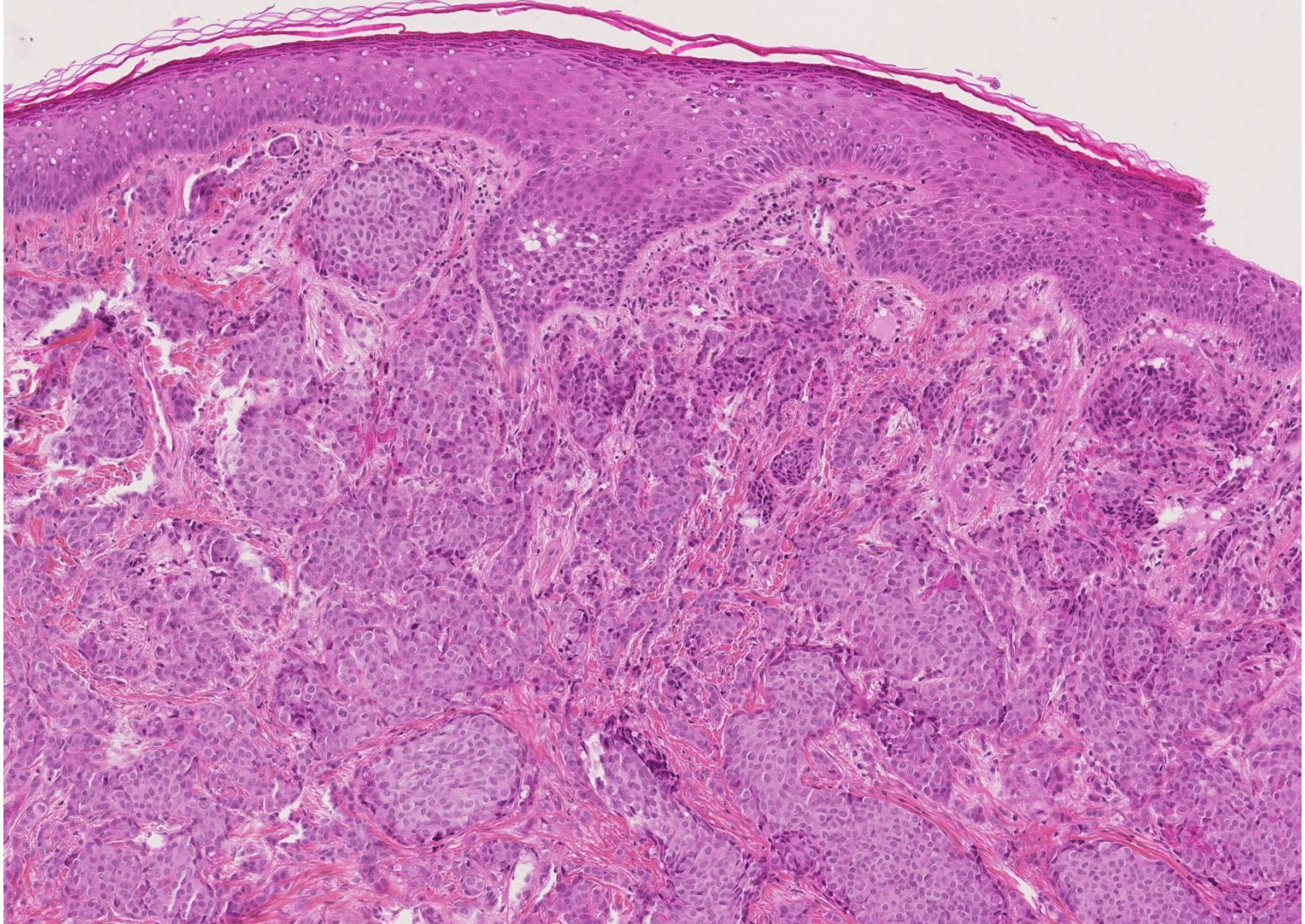


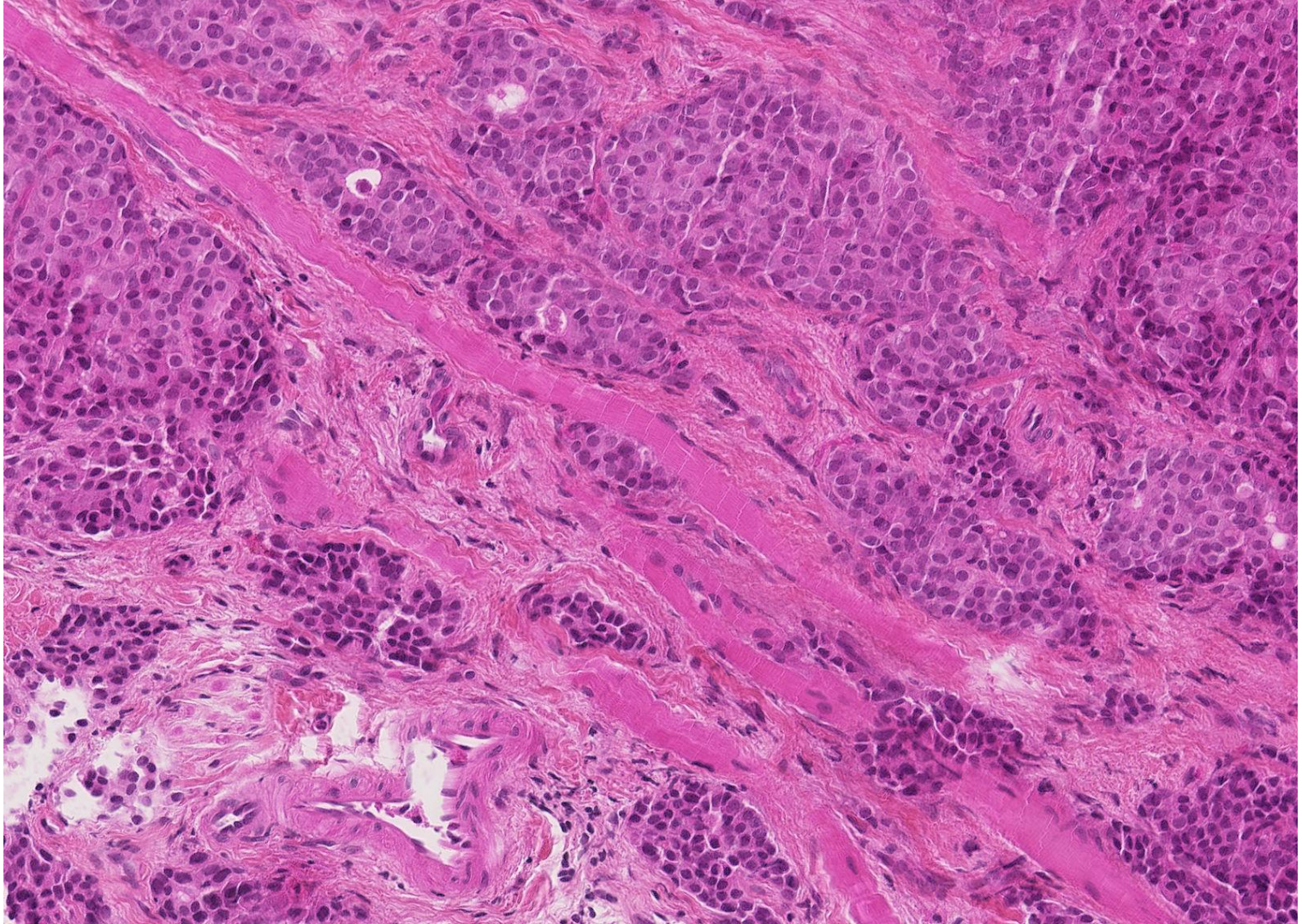


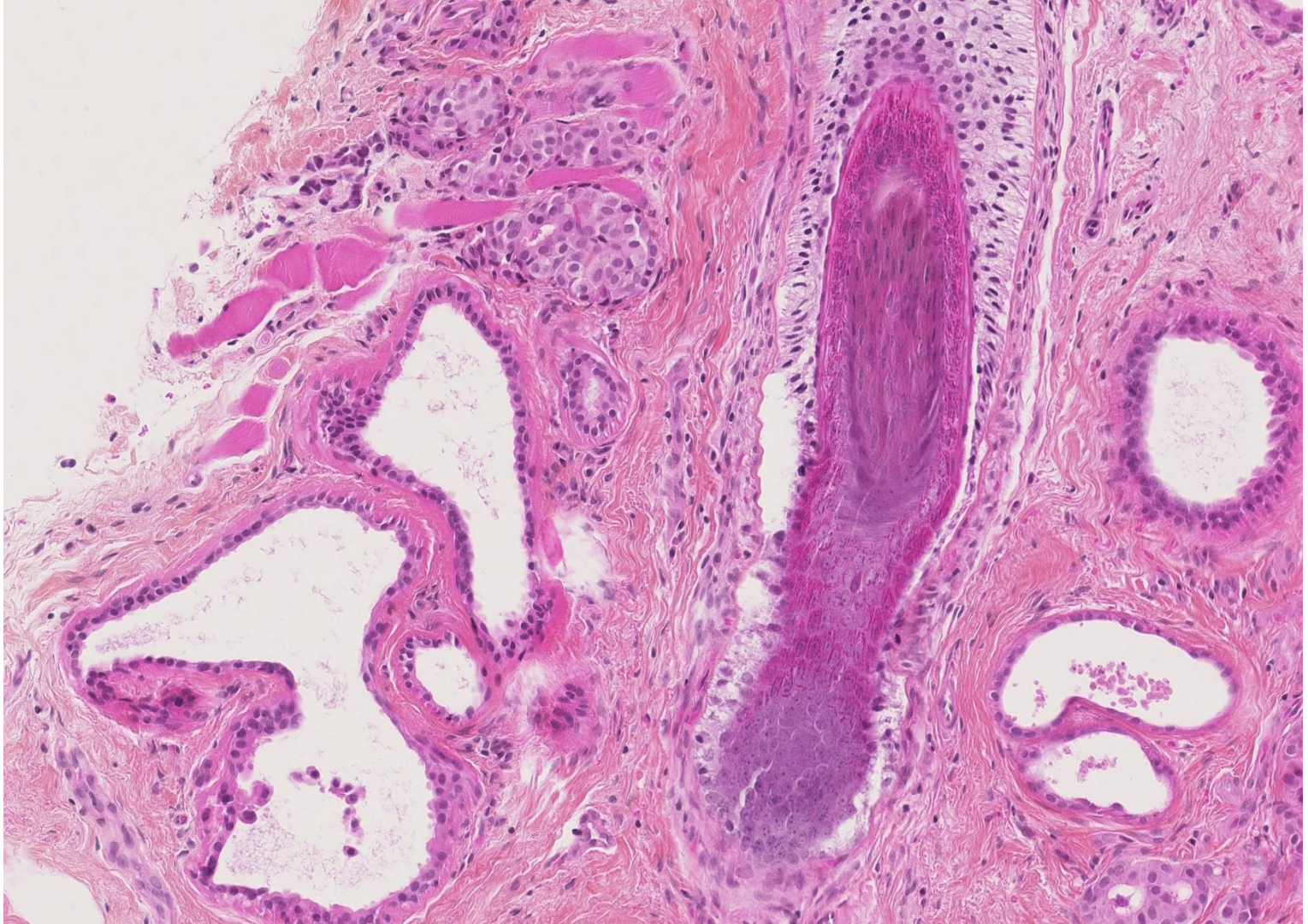
Cas 6

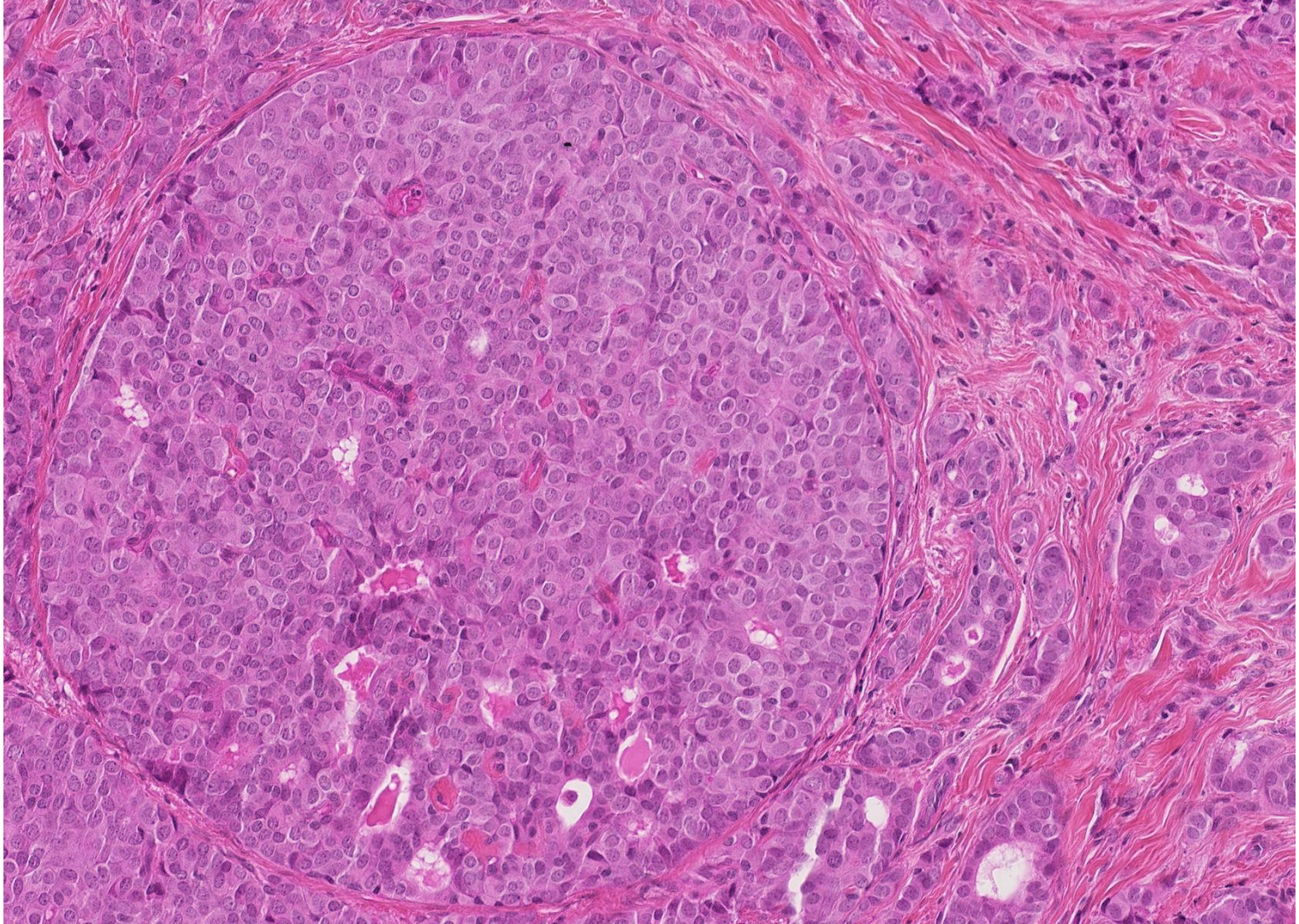
- Homme de 72 ans
- Tumeur de la paupière, 1cm
- Evolution : quelques mois

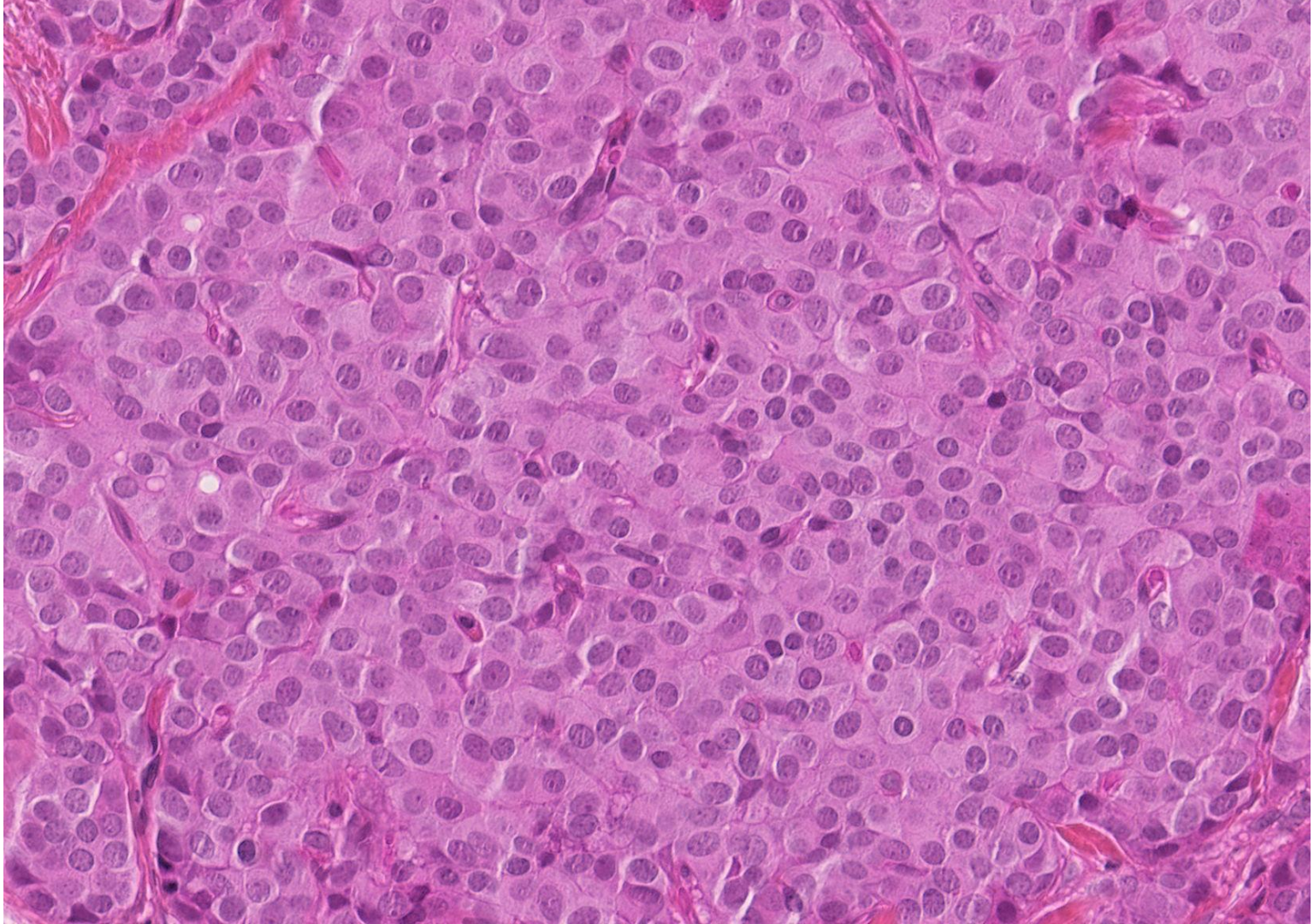




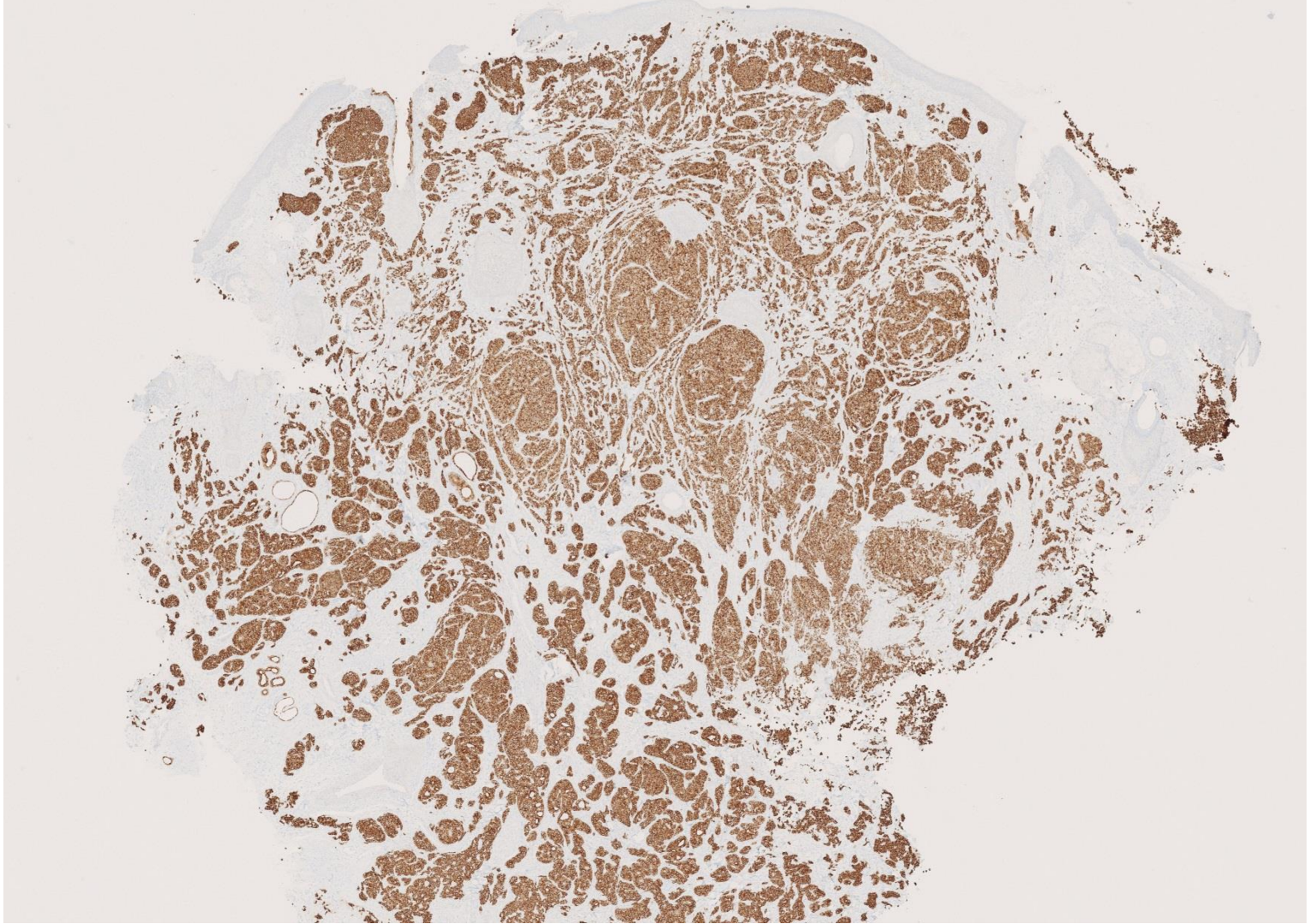








CK7



QCM interactif

- Quel diagnostic vous parait le plus probable ?

A- Carcinome annexiel microkystique

B- Carcinome adénoïde kystique

C- Porocarcinome

D- Autre carcinome sudoral

E- Métastase d’adénocarcinome non cutané

START VOTE

QCM interactif

- Quel diagnostic vous parait le plus probable ?

A- Carcinome annexiel microkystique

B- Carcinome adénoïde kystique

C- Porocarcinome

D- Autre carcinome sudoral

E- Métastase d’adénocarcinome non cutané

QCM (vote en ligne)

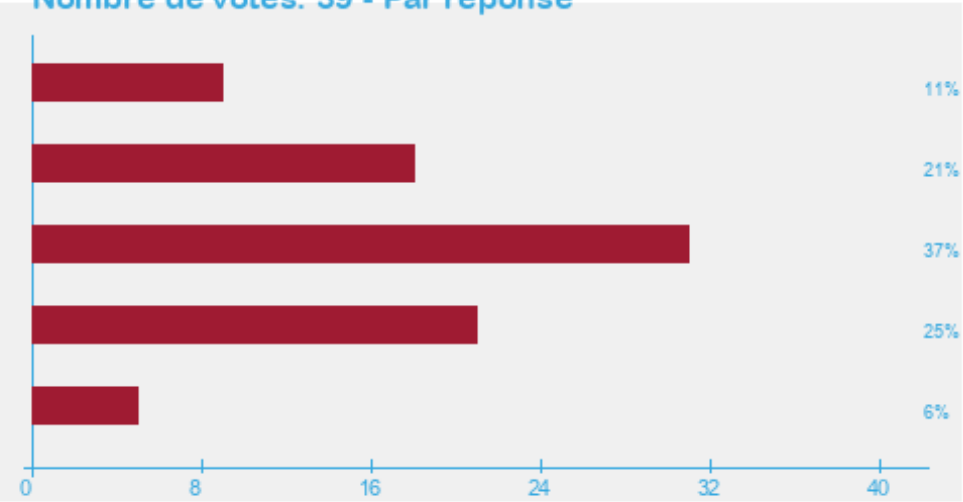
- Vous pensez à une métastase cutanée, quel(s) immunomarquage(s) positif(s) vous permettrai(en)t d'affirmer ce diagnostic ?

A – Récepteur aux androgènes
B - Récepteur aux oestrogènes
C - GATA3
D - mammaglobine
E - p63

TEC_06

Vous pensez à une métastase cutanée, quel(s) immunomarquage(s) positif(s) vous permettrai(en)t d'affirmer ce diagnostic ?

Nombre de votes: 39 - Par réponse



[9] A - Récepteur aux androgènes

[18] B - Récepteur aux œstrogènes

[31] C - GATA3

[21] D - Mammaglobine

[5] E - p63

Total: 84

Réponse attendue : aucun

Différencier adénocarcinome cutané primitif et secondaire

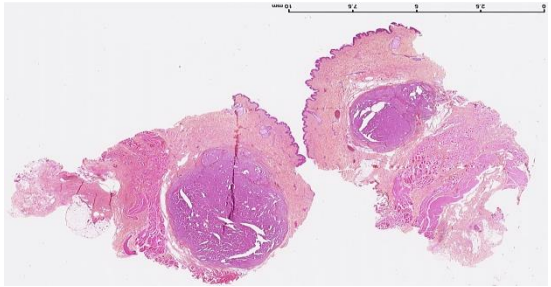
- Outil le plus sensible et spécifique
  - bilan d'extension clinique et paraclinique +++
- Immunohistochimie
  - Marqueurs « organe - spécifiques »
  - Marqueurs non différentiels
  - Marqueurs utiles
- Analyse transcriptomique / génomique
  - Peu de données

Différencier adénocarcinome cutané primitif et secondaire :

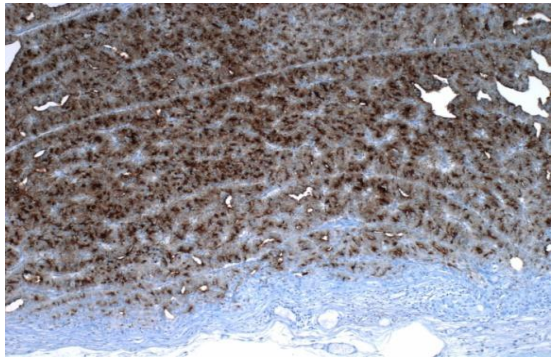
Marqueurs « organe - spécifiques »

- TTF1, thyroglobuline, thyrocalcitonine
- PSA, PLAP, PAP
- RCC, PAX8
- Hepato

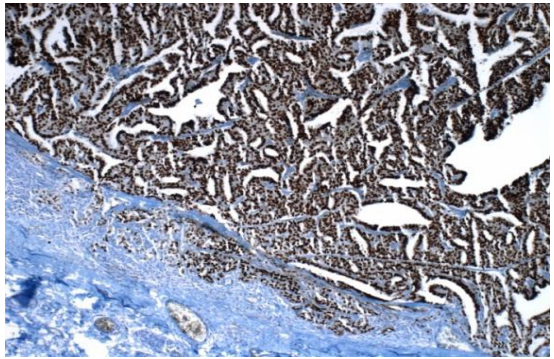
ADK cutanés primitifs toujours négatifs



Métastase d'un carcinome thyroïdien



Thyroglobuline



TTF1

Différencier adénocarcinome cutané primitif et secondaire :

Marqueurs non/peu différentiels

- EMA
- RE, RP, HER2
- RA
- GCDFP15
- MUC1,MUC2
- GATA3
- Mammaglobine

→ Non différentiels

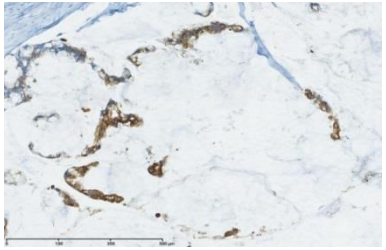
Kazakov D et al. Am J Surg Pathol 2005
Dias-Santagata D et al. Mod Pathol 2011
Le LP et al. Plos One 2012
Rollins-Raval M et al. Arch Pathol Lab Med 2011

Rollins-Raval M et al. Arch Pathol Lab Med 2011
Fernandez-Flores A. Cesk Patol 2009

Différencier adénocarcinome cutané primitif et secondaire :

Marqueurs utiles les + sensibles/spécifiques

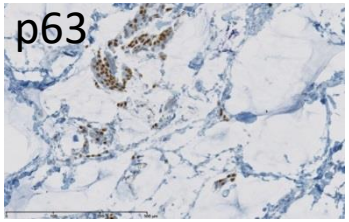
- CK20



Métastase d'adénocarcinome mucineux colique

Spécificité ~100% pour l'origine extra-cutanée

- CK5/6, p63/p40,D2-40 (panel)



Adénocarcinome eccrine mucineux cutané primitif

Sensibilité et spécificité ~90% (pour différencier avec ADK origine mammaire ou pulmonaire)

Non différentiel avec les métastases de carcinomes salivaires

Immunohistochemical Distinction of Primary Sweat Gland Carcinoma and Metastatic Breast Carcinoma

Am J Clin Pathol 2015;143:430-436

Can It Always Be Accomplished Reliably?

Mark J. Mentrikoski, MD, and Mark R. Wick, MD

Table 2

Immunohistochemical Staining Results of p63, CK5/6, D2-40, Mammaglobin, and GATA3 in Primary Sweat Gland Carcinomas and Metastatic Breast Carcinoma

	Grade of Reactivity, No. (%)									
	Primary Sweat Gland Carcinoma (n = 21)					Metastatic Breast Carcinoma to Skin (n = 33)				
Marker	Total Positive	0	1+	2+	3+	Total Positive	0	1+	2+	3+
p63	17 (81)	4 (19)	1 (5)	0	16 (76)	2 (6)	31 (94)	1 (3)	1 (3)	0
CK5/6	15 (71)	6 (29)	0	3 (14)	12 (57)	2 (6)	31 (94)	0	1 (3)	1 (3)
D2-40	11 (52)	10 (48)	0	5 (24)	6 (29)	2 (6)	31 (94)	1 (3)	0	1 (3)
Mammaglobin	1 (5)	20 (95)	1 (5)	0	0	15 (45)	18 (55)	0	1 (3)	14 (42)
GATA3	15 (71)	6 (29)	1 (5)	8 (38)	6 (29)	30 (91)	3 (9)	0	3 (9)	27 (82)

Table 3

Sensitivity and Specificity, With *P* Values, for Individual Immunohistochemical Stains

Stain	p63	CK5/6	D2-40	Mammaglobin	GATA3
SGC (n = 21), No. (%)	17 (81)	15 (71)	11 (52)	1 (5)	15 (71)
MBCS (n = 33), No. (%)	2 (6)	2 (3)	2 (6)	15 (45)	30 (91)
P value	<.0001	<.0001	.0002	.007	.1306
Sensitivity, %	81[a]	71[a]	52[a]	45[b]	91[b]
Specificity, %	94[a]	94[a]	94[a]	95[b]	29[b]

[a] Sensitivity and specificity for the diagnosis of primary sweat gland carcinoma (SGC).
[b] Sensitivity and specificity for the diagnosis of metastatic breast carcinoma to skin (MBCS).

	Apocrine carcinoma		*P*
	Cutaneous	Mammary	
Adipophilin	5/14 (36%)	22/25 (88%)	.0013 [a]
3+	0	10	
2+	2	7	
1+	3	5	
0	9	3	
ER	7/14 (50%)	3/26 (12%)	.0180 [a]
HER2/neu, 3+	0/14 (0%)	5/26 (19%) [b]	.1426
PR	4/14 (29%)	1/26 (4%)	.0426 [a]
AR	14/14 (100%)	26/26 (100%)	1.0
CK5/6	10/12 (83%)	19/25 (76%)	1.0
p63	1/11 (9%)	1/25 (4%)	1.0
GATA3	13/14 (93%)	23/25 (92%)	1.0
Mammaglobin	8/14 (57%)	13/26 (50%)	1.0

[a] Statistically significant.
[b] Four of four exhibited *HER2* gene amplification.

Piris A et al, Human Pathol 2014

JOURNAL OF CUTANEOUS PATHOLOGY

SOX10 et tumeurs annexielles cutanées

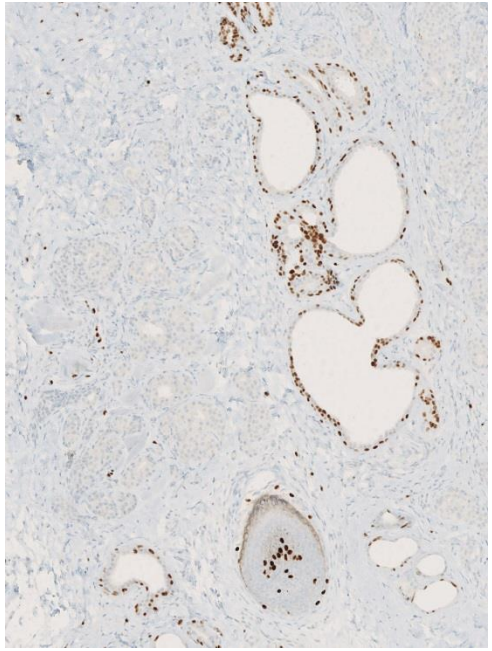


TABLE 5 Comparative SOX-10 immunohistochemistry of benign cutaneous adnexal tumors

Tumor type	Positivity (*n*, %)	4+	3+	2+	1+	0
Tumors with apocrine/eccrine differentiation	69/140 (49)	35	22	12	12	59
Cylindroma	17/20 (85)	12	5	0	1	2
Spiradenoma	19/20 (95)	17	2	0	1	0
Hidradenoma	2/20 (10)	1	1	0	0	18
Syringoma	0/20 (0)	0	0	0	0	20
Mixed tumor	20/20 (100)	3	11	6	0	0
Syringocystadenoma papilliferum	11/20 (55)	2	3	6	8	1
Poroma	0/20 (0)	0	0	0	2	18
Tumors with sebaceous differentiation	0/10 (0)	0	0	0	0	10
Sebaceoma	0/5 (0)	0	0	0	0	5
Sebaceous adenoma	0/5 (0)	0	0	0	0	5
Tumors with follicular differentiation	0/34 (0)	0	0	0	0	34
Pilomatricoma	0/10 (10)	0	0	0	0	10
Trichilemmoma	0/10 (0)	0	0	0	0	10
Trichoepithelioma	0/8 (0)	0	0	0	0	8
Trichoblastoma	0/6 (0)	0	0	0	0	6

TABLE 6 Comparative SOX10 immunohistochemistry of malignant cutaneous adnexal tumors

Tumor type	Positivity (*n*, %)	4+	3+	2+	1+	0
Microcystic adnexal carcinoma	1/5 (20)	0	0	1	1	3
Adenoid basal cell carcinoma	0/5 (0)	0	0	0	0	5
Squamoid eccrine ductal carcinoma	0/1 (0)	0	0	0	0	1
Porocarcinoma	0/2 (0)	0	0	0	1	1
Mucinous carcinoma	0/1 (0)	0	0	0	0	1
Endocrine mucin-producing sweat gland carcinoma	0/1 (0)	0	0	0	0	1
Extramammary Paget's disease	0/4 (0)	0	0	0	0	4
Matrical carcinoma	0/3 (0)	0	0	0	1	2
Sebaceous carcinoma	0/7 (0)	0	0	0	0	7
Digital papillary adenocarcinoma	1/1 (100)	0	1	0	0	0

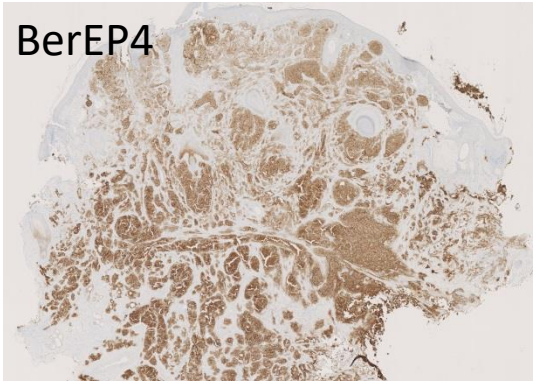
Evangelista, J Cutan Pathol 2017

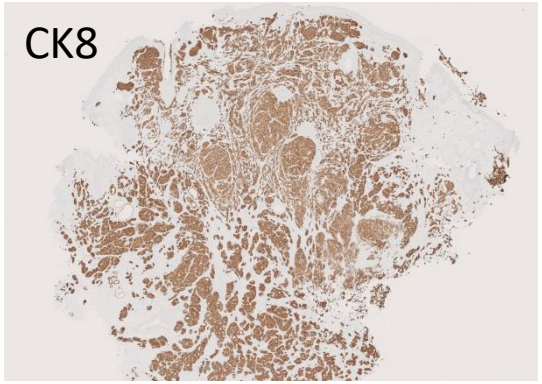
IHC des tumeurs sudorales

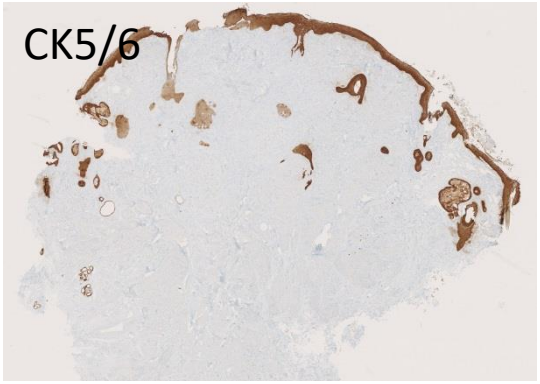
1) Morphologie et clinique d'abord – diagnostic différentiel

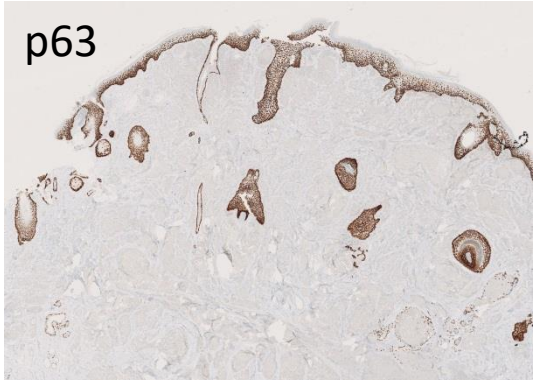
2) Connaitre le phénotype « habituel » des différents sous-types

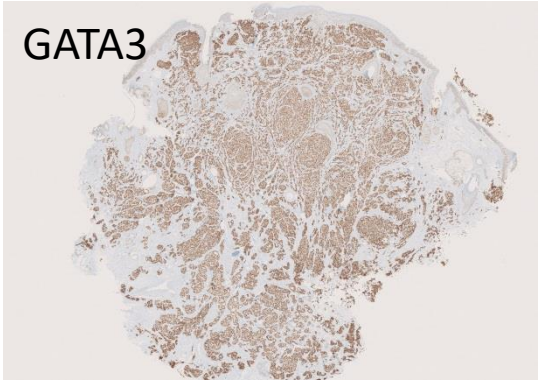
3) Objectif de l'IHC ?
   - Diagnostic de sous-type
   - Eliminer une métastase
   - (Chercher une différenciation annexielle dans un carcinome peu différencié)

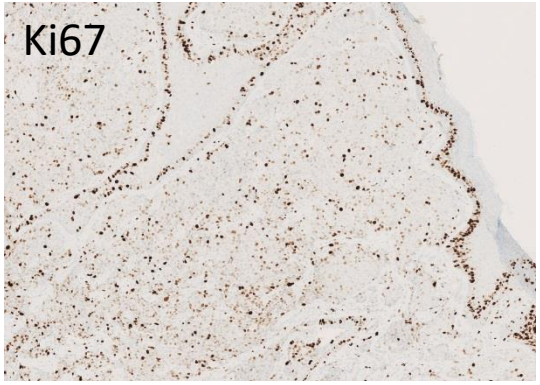

BerEP4


CK8

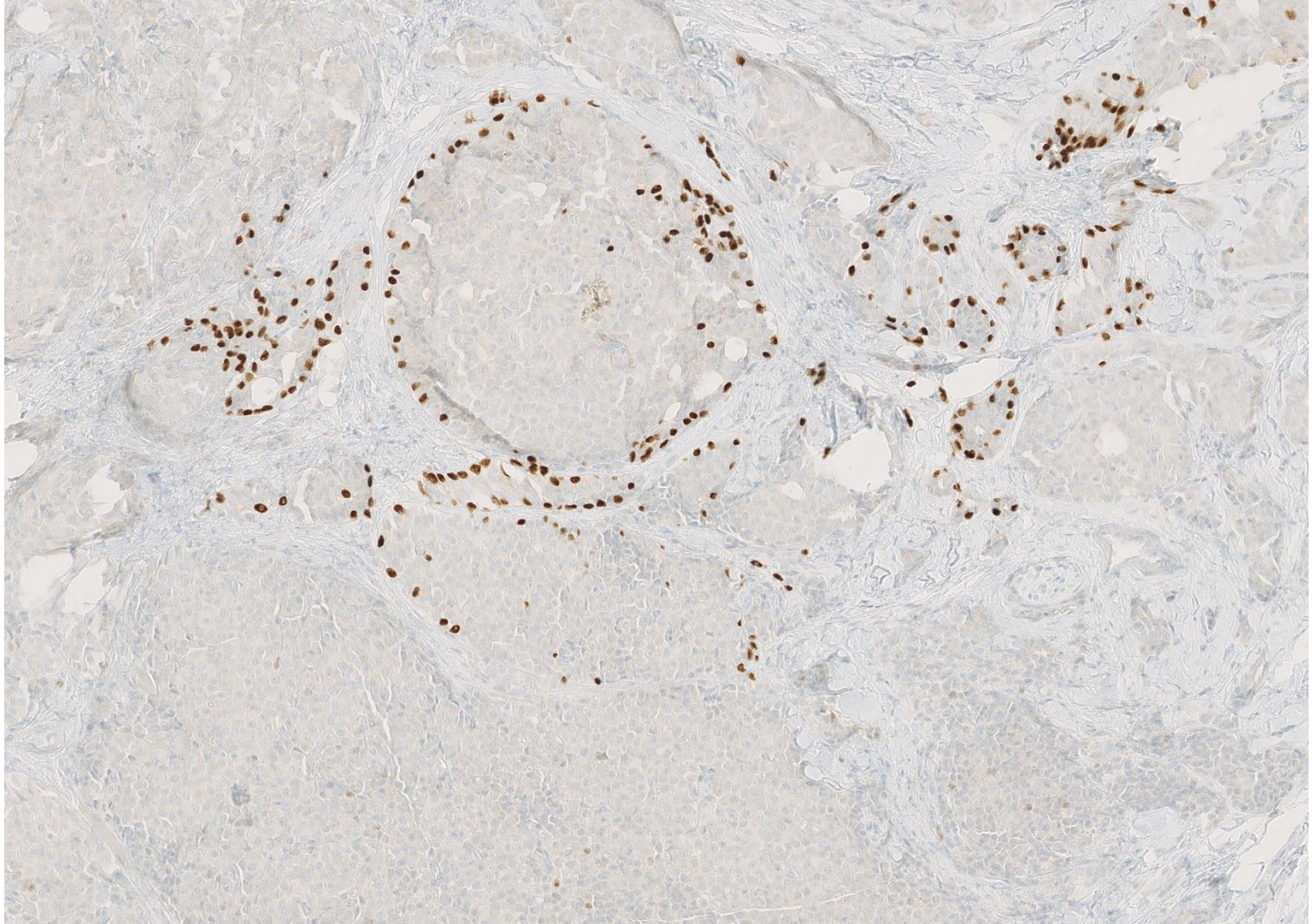

CK5/6


p63


GATA3


Ki67

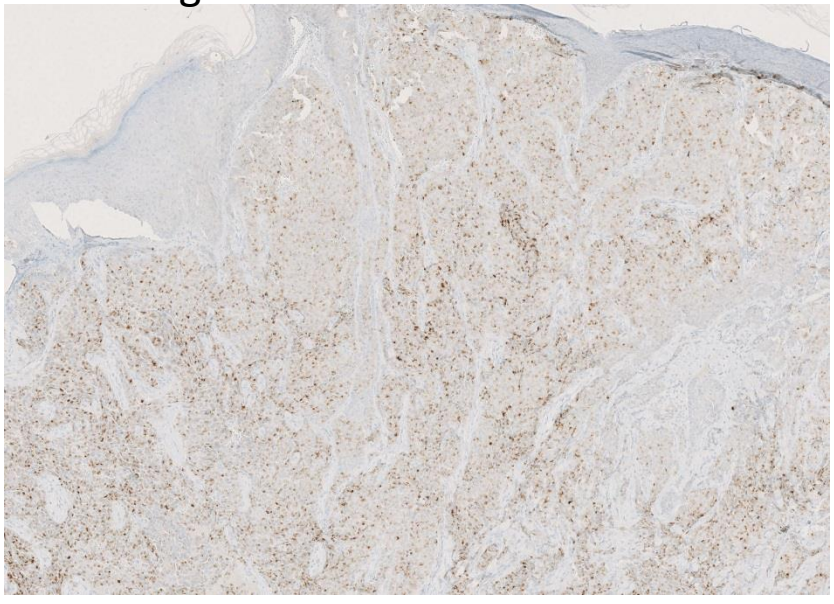
p63



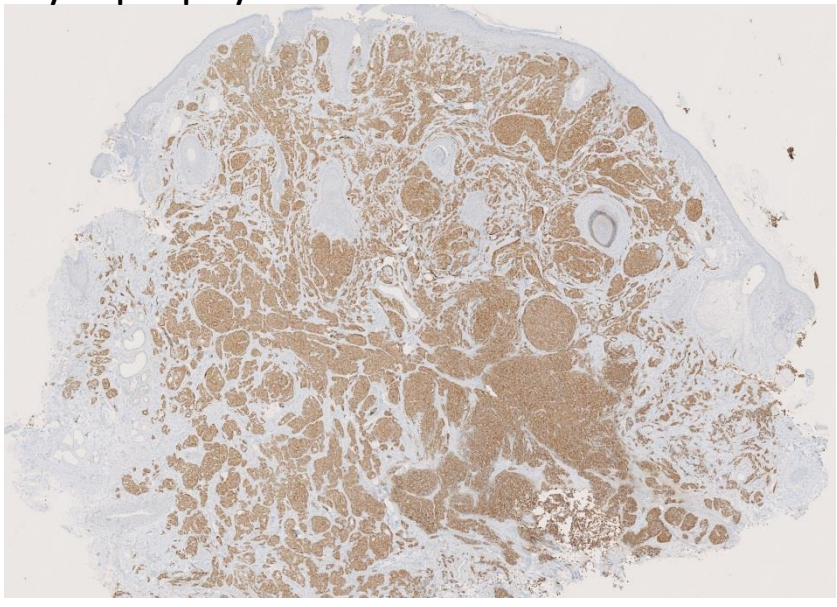
OMS 2018 des Tumeurs cutanées : nouvelle classification des tumeurs annexielles

Tumeurs à différenciation apocrine et eccrine	
Malignes	**Bénignes**
Adénocarcinome annexiel SAI Carcinome annexiel microkystique Porocarcinome Carcinome sur spiradénome, cylindrome ou spiradénocylindrome (ancien : spiradénocarcinome) Tumeur mixte maligne Hidradénocarcinome Carcinome mucineux **Carcinome sudoral endocrine à production de mucine** Adenocarcinome papillaire digital Carcinome adénoïde kystique Carcinome apocrine Carcinome eccrine ductal squamoïde Syringocystadénocarcinome papillifère **Carcinome secrétoire** Carcinome cribriforme Carcinome histiocytoïde/à cellules en bague à châton	Hidrocystome/cystadénome Syringome Porome Syringofibroadénome Hidradénome Spiradénome Cylindrome Adénome tubuleux Syringocystadénome papillifère Tumeur mixte Myoépithéliome

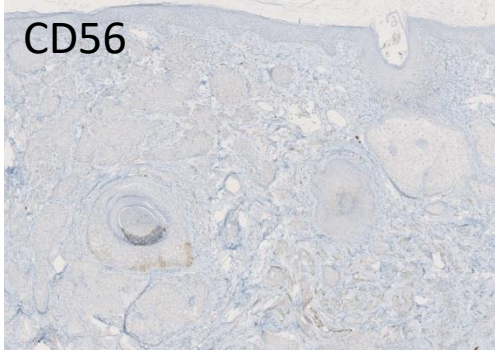
Chromogranine



Synaptophysine

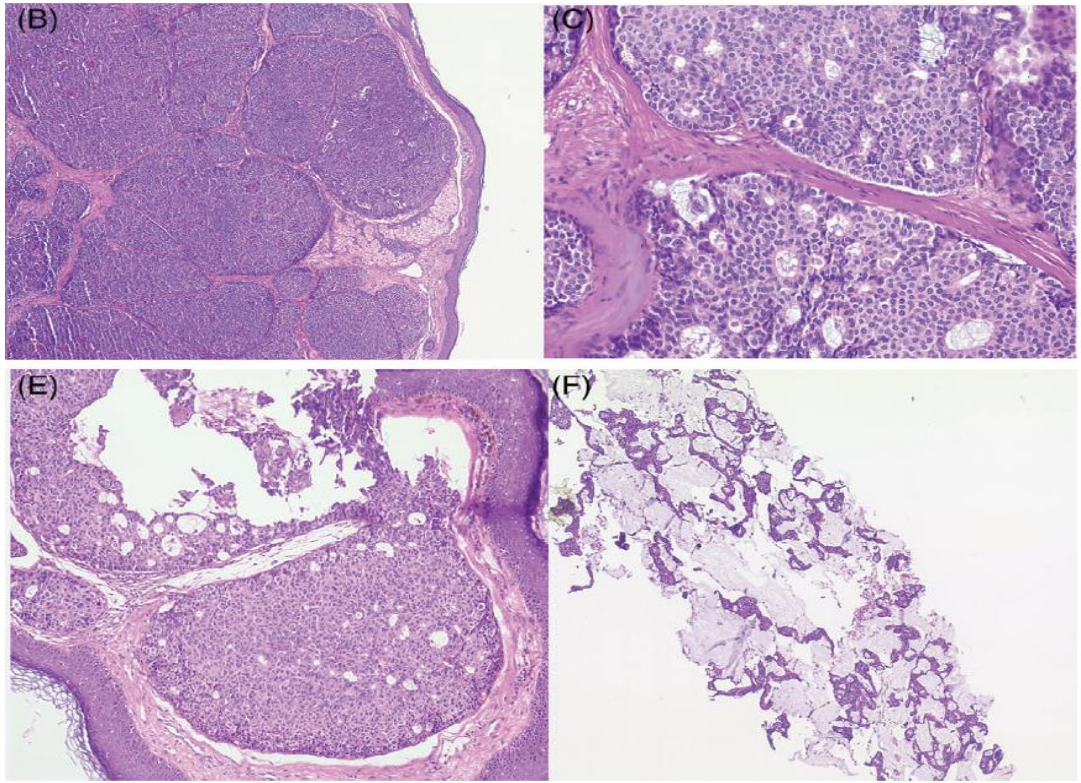


CD56



Carcinome sudoral endocrine
à production de mucine

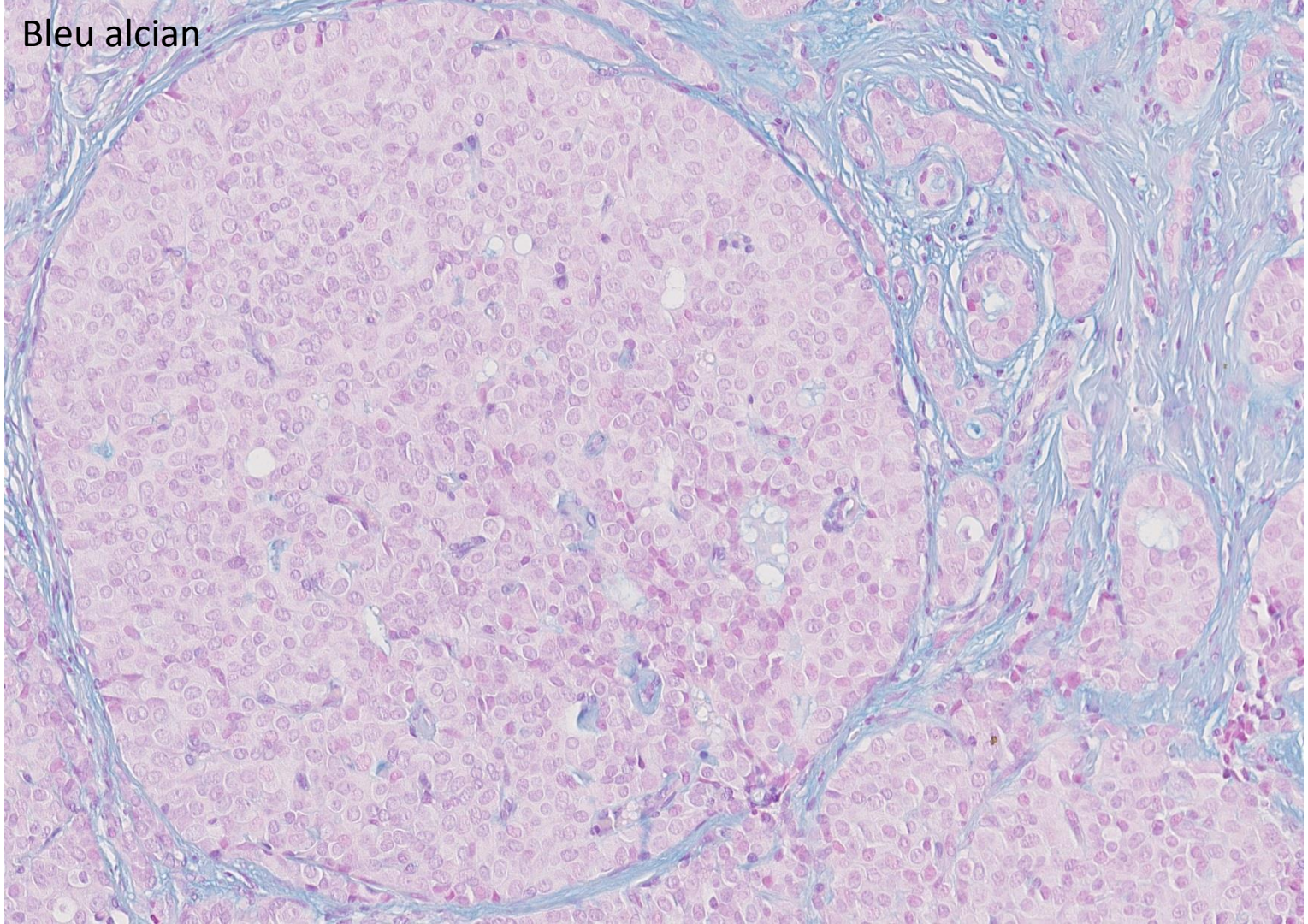
Endocrine mucin-producing sweat gland carcinoma

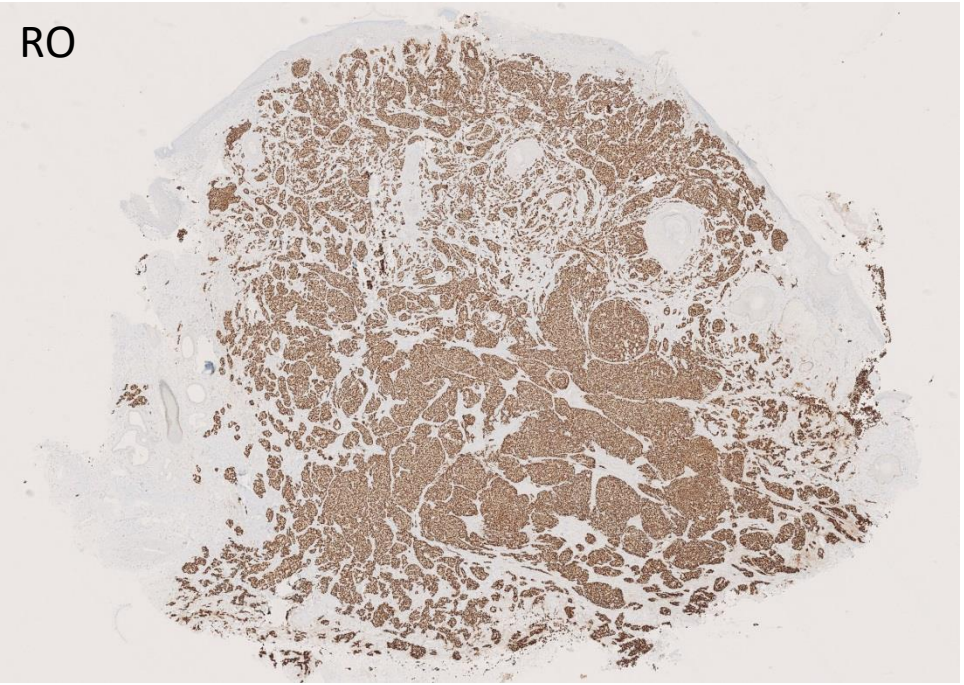


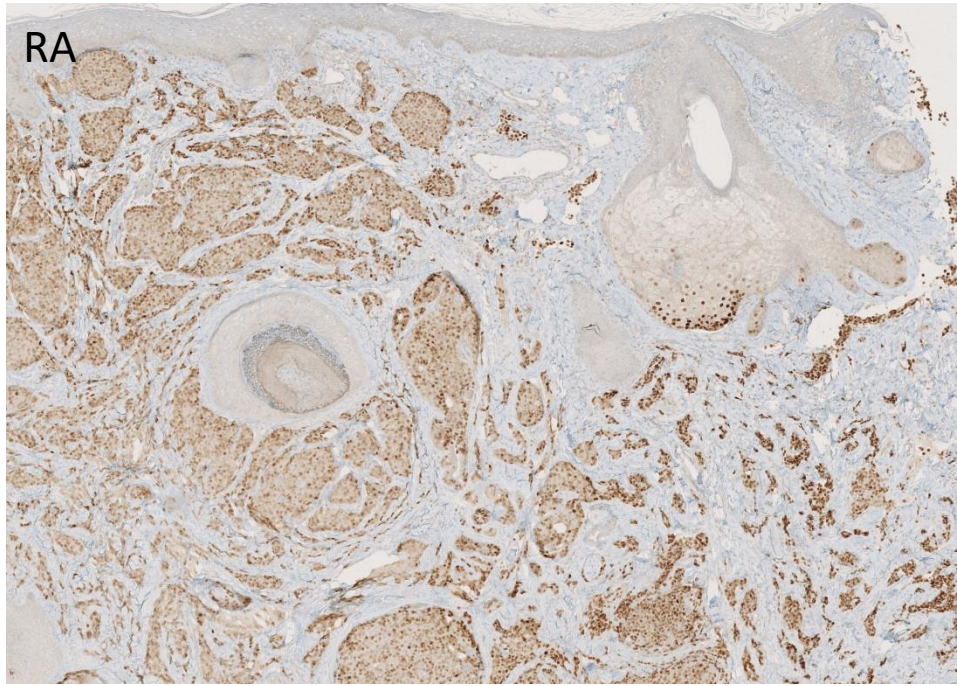
BerEP4 + CK7+ RE+ RP+ RA+
Synaptophysine + Chromogranine +

Question non résolue : précurseur de l'adénocarcinome mucineux ?

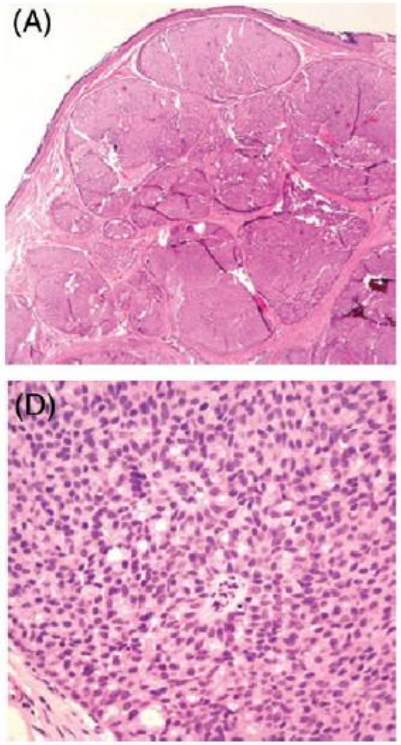
J Cutan Pathol. 2018;45:674–680.


Bleu alcian


RO

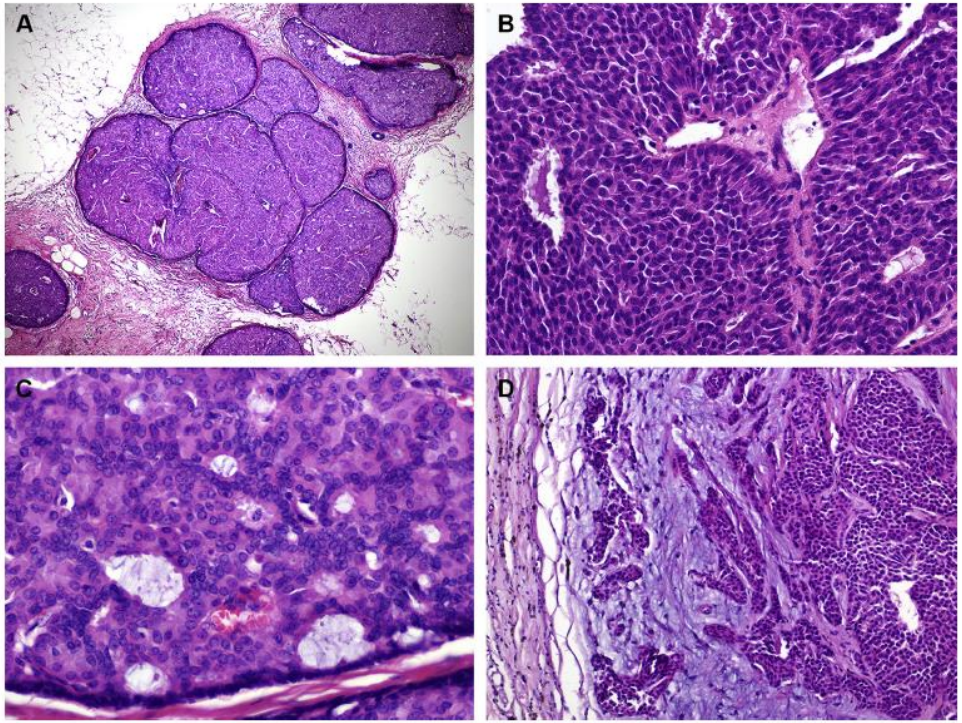

RA

Endocrine mucin-producing sweat gland carcinoma



Qin, J Cutan Pathol 2018

Analogue cutané du carcinome papillaire solide du sein



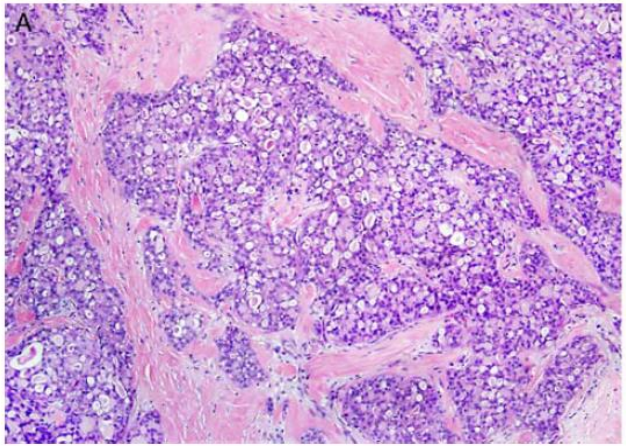
Guo, Breast 2016

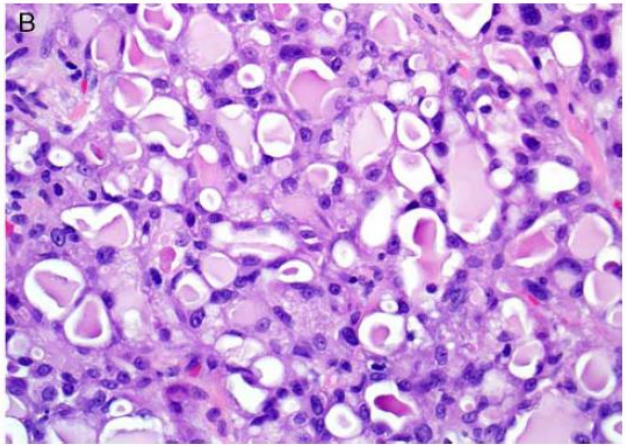
Secretory Carcinoma of the Skin Harboring *ETV6* Gene Fusions

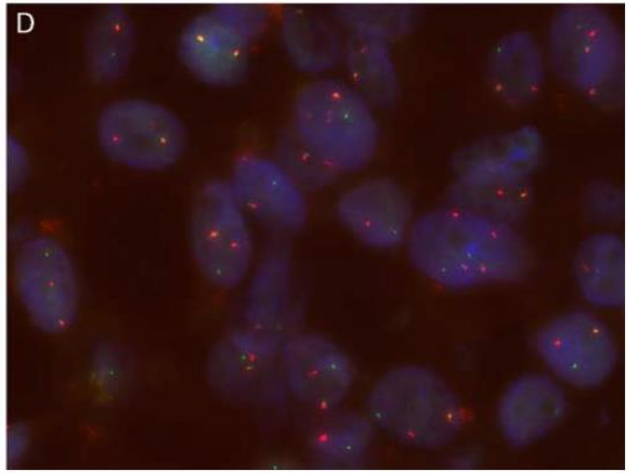
A Cutaneous Analogue to Secretory Carcinomas of the Breast and Salivary Glands

Justin A. Bishop, MD,† Janis M. Taube, MD,*‡ Albert Su, MD,† Scott W. Binder, MD,† Dmitry V. Kazakov, MD,§‖ Michal Michal, MD,§ and William H. Westra, MD*†‡*

(*Am J Surg Pathol* 2017;41:62–66)

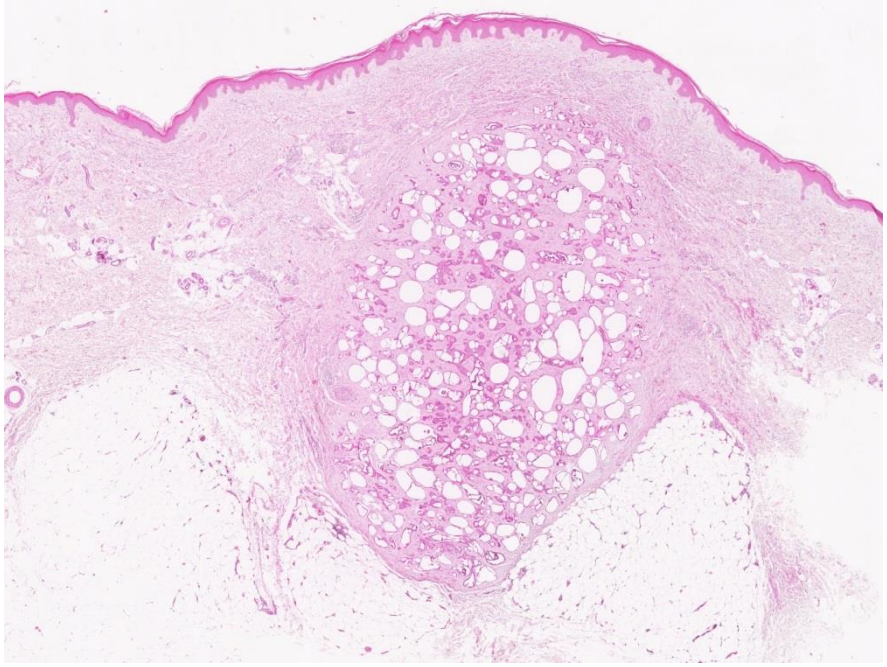


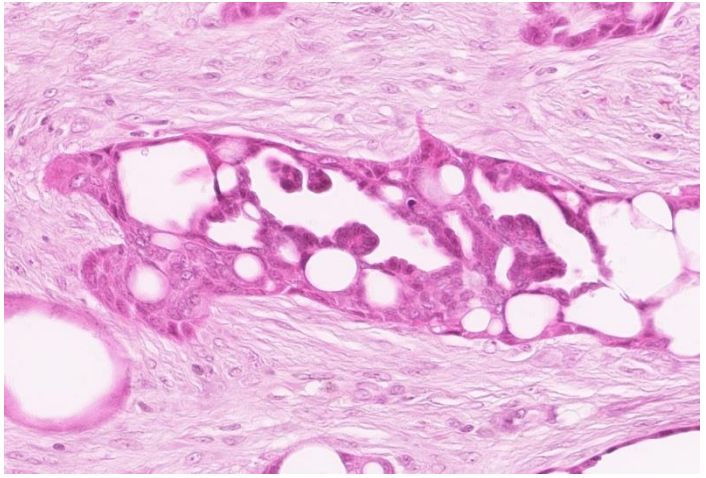


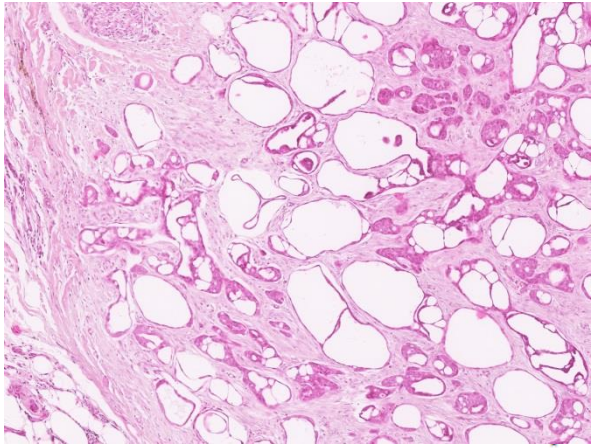


Primary cutaneous cribriform apocrine carcinoma: A clinicopathologic and immunohistochemical study of 26 cases of an under-recognized cutaneous adnexal neoplasm

Arno Rütten, MD,[a] Heinz Kutzner, MD,[a] Thomas Mentzel, MD,[a] Markus Hantschke, MD,[a] Fritof Eckert, MD,[b] Jorge Angulo, MD,[c] Jose Luis Rodríguez Peralto, MD,[d] and Luis Requena, MD[c]
Friedrichshafen and Munich, Germany; and Madrid, Spain







(J Am Acad Dermatol 2009;61:644-51.)

Réseau INCa Cancers rares CARADERM

CARADERM
www.caraderm.org

CAncers **RA**res
DERMatologiques

National coordination: L. MORTIER (Lille)

Carcinomes annexiels

T. Jouary
B. Cribier
M. Battistella

CBC avancé

N. Basset-Seguin

Carcinome de Merkel

P. Saiag

GCC
Groupe de Cancérologie Cutanée

INSTITUT NATIONAL DU CANCER

Pourquoi un réseau Carcinomes annexiels ?

- Nombreuses questions cliniques non résolues
  - Chirurgie : marges ? Chirurgie micrographique ?
  - Ganglion sentinelle ?
  - Imagerie : laquelle, quand ?
  - Suivi : comment, combien de temps ?
  - Maladie métastastique : chimiothérapie, thérapie ciblée, immunothérapie ?

- Challenge diagnostique pour les pathologistes
  - Sous-types nombreux et évolutifs
  - Critères de malignité non consensuels

- Collaboration nécessaire pour le développement d'études thérapeutiques

CARADERM : Double lecture ACP

CARADERM

Coordination

M. Battistella

CHU Saint Louis

Réunions nationales

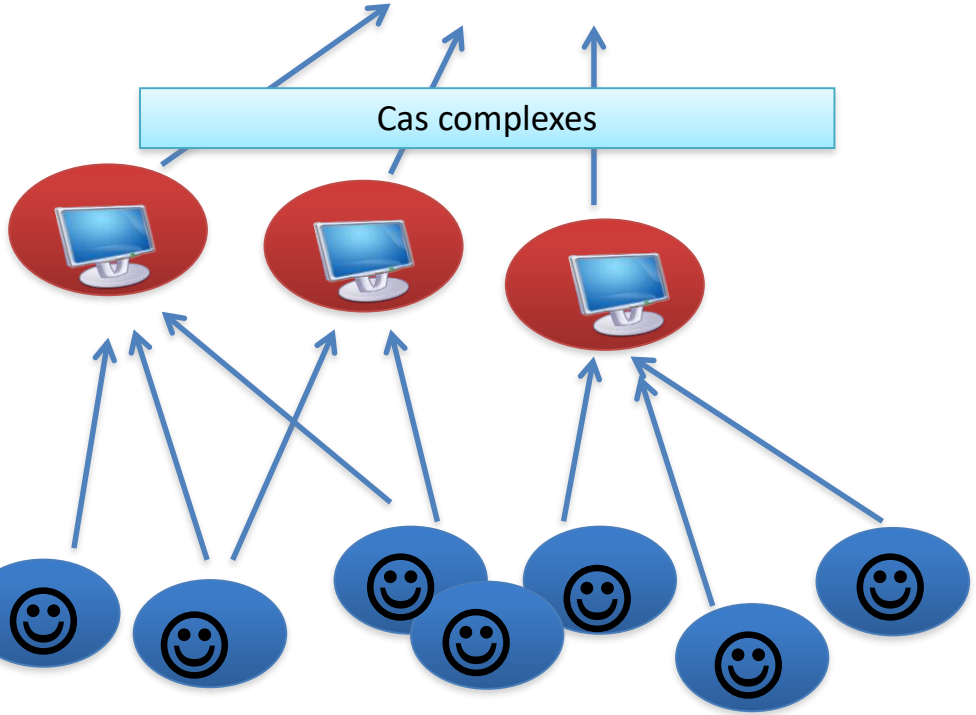
CHU Strasbourg

B. Cribier

Double lecture

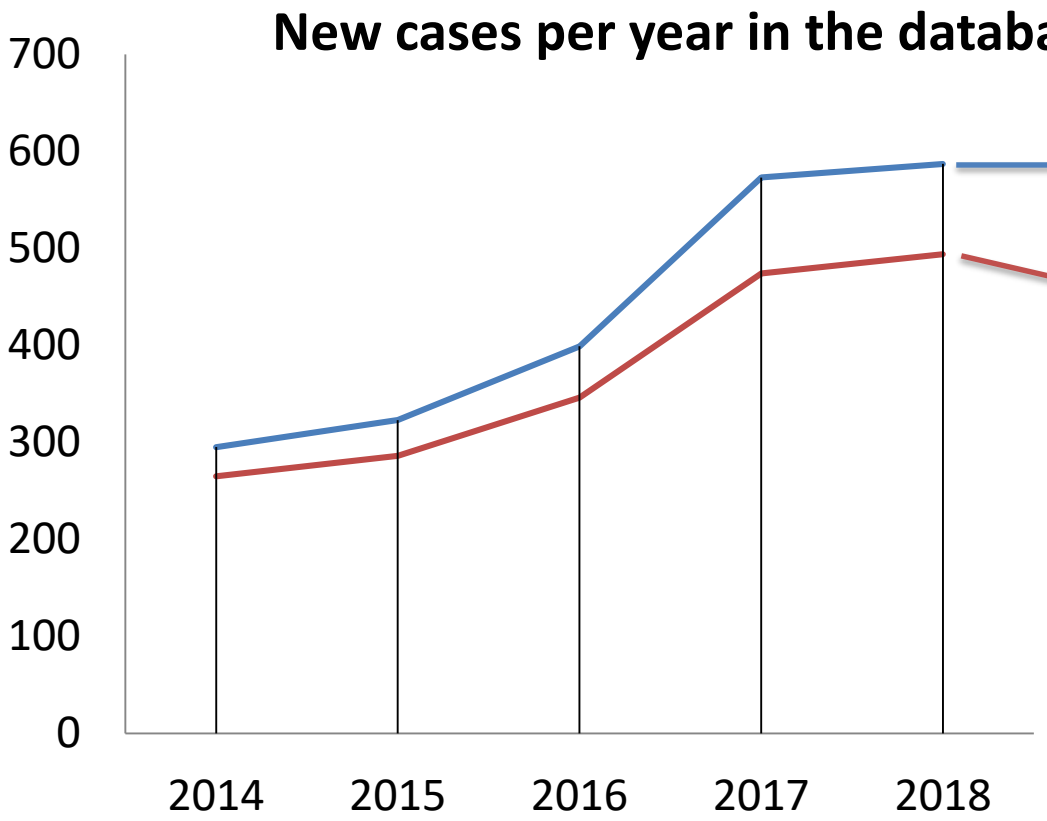
Centres régionaux (CRE)

Cas complexes



Première lecture

Activité – Nouveaux cas de carcinomes annexiels



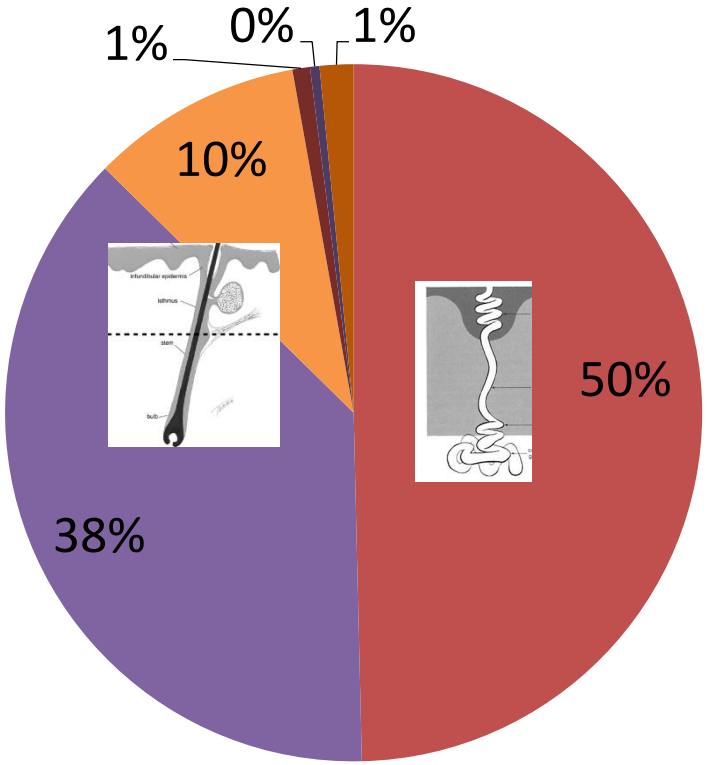
2177 cas (2014-2018)

86 % avec double lecture

Incidence calculée (2018):
8.89/million-année

CARADERM

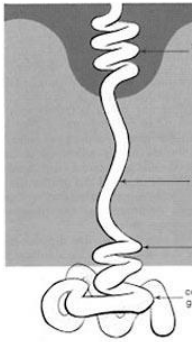
Distribution des sous-types de carcinomes annexiels

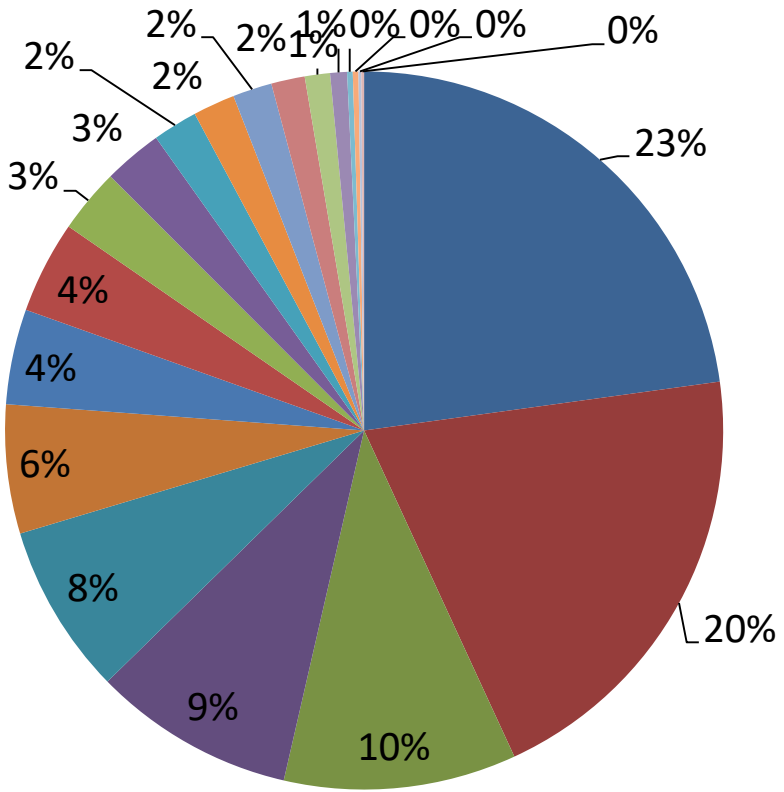


2014-2018

CARADERM

Distribution des sous-types de carcinome sudoral





- Porocarcinoma
- Extramammary Paget disease
- Microcystic adnexal carcinoma
- Hidradenocarcinoma
- Sweat gland adenocarcinoma NOS
- Apocrine carcinoma
- Adenoid cystic carcinoma
- Digital papillary adenocarcinoma
- Mucinous carcinoma
- Poroid hidradenocarcinoma
- Eccrine ductal squamoid carcinoma

2014-2018

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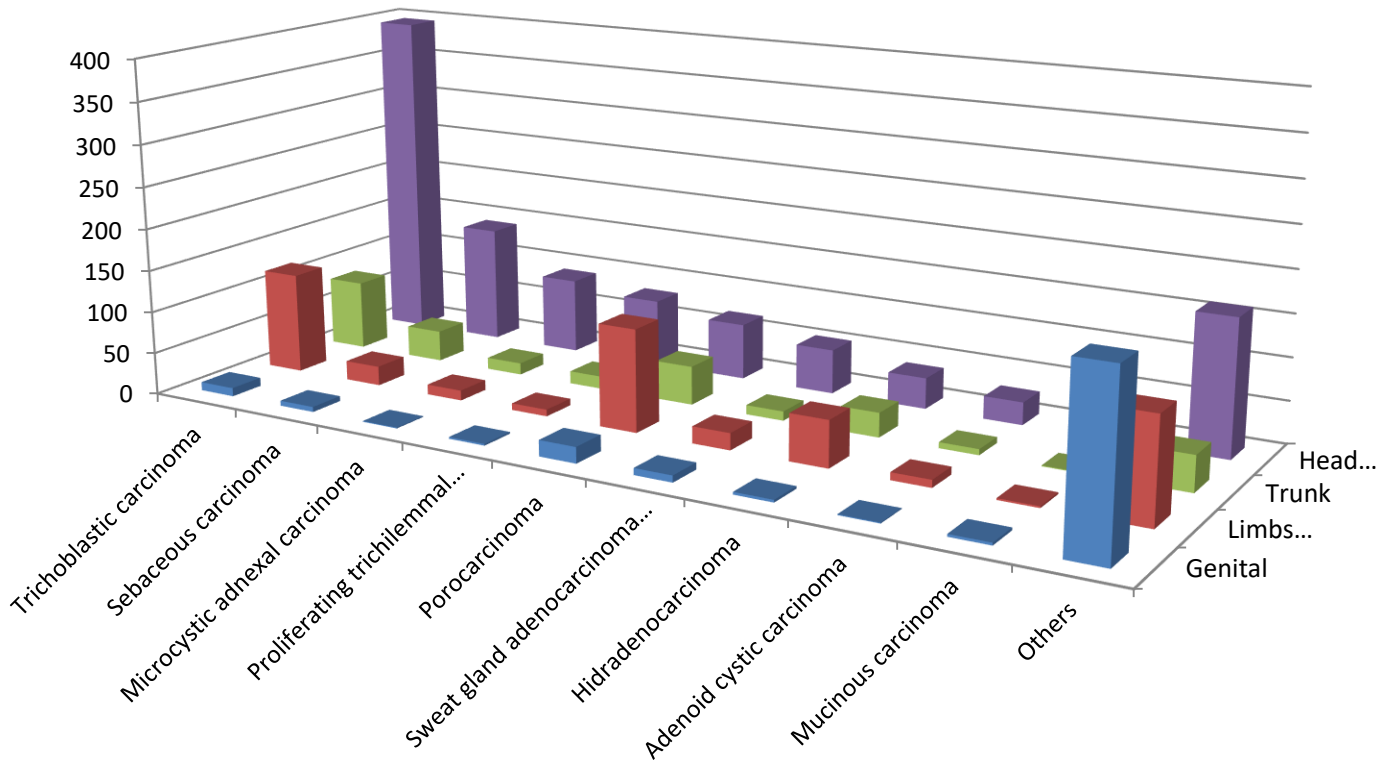
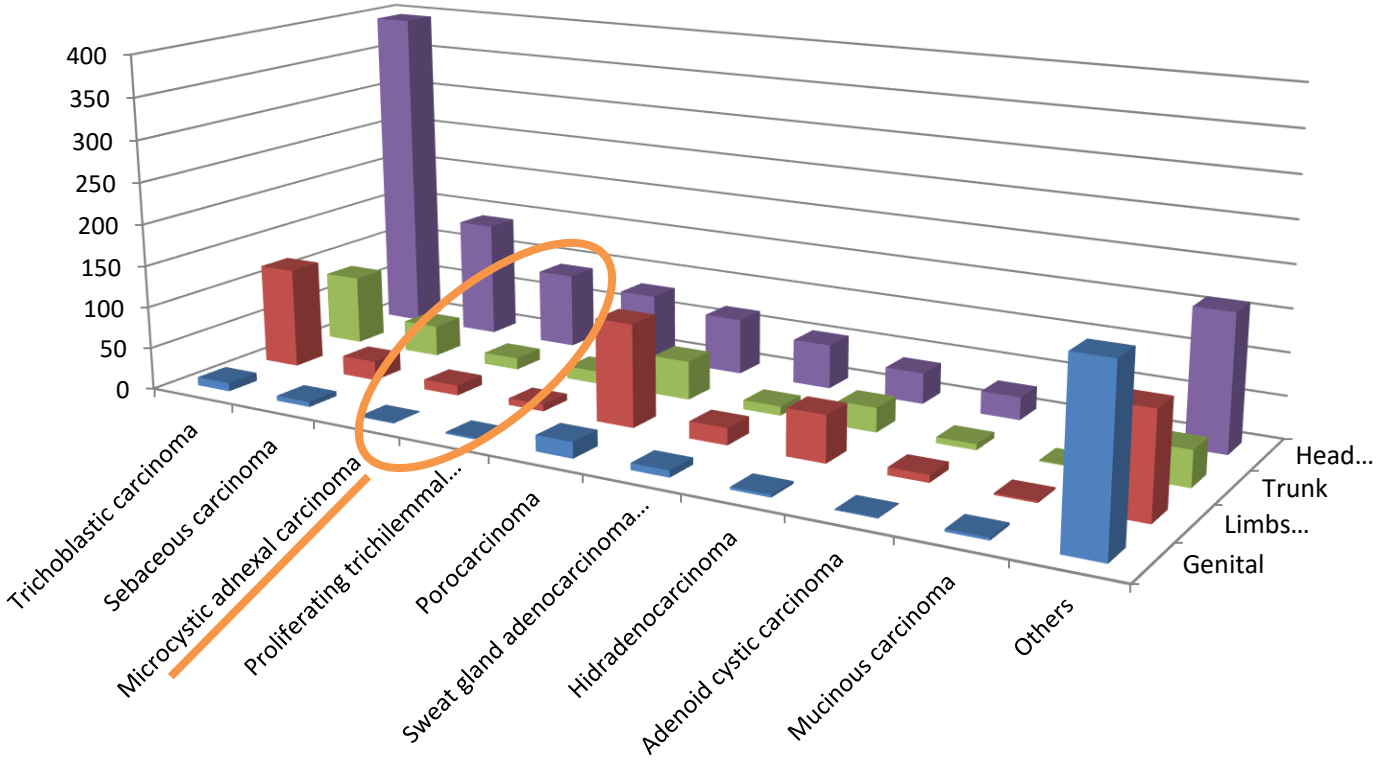
Carcinomes annexiels : analyse des topographies



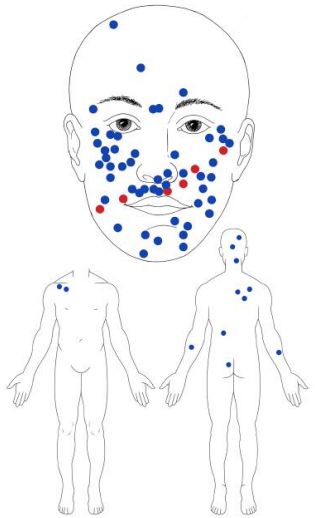
N=2177
Data 2014-18

CARADERM

Adnexal carcinoma: anatomical area analysis



Demographics and outcomes of microcystic adnexal carcinoma



King et al, J Am Acad Dermatol 2018

N=2177
Data 2014-18

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Synthèse : Tumeurs sudorales

- Nombreux sous-types bénins et malins
- Parenté moléculaire / morphologique
  - Tumeurs salivaires
  - Tumeurs mammaires
- IHC : prudence dans la prescription et l'interprétation
- Malignité : évaluation parfois difficile
  - ATUMP
- Caraderm : domaine avec le plus de discordance diagnostique