Trento, May 10, 2024

Diagnostic Challenges with Epithelial Tumors

KJ Busam, MD

Diagnostic Challenges with Sweat Gland Carcinomas

- Is a tumor benign or malignant (or uncertain)
- Is the tumor a primary skin cancer or a metastasis?
- If primary carcinoma, what is the risk for recurrence?
  - Conservative vs wide excision
  - Sentinel lymph node biopsy
- Is the carcinoma of sweat gland or other cutaneous origin

Basic Approach: Benign or Malignant

Adenoma

- Circumscribed
- Cytologically bland
- Cell elements
  - Duct epithelial surrounded by myoepithelial cells
  - Myoepithelial cells may dominate

Carcinoma

- Infiltrative
- Cytologically atypical
- Cell elements
  - Ductal carcinomas:
    No myoepithelial cells = carcinoma
  - Caution: Some carcinomas have epithelial and myoepithelial cells

Ductal vs Epithelial/Myoepithelial Carcinoma

Ductal Carcinomas

- Ductal carcinoma, NOS
- Mucinous carcinoma
- Cribriform carcinoma
- Secretory carcinoma

Epithelial – Myoepithelial Carcinomas

- Adenoid cystic carcinoma
- Malignant mixed tumor
- Cylindro/spiradenocarcinoma
- Digital papillary adenocarcinoma

CME Article

The Utility of Myoepithelial Cell Layer Identification in Adnexal Carcinomas

Jose A. Plaza, MD, Catherine Chung, MD,† Mark Wick, MD,‡ Martin Sangueza, MD,§ and Alejandro Gru, MD¶*

Basic Approach: Risk for Metastasis

Low or none

- Cribriform carcinoma
- Endocrine MP-carcinoma
- Pure mucinous carcinoma
- MAC

Risk for metastasis

- Porocarcinoma
- Hidradenocarcinoma
- Cylindro/spiradenocarcinoma
- EMPD, invasive
- Mixed mucinous carcinoma
- Digital papillary adenocarcinoma

Basic Approach: Is there a precursor or not?

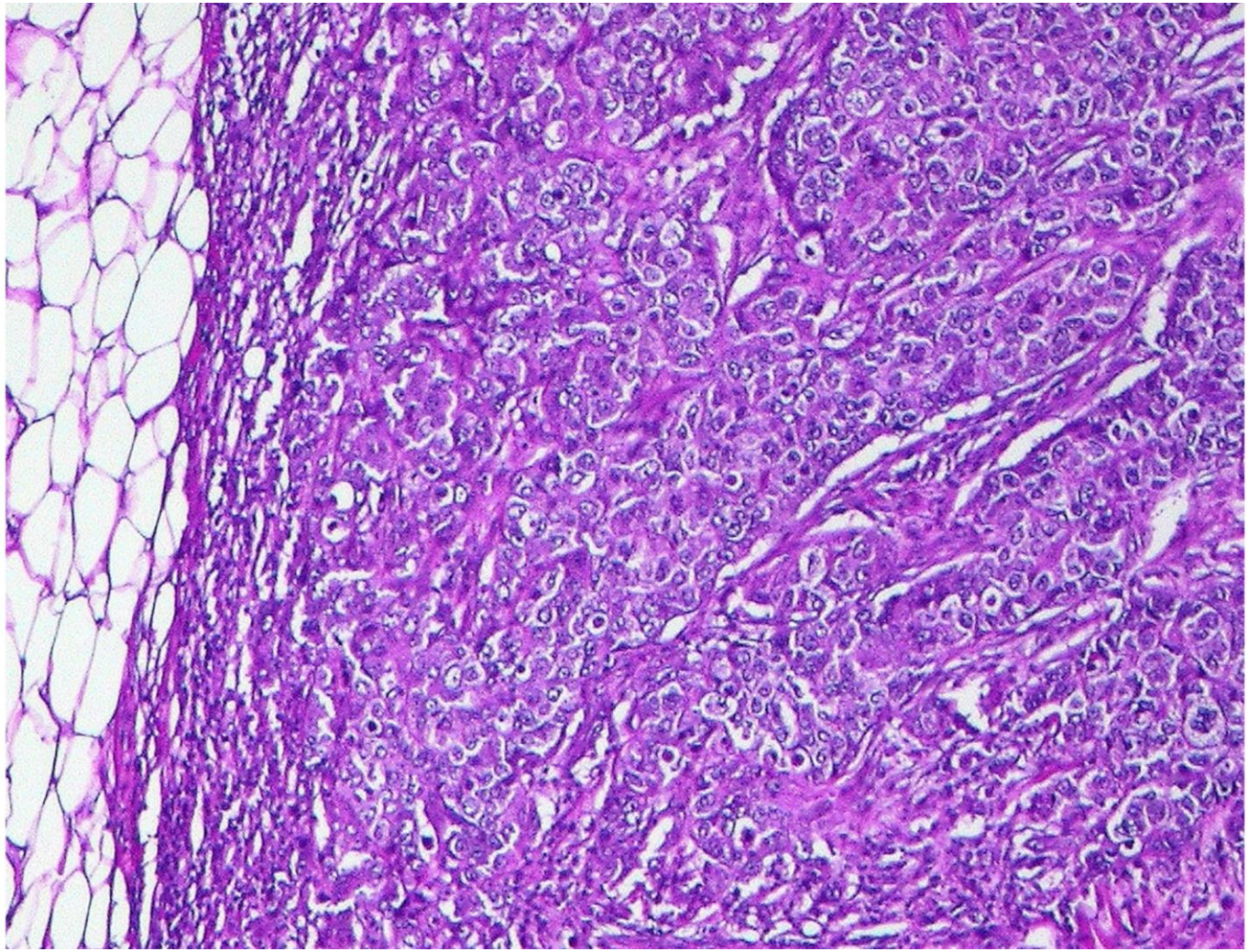
Adenoma-associated

- Carcinoma ex cylindroma
- Carcinoma ex spiradenoma
- Carcinoma ex hidradenoma
- Carcinoma ex poroma
- Carcinoma ex mixed tumor

De Novo

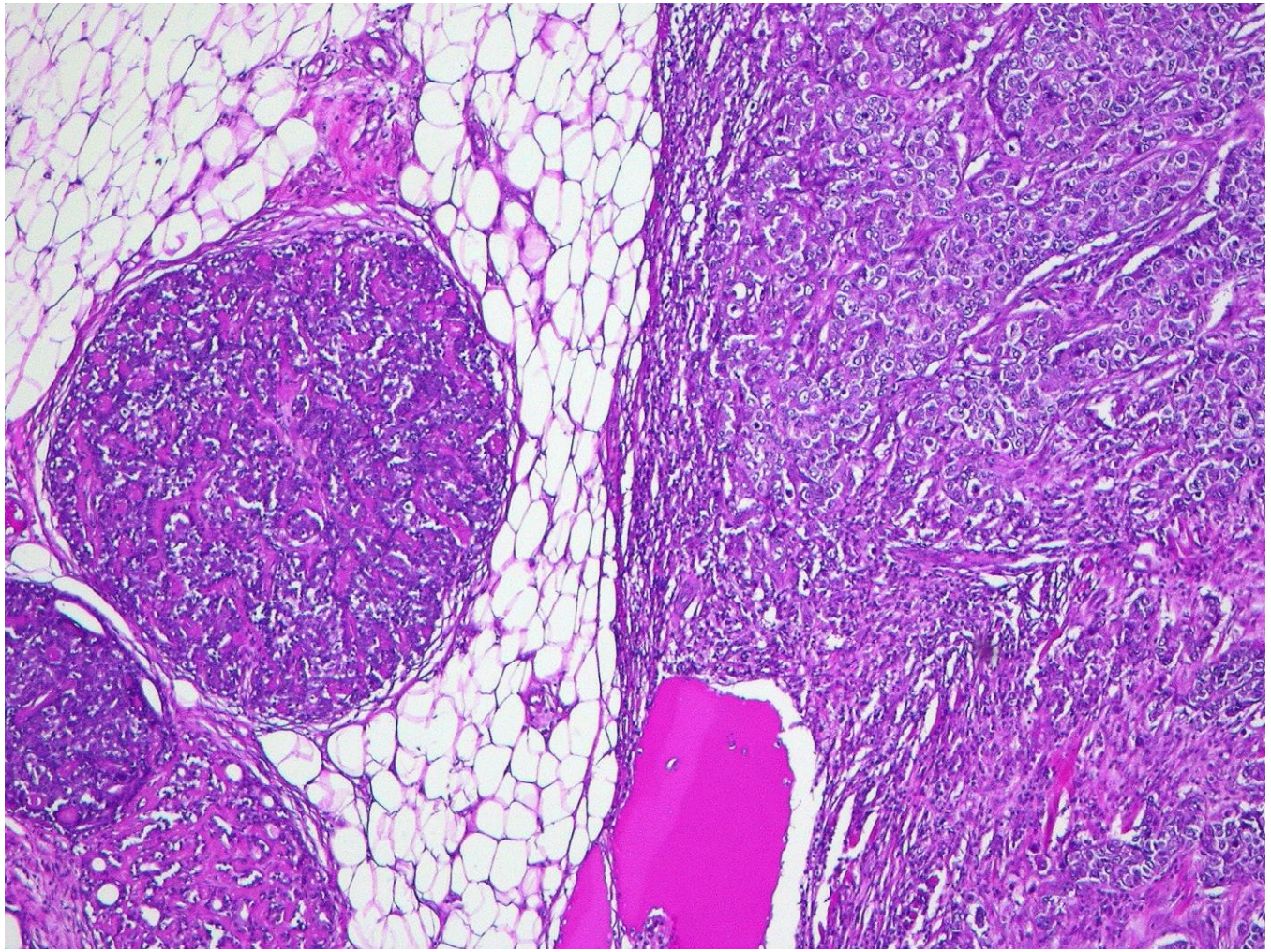
- Mucinous carcinoma
- Endocrine mucin-prod. carcinoma
- Papillary Digital Adenocarcinoma
- Cribriform carcinoma
- Adenoid cystic carcinoma

Adenocarcinoma in Subcutis



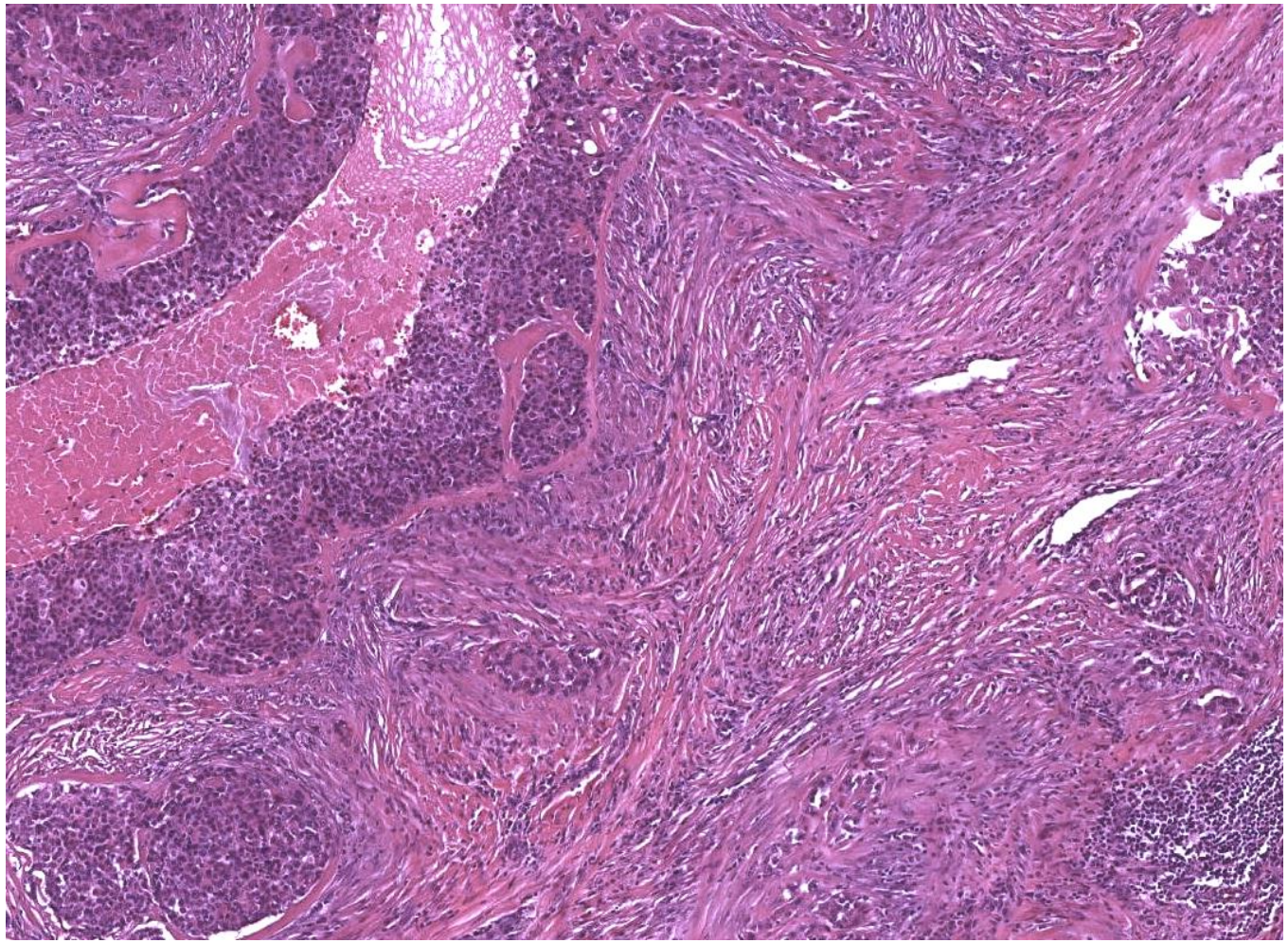
Carcinoma ex Spiradenoma (Spiradenocarcinoma)

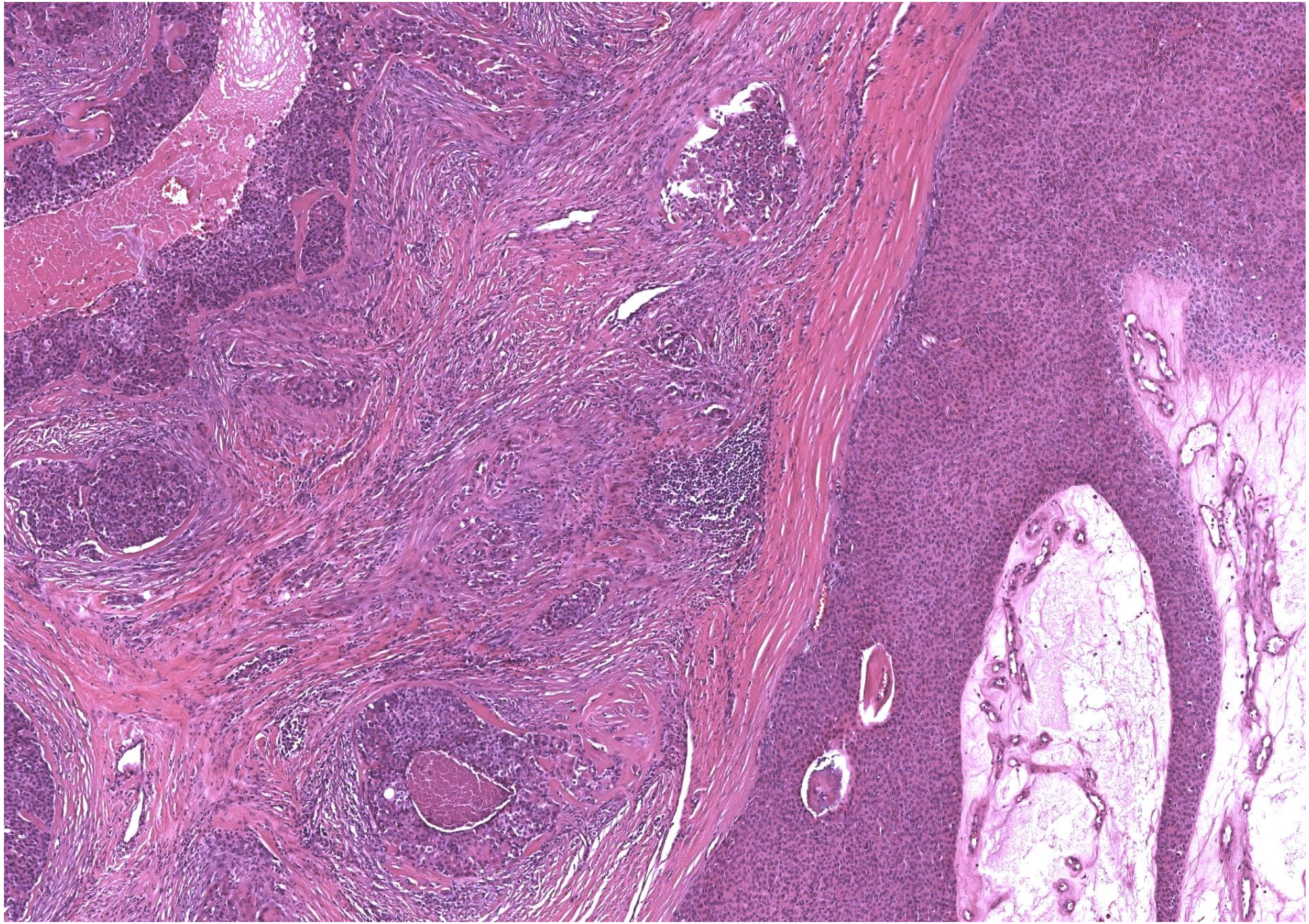
Spiradenoma



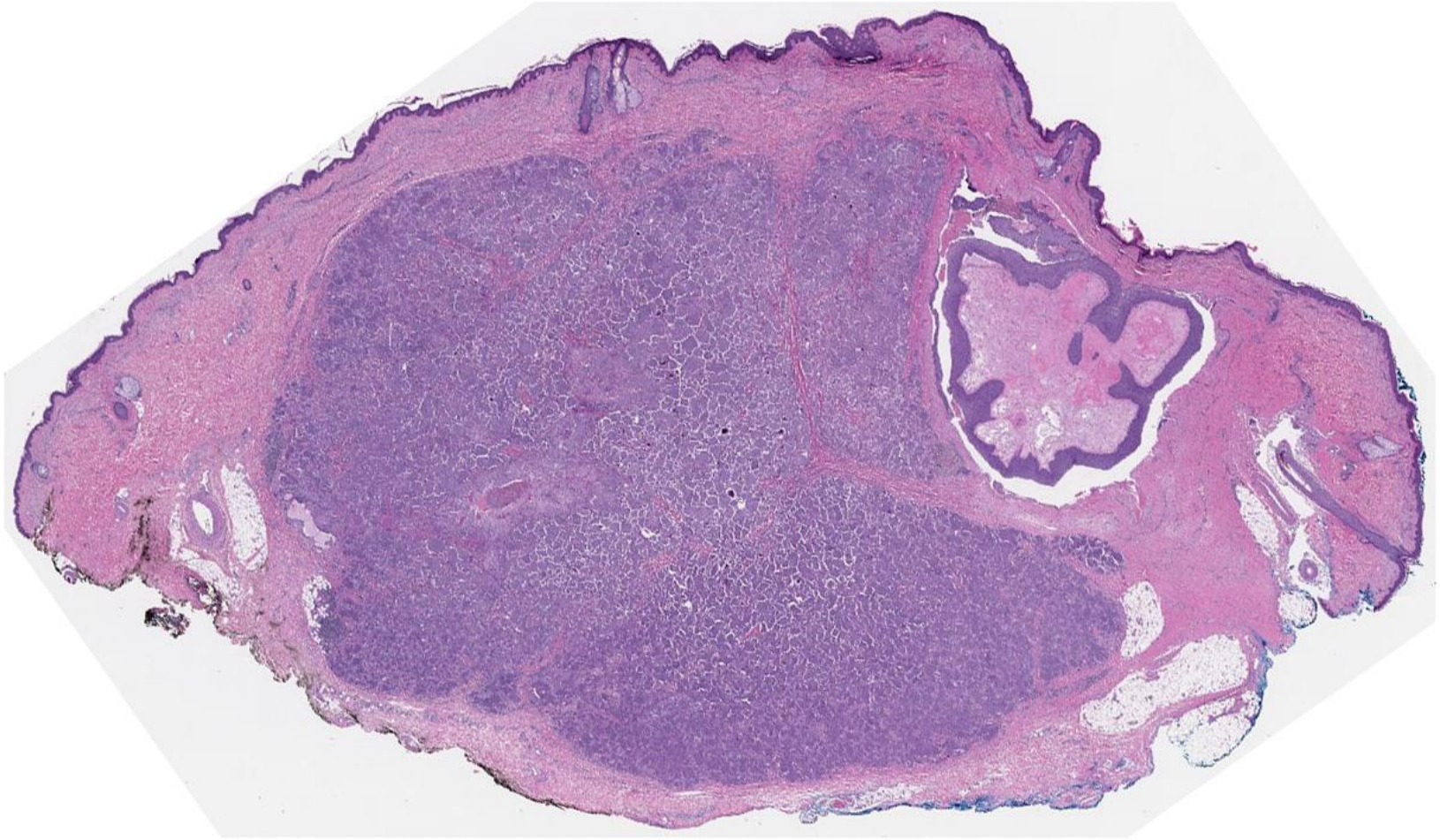
Adenocarcinoma

What is Your Diagnosis?





Porocarcinoma (carcinoma a/w poroma)



Molecular Approach – Gene Fusions

cancers

MDPI

Review

Recent Advances on Immunohistochemistry and Molecular Biology for the Diagnosis of Adnexal Sweat Gland Tumors

Nicolas Macagno [1,2,3,*], Pierre Sohier [1,4,5], Thibault Kervarrec [1,6,7], Daniel Pissaloux [8,9], Marie-Laure Jullie [1,10], Bernard Cribier [1,11] and Maxime Battistella [1,6,12]

Table 2. Summary of the most frequent molecular alterations in sweat gland neoplasms.

Diagnosis	Molecular Alteration	Frequency (%)
Adenoid cystic carcinoma	*MYB::NFIB* fusion *MYBL1::NFIB* fusion	73–83% 20–23%
Cutaneous mixed tumor	*PLAG1* fusion *HMGA2* fusion	33% unknown
Cylindroma	*CYLD* inactivation	near 100%
Spiradenoma	*CYLD* inactivation *ALPK1* p.V1092A mutation	29% 43%
Spiradenocarcinoma	*CYLD* inactivation *ALPK1* p.V1092A mutation	8% 33%
Hidradenoma	*CRTC1::MAML2* fusion *CRTC3::MAML2* fusion	50–75% rare
Hidradenocarcinoma	*CRTC1::MAML2* fusion	unknown
Myoepithelioma	*EWSR1* fusion *FUS* fusion	82% 18%
Poroma	*YAP1* fusion *NUTM1* fusion	88% 17–55%
Porocarcinoma	*YAP1* fusion *NUTM1* fusion	8–63% 11–54%
Secretory carcinoma	*ETV6:NTRK3* fusion	near 100%
Syringocystadenoma papilliferum and tubular adenoma	*BRAF* p.V600E mutation *HRAS* p.G13R mutation *KRAS* p.G12D mutation	50–64% 7–26% rare

Exploring Diagnostic Opportunities

The Journal of Clinical Investigation

CONCISE COMMUNICATION

Recurrent YAP1-MAML2 and YAP1-NUTM1 fusions in poroma and porocarcinoma

Shigeki Sekine,[1,2] Tohru Kiyono,[3,4] Eijitsu Ryo,[2] Reiko Ogawa,[2] Susumu Wakai,[1] Hitoshi Ichikawa,[5] Koyu Suzuki,[6] Satoru Arai,[7] Koji Tsuta,[8] Mitsuaki Ishida,[8] Yuko Sasajima,[9] Naoki Goshima,[10] Naoya Yamazaki,[11] and Taisuke Mori[1,2]

Received: 21 September 2020 | Revised: 2 November 2020 | Accepted: 16 November 2020

DOI: 10.1111/cup.13924

ORIGINAL ARTICLE

JCP JOURNAL OF CUTANEOUS PATHOLOGY WILEY

Utility of YAP1 and NUT immunohistochemistry in the diagnosis of porocarcinoma

Eleanor Russell-Goldman | Jason L. Hornick | John Hanna

Received: 7 May 2016 | Revised: 12 January 2017 | Accepted: 13 January 2017

DOI 10.1111/cup.12904

WILEY JCP JOURNAL OF CUTANEOUS PATHOLOGY

ORIGINAL ARTICLE

MYB, CD117 and SOX-10 expression in cutaneous adnexal tumors

Mara Therese P. Evangelista | Jeffrey P. North

Limited Sensitivity and/or Specificity

Porocarcinoma with YAP1::NUTM1 Fusion

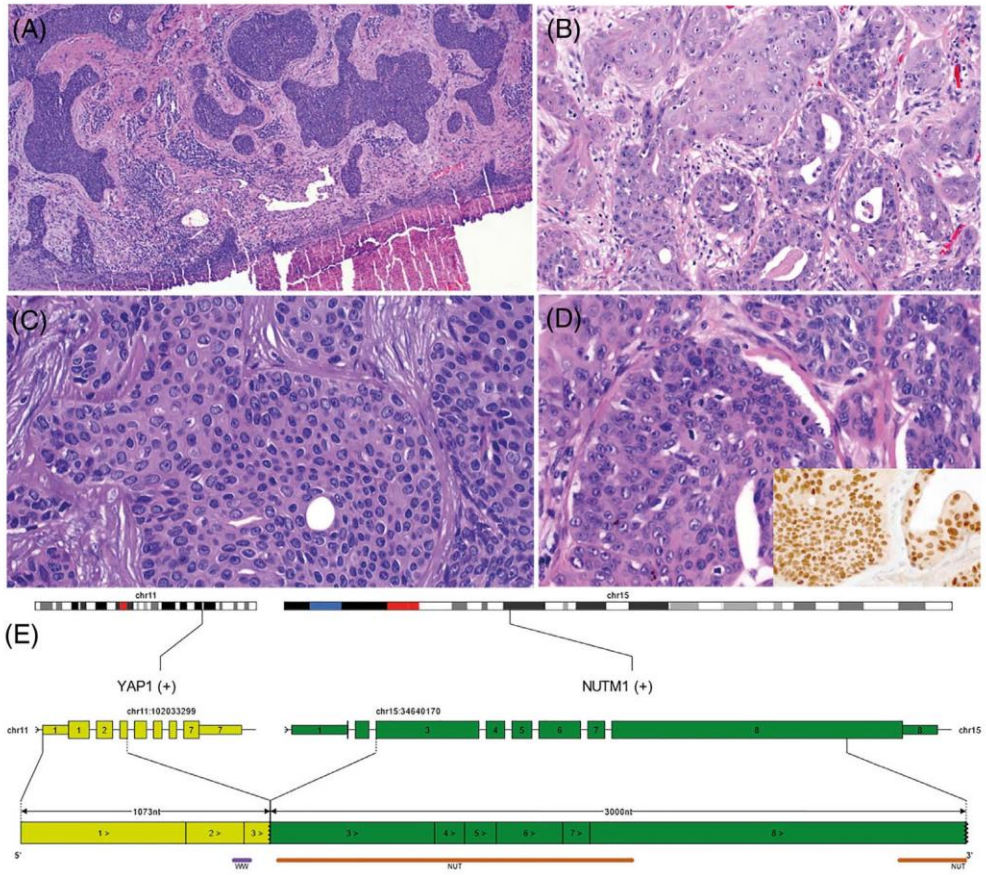
Received: 17 January 2022 | Revised: 27 January 2022 | Accepted: 1 February 2022
DOI: 10.1002/gcc.23031

REVIEW ARTICLE

WILEY

Fusion-positive skin/adnexal carcinomas

Abbas Agaimy



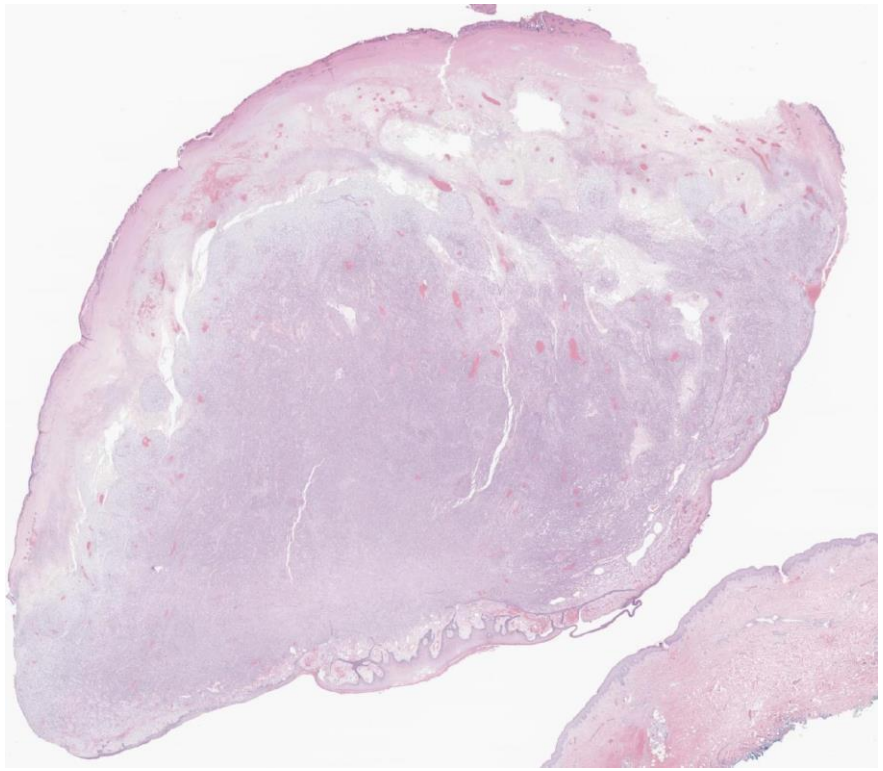
Received: 20 August 2023 | Revised: 16 November 2023 | Accepted: 29 November 2023
DOI: 10.1111/cup.14575

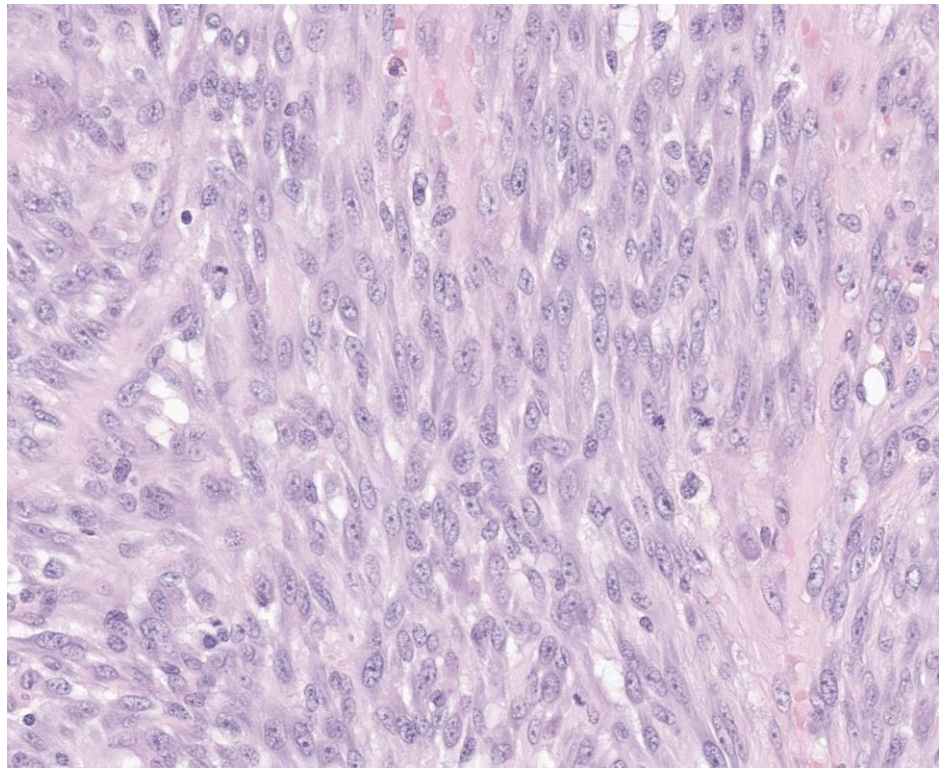
CASE STUDY

JCP JOURNAL OF CUTANEOUS PATHOLOGY WILEY

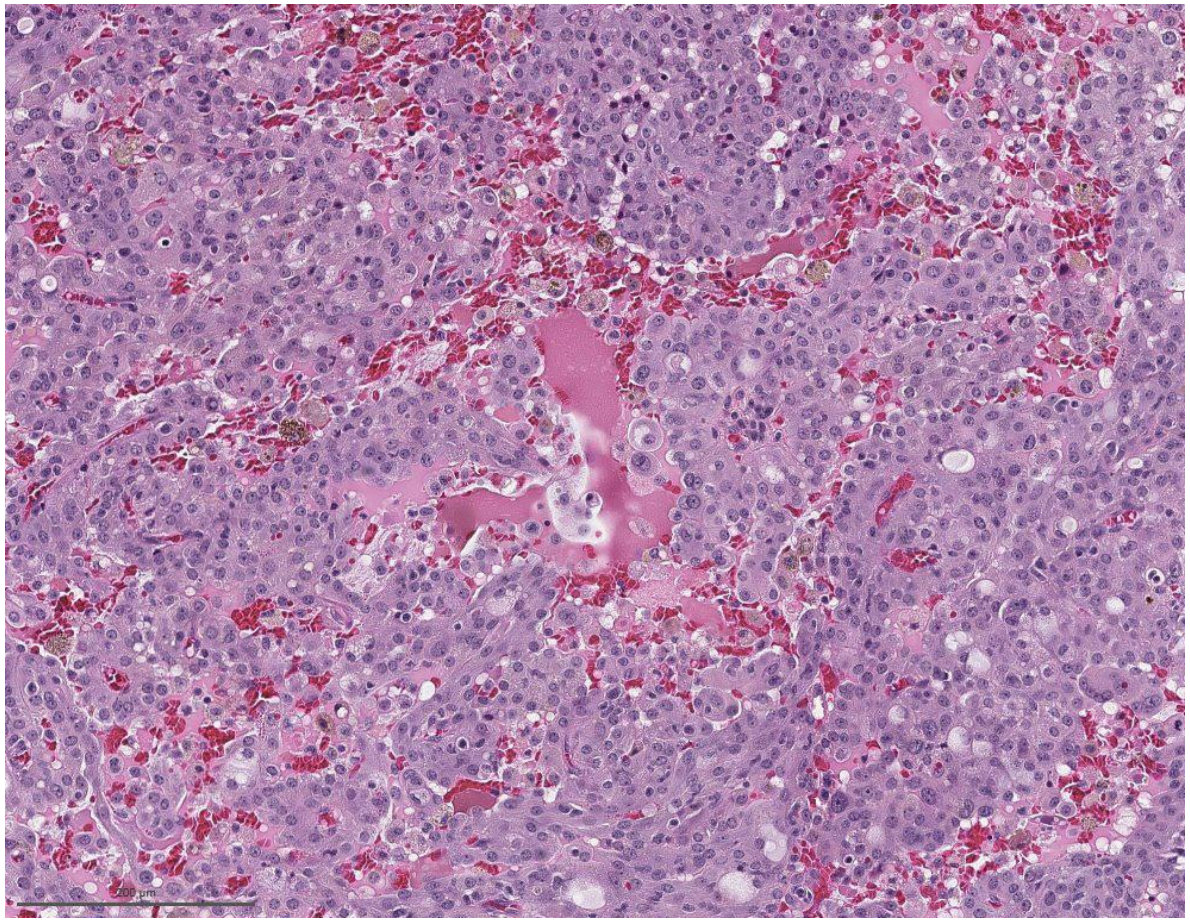
Spindle cell porocarcinoma with a novel *YAP1::MAML3* fusion

Philippa Li MD[1] | Klaus J. Busam MD[2]





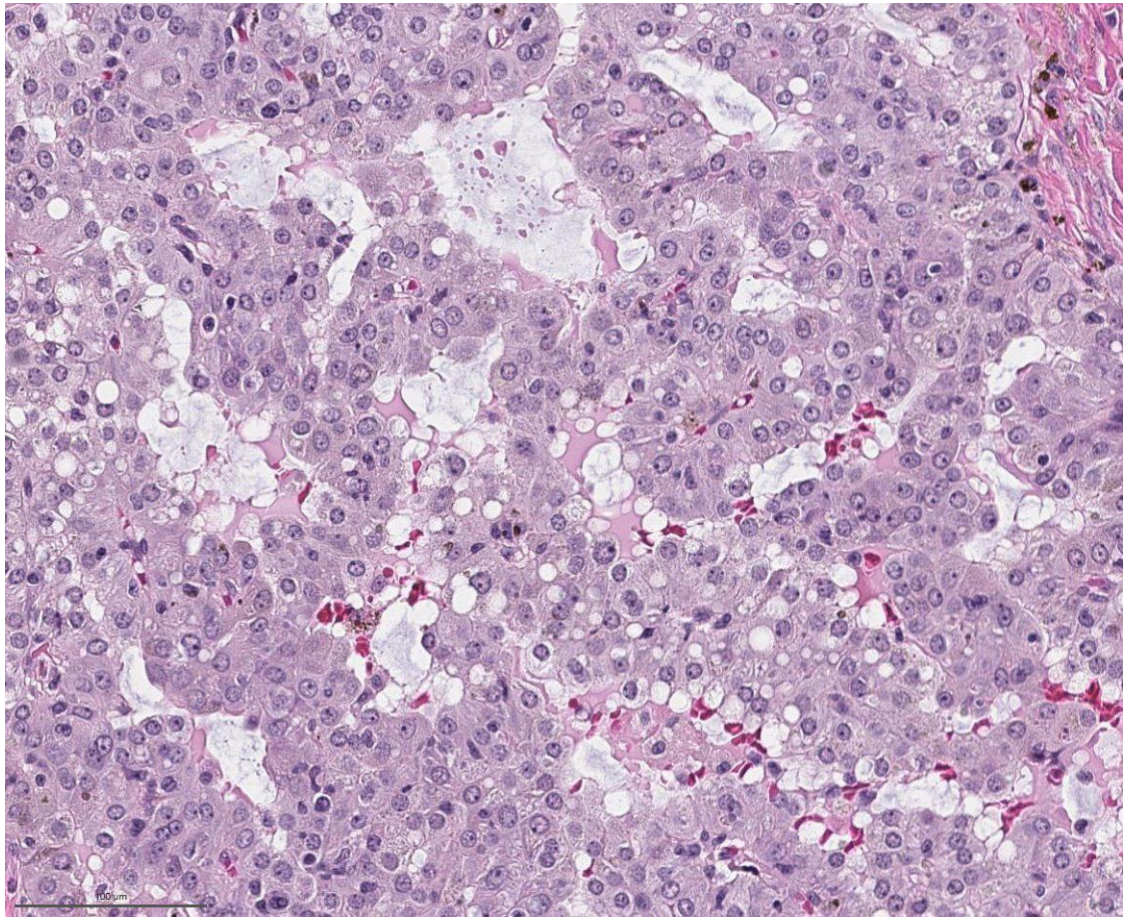
Secretory Carcinoma

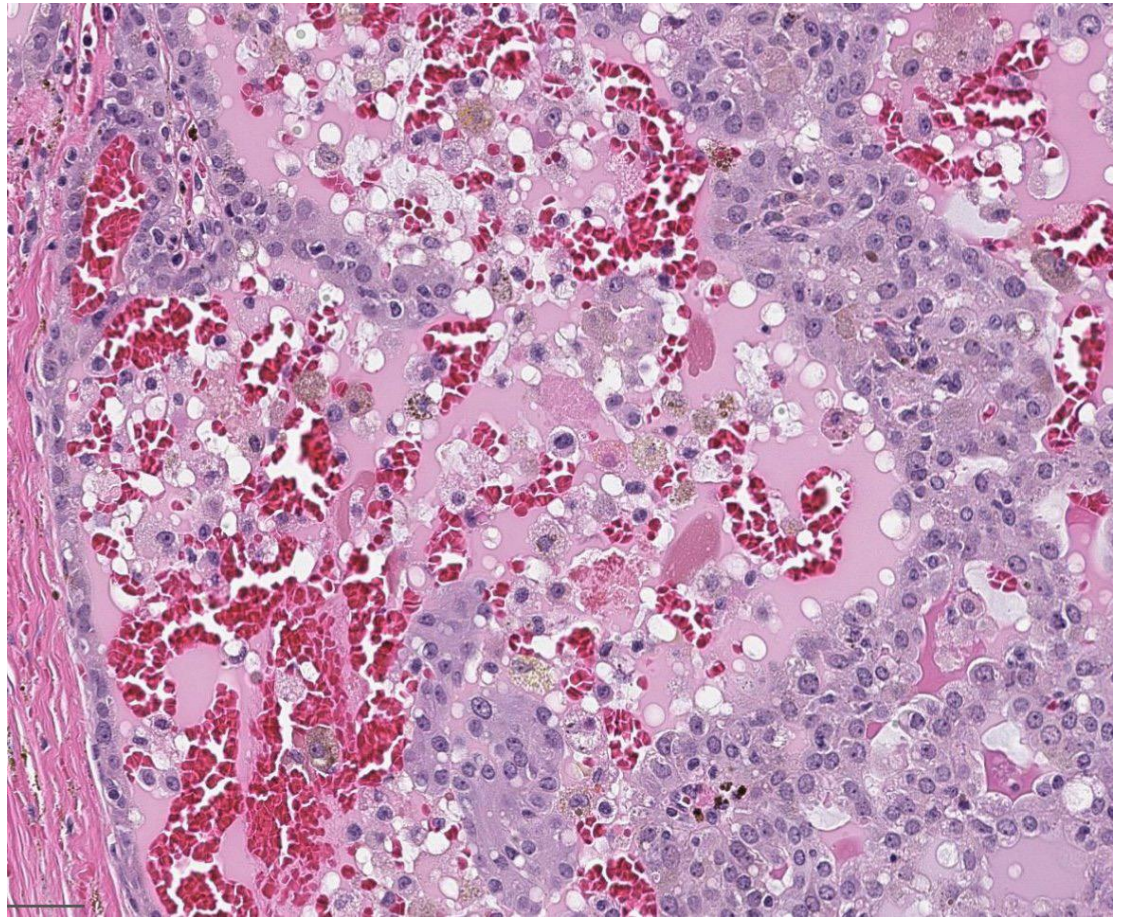


Variant of apocrine carcinoma

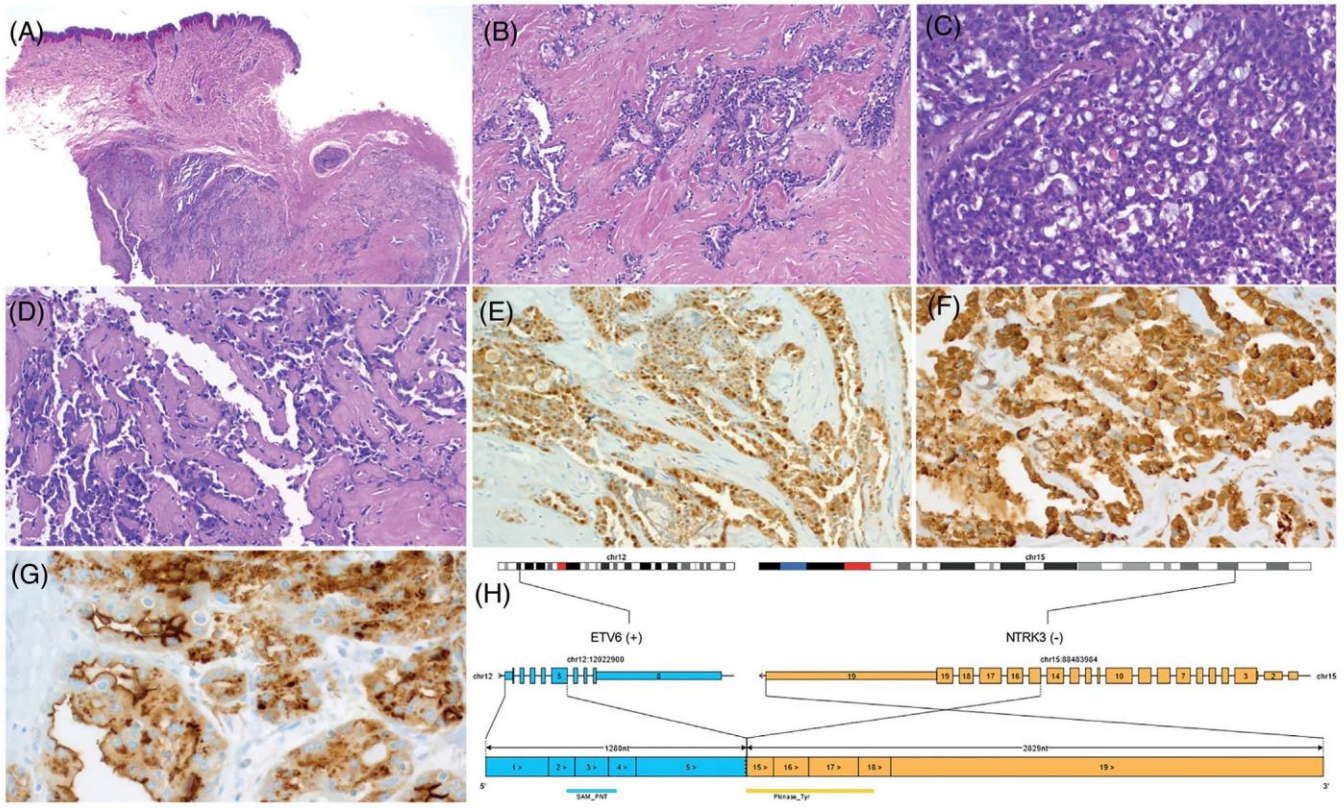
- Breast
- Salivary Gland
- Skin
- Other

Secretory Carcinoma





Secretory Carcinoma – Gene Fusions



Secretory Carcinoma

ORIGINAL ARTICLE

Secretory Carcinoma of the Skin

Report of 6 Cases, Including a Case With a Novel NFIX-PKN1 Translocation

Liubov Kastnerova, MD,† Boštjan Luzar, MD, PhD,‡ Keisuke Goto, MD,§‖¶#** Viktor GrishakovMD,†† Zoran Gatalica, MD,‡‡ Jivko Kamarachev, MD,§§ Petr Martinek, PhD,*† Veronika Hájková, MSc,† Petr Grossmann, PhD,*† Hiroshi Imai, MD, PhD,‖‖ Hideaki Fukui, MD,¶¶ Michal Michal, MD,*† and Dmitry V. Kazakov, MD, PhD*†*

Am J Surg Pathol 2019;43:1092 = 98

ORIGINAL ARTICLE

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

Generally reported as “indolent” carcinoma

Secretory Carcinoma

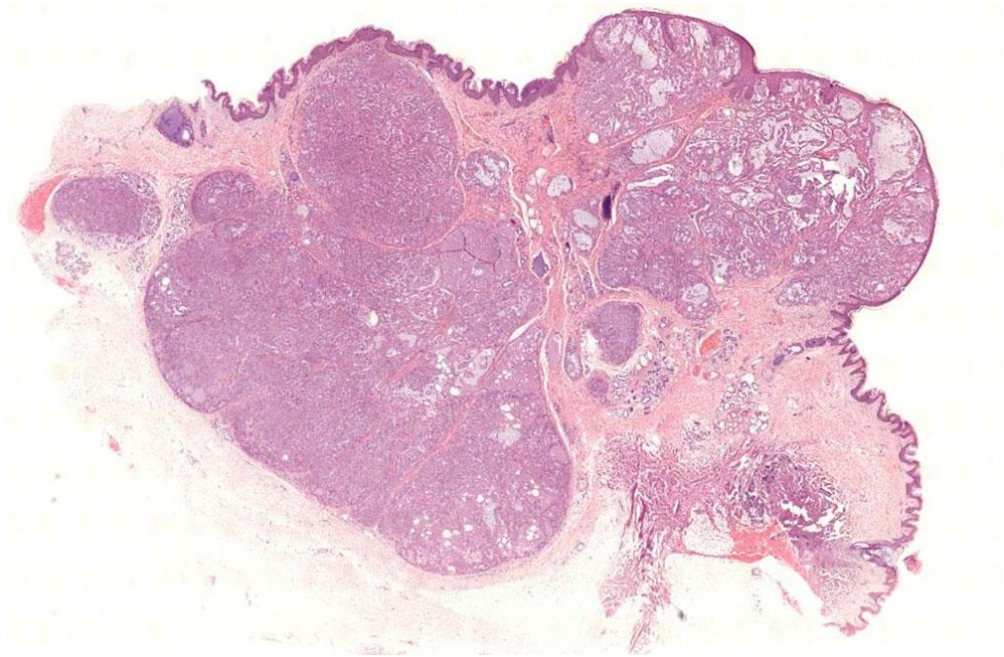
Received: 29 January 2021 | Revised: 12 March 2021 | Accepted: 6 April 2021
DOI: 10.1111/cup.14028

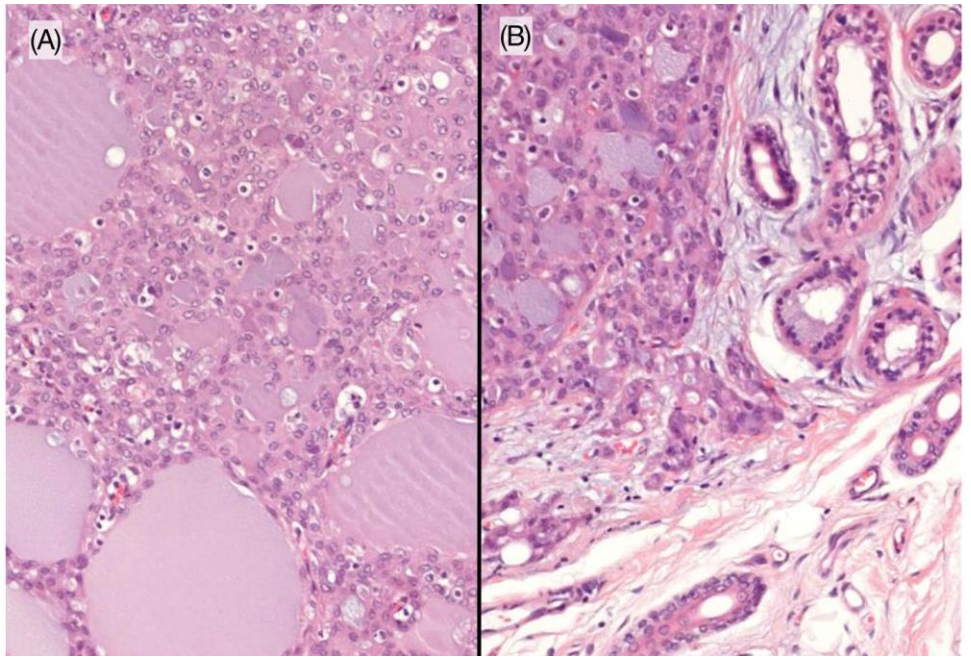
CASE REPORT

JCP JOURNAL OF CUTANEOUS PATHOLOGY WILEY

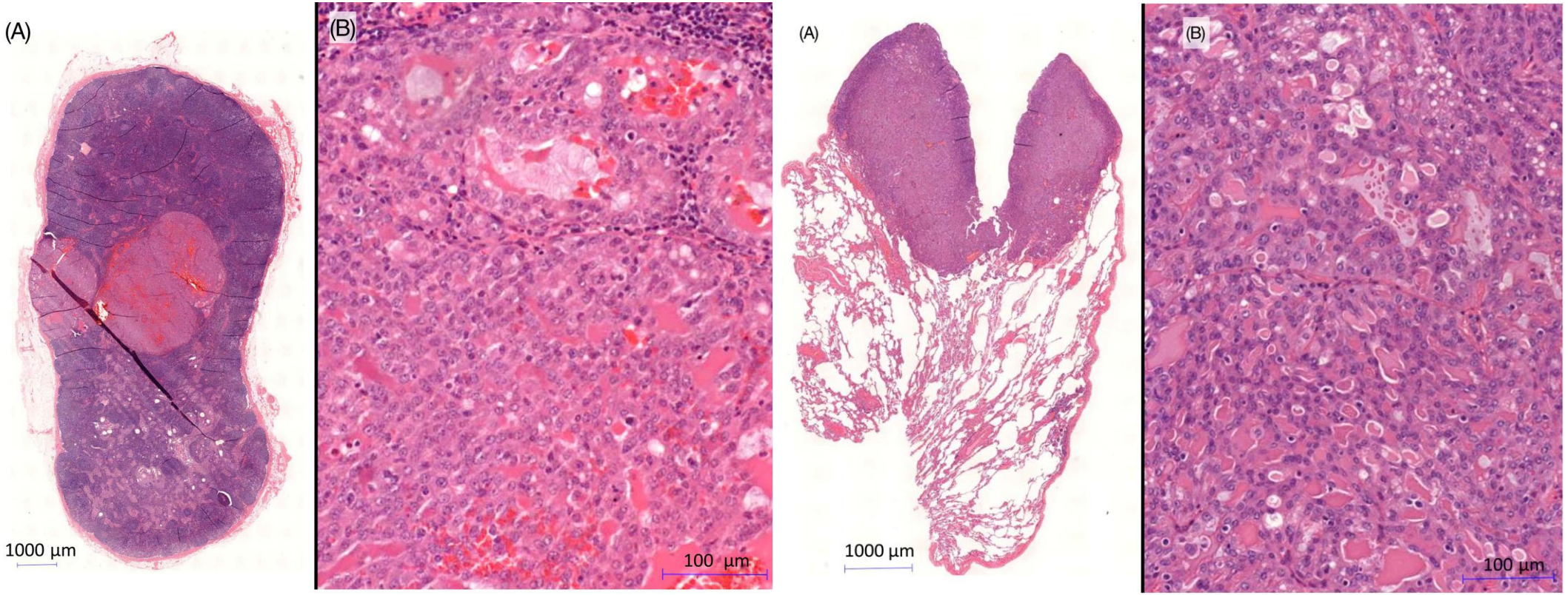
Secretory carcinoma of the skin with lymph node metastases and recurrence in both lungs: A case report

Kohei Taniguchi[1] | Hiroyuki Yanai[1] | Tatsuya Kaji[2] | Toshio Kubo[3] | Daisuke Ennishi[4] | Akira Hirasawa[5] | Tadashi Yoshino[1,6]





Metastatic Secretory Carcinoma



Microsecretory Carcinoma

Received: 29 April 2022 | Revised: 27 May 2022 | Accepted: 6 June 2022
DOI: 10.1111/cup.14271

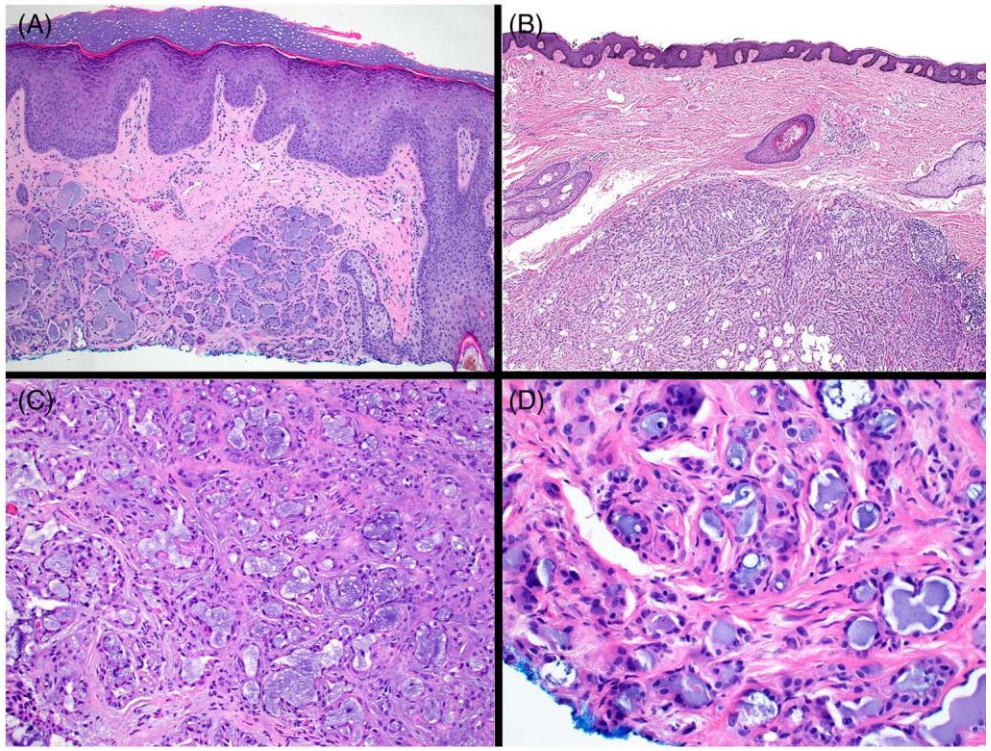
ORIGINAL ARTICLE

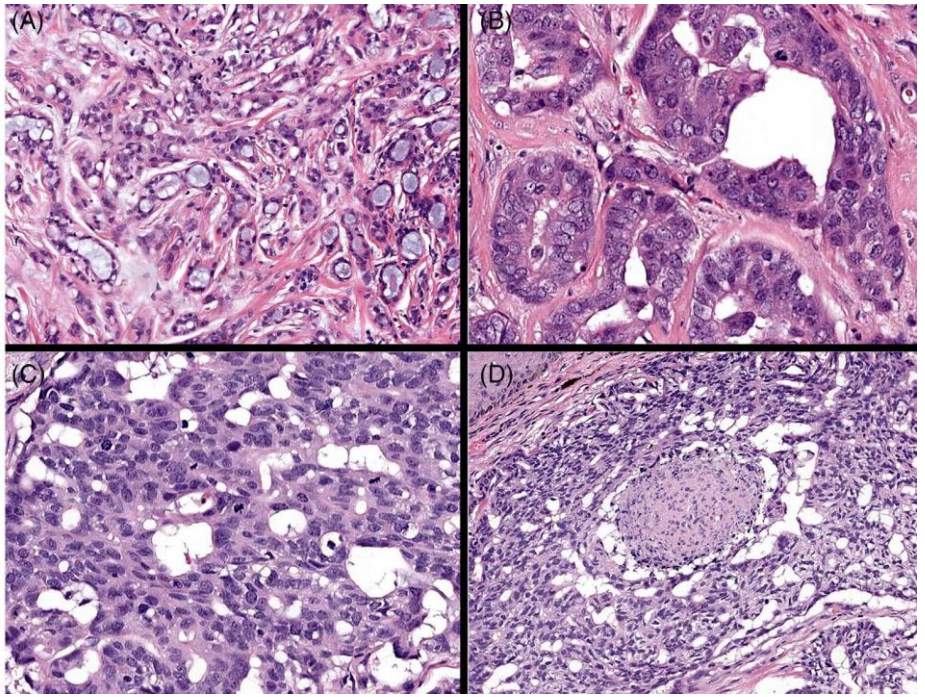
JCP JOURNAL OF CUTANEOUS PATHOLOGY WILEY

Microsecretory adenocarcinoma of the skin harboring recurrent *SS18* fusions: A cutaneous analog to a newly described salivary gland tumor

Justin A. Bishop[1] | Erik A. Williams[2] | Anne C. McLean[1] | Jeffrey Gagan[1] | Lisa M. Rooper[3] | Richard C. K. Jordan[2] | Philip E. LeBoit[2]

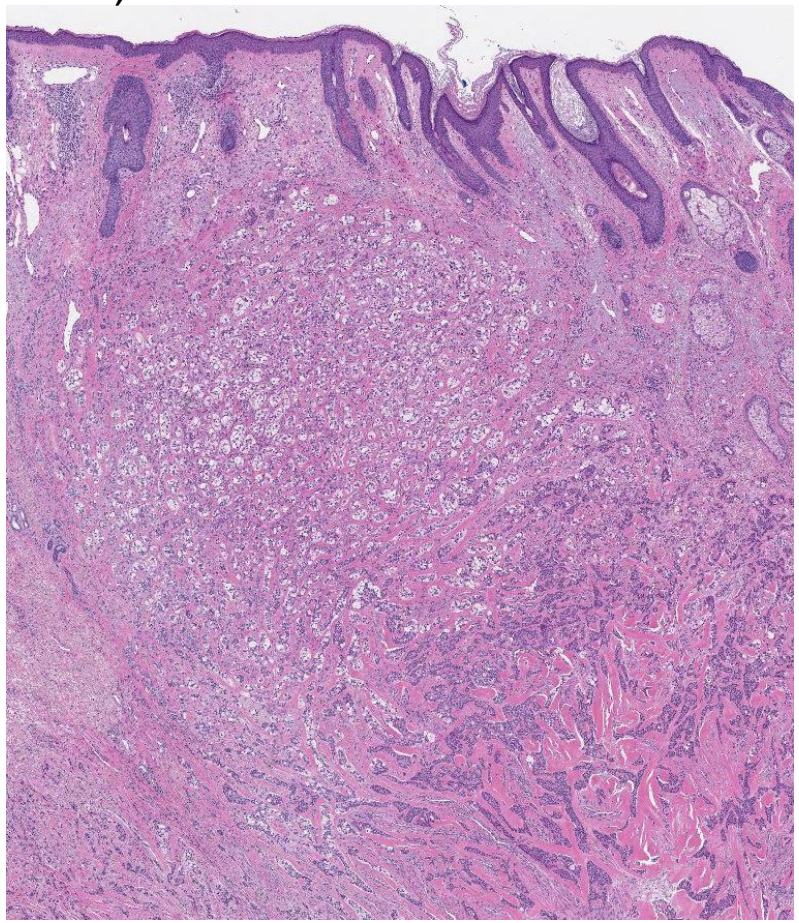
Microsecretory Carcinoma - Pathology

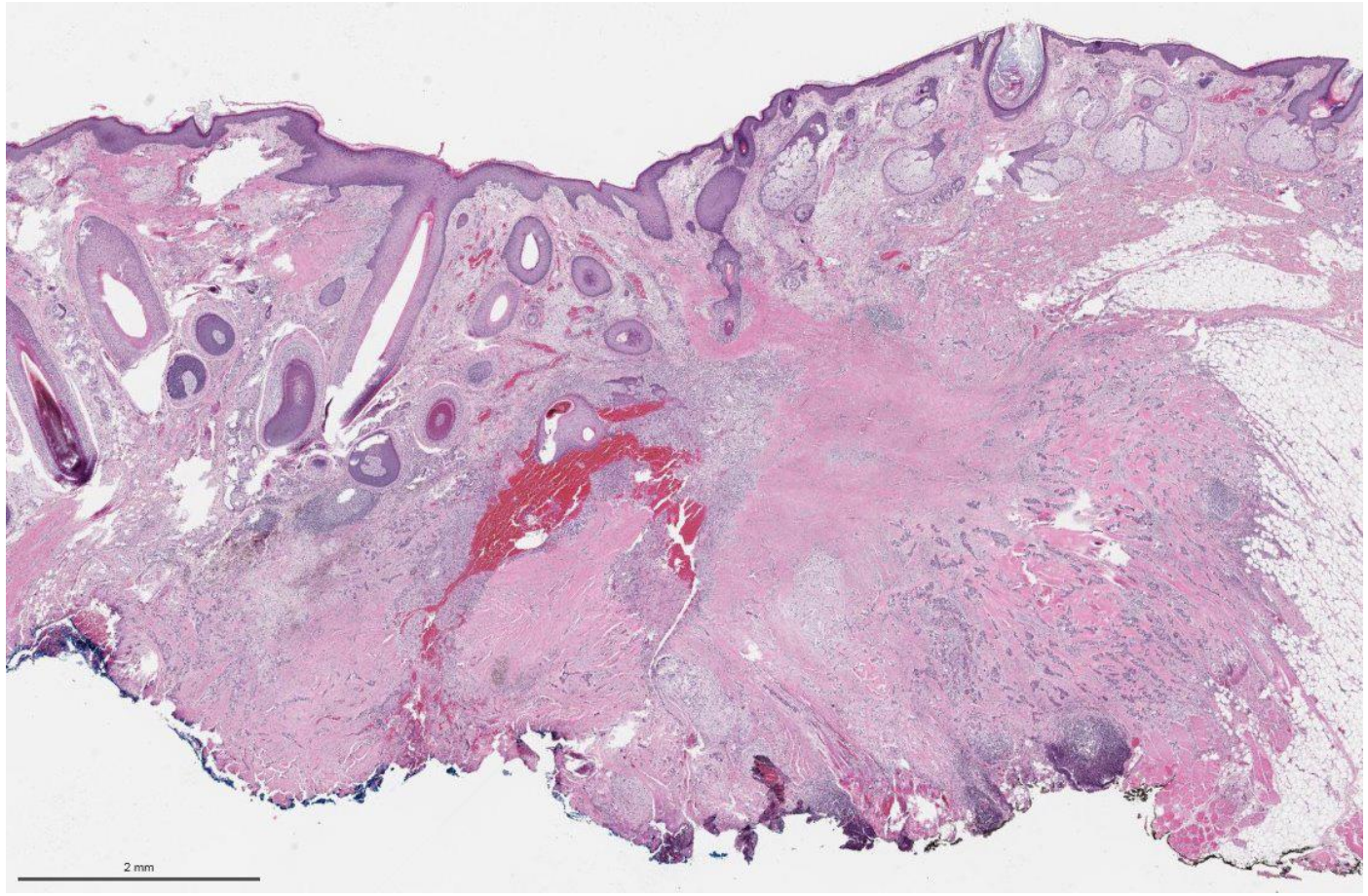




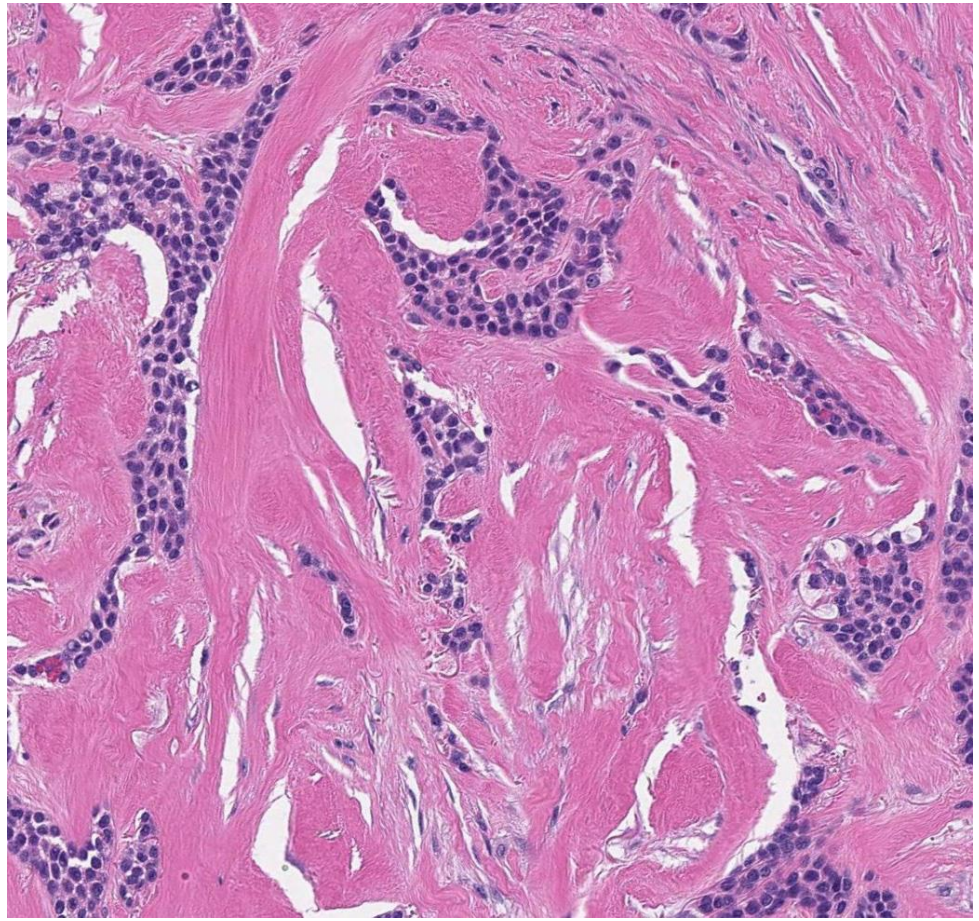
Hyalinizing Clear Cell Carcinoma

72M, nose

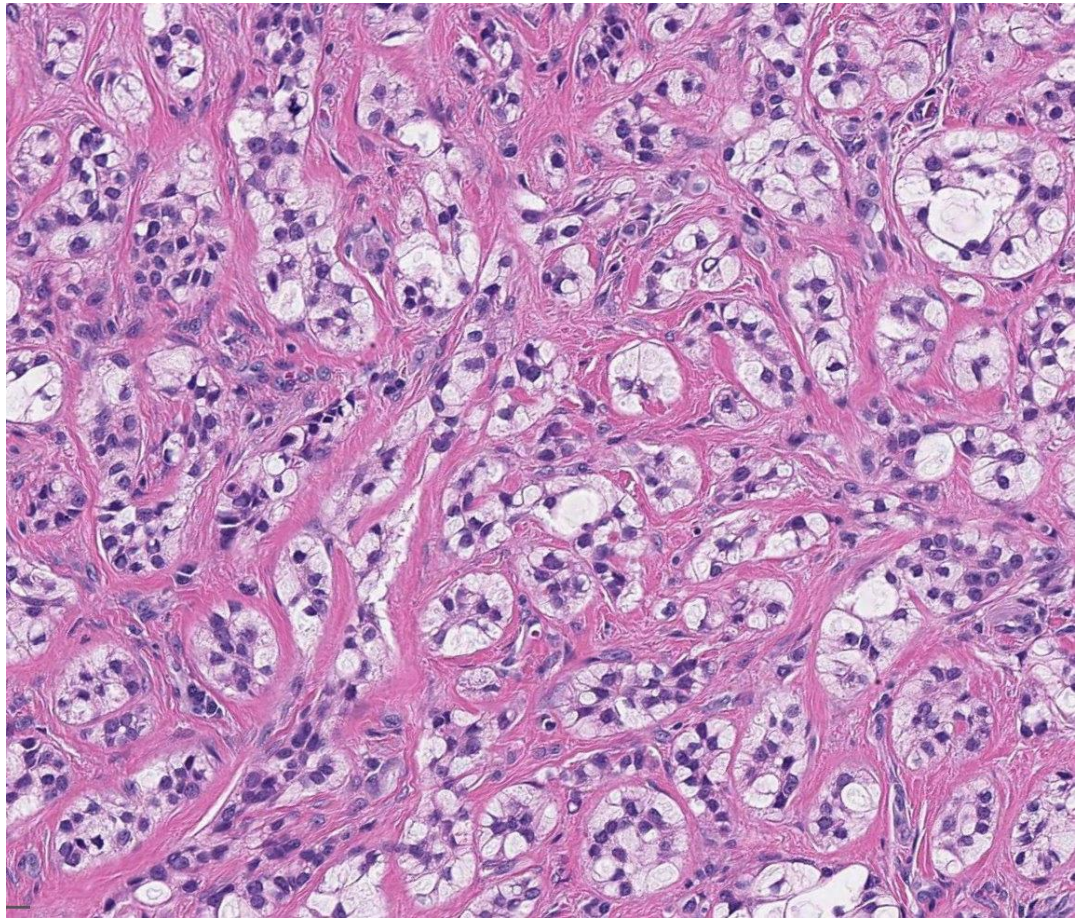




Hyalinizing Clear Cell Carcinoma



Hyalinizing Stroma



Clear Cells

Molecular: EWSR1-ATF1

Ductal vs Epithelial/Myoepithelial Carcinoma

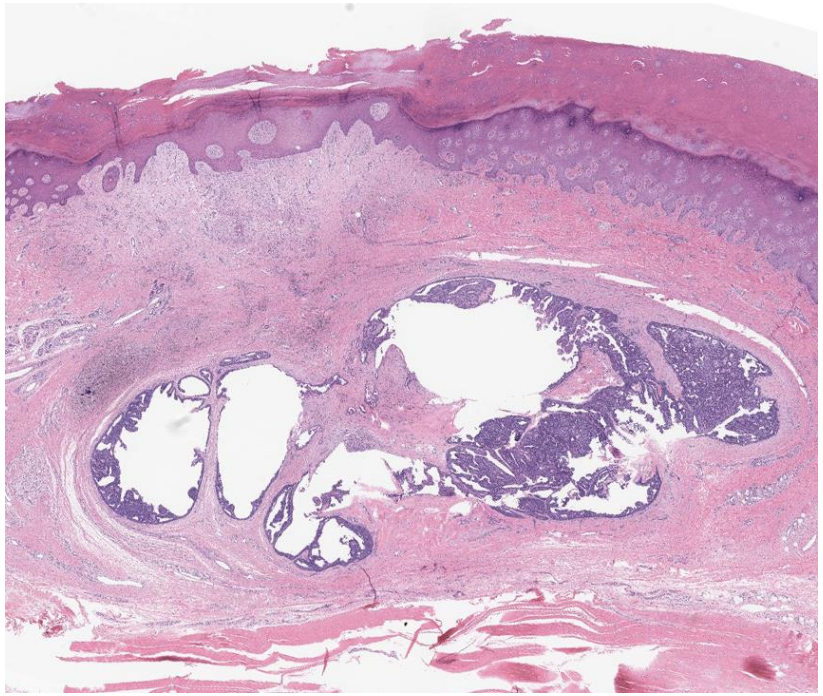
Ductal Carcinomas

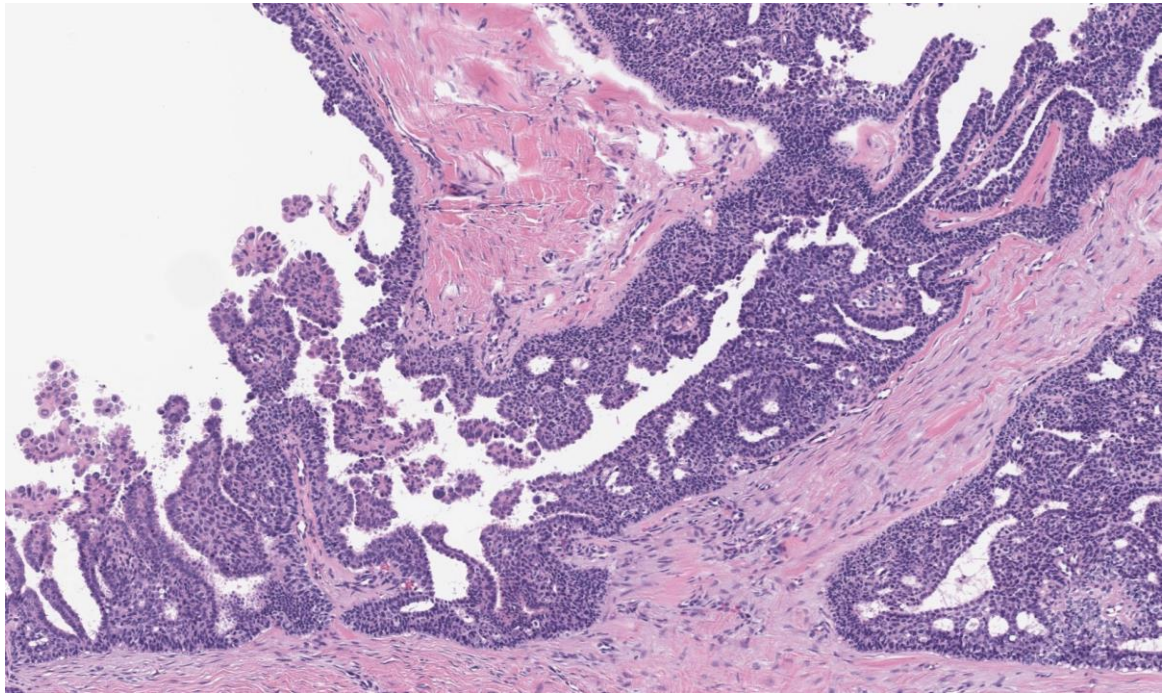
- Ductal carcinoma, NOS
- Mucinous carcinoma
- Cribriform carcinoma
- Secretory carcinoma

Epithelial – Myoepithelial Carcinomas

- Adenoid cystic carcinoma
- Malignant mixed tumor
- Cylindrocarcinoma
- **Digital papillary adenocarcinoma**

Digital Papillary Adenocarcinoma (DPAC)

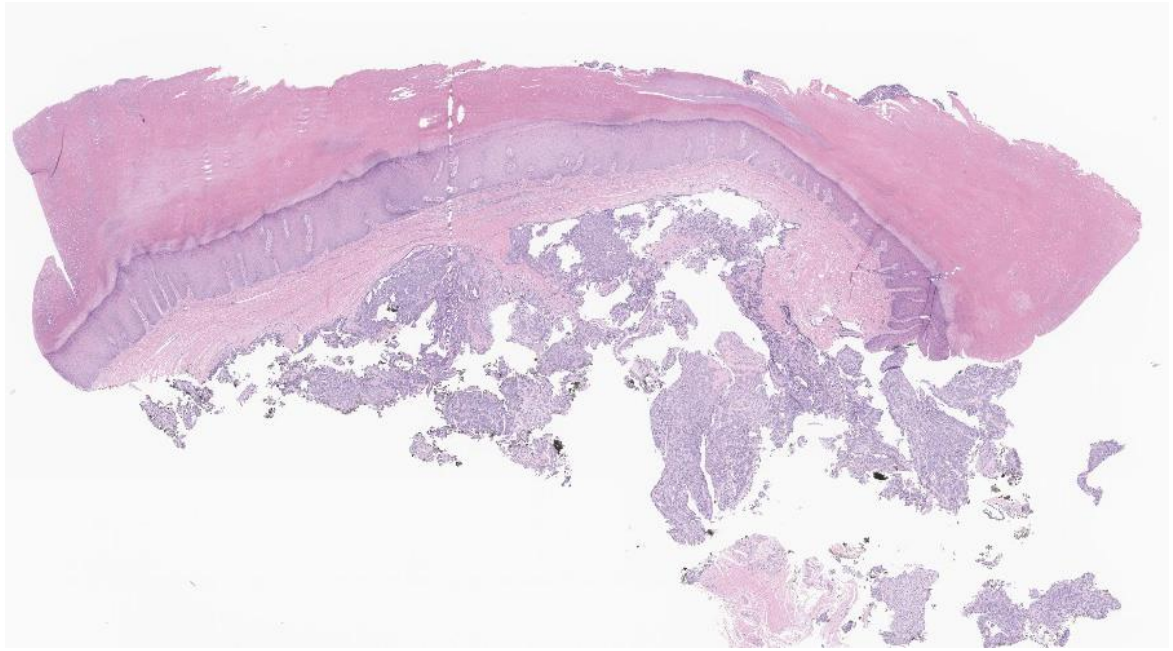


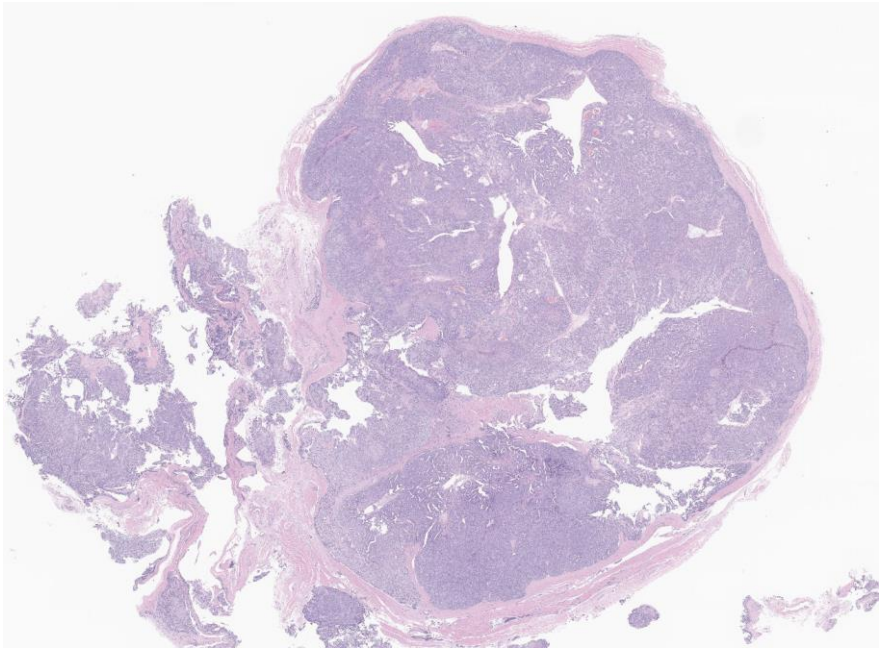


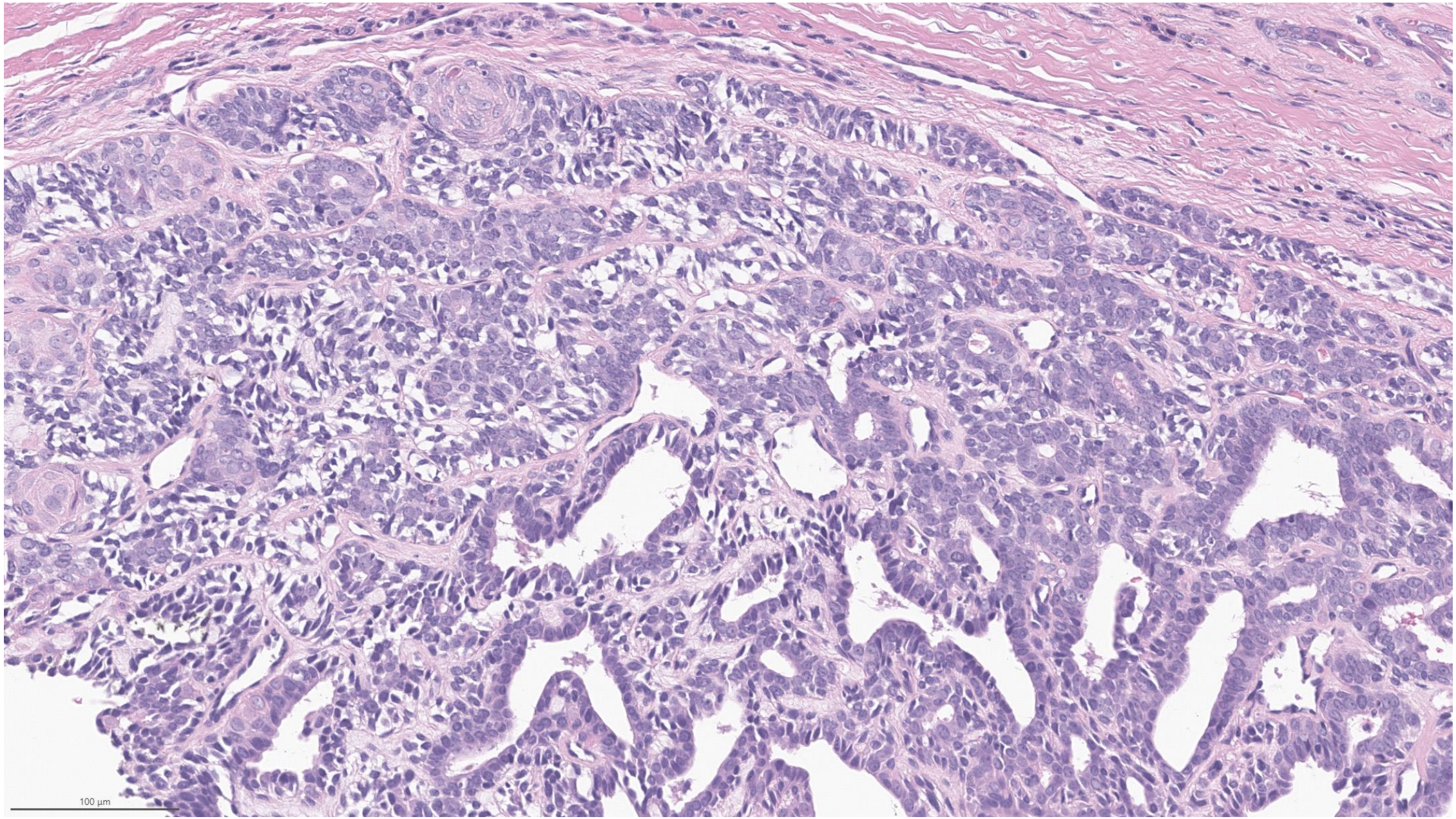
DPAC – Basic Facts

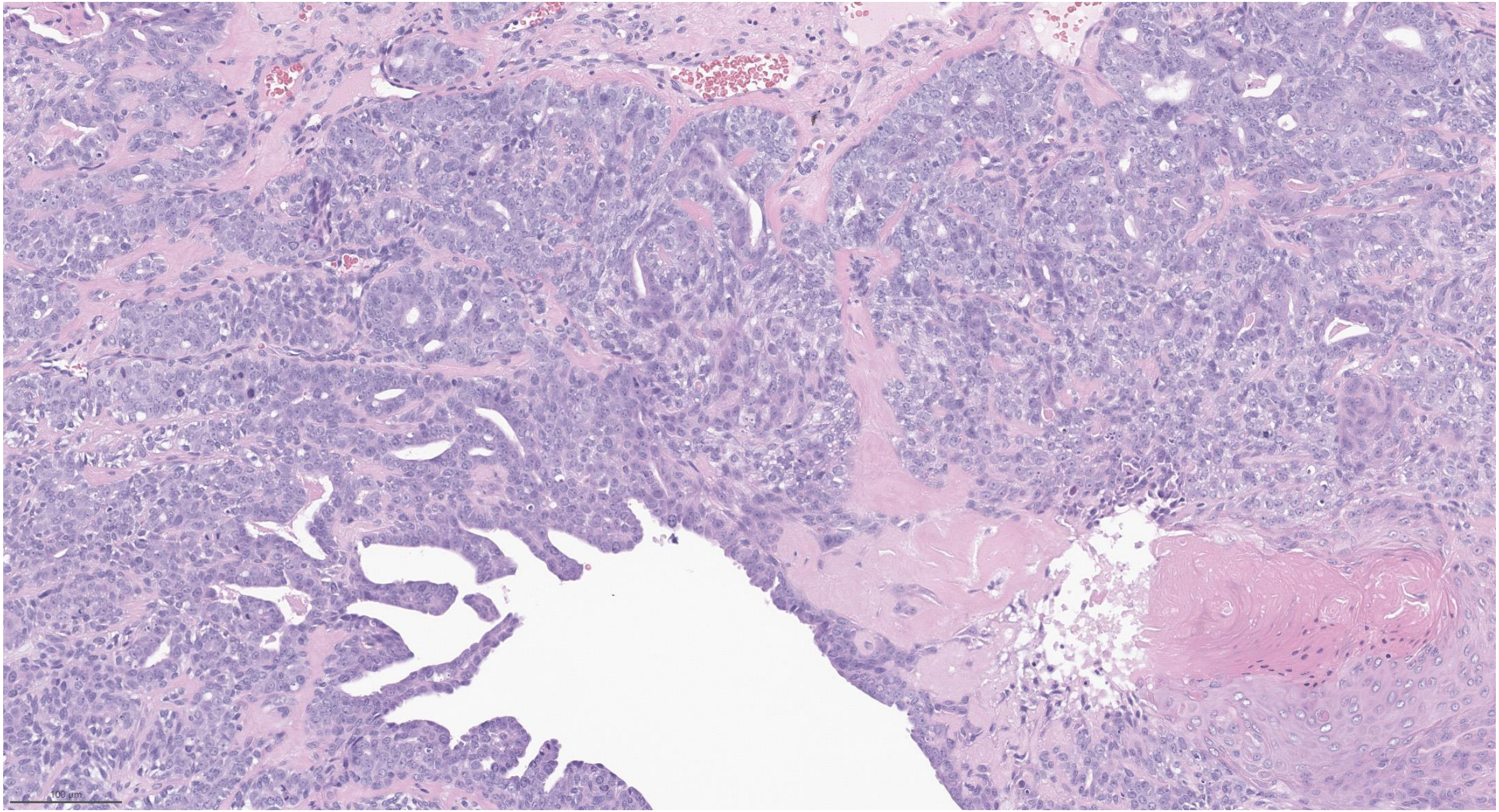
- Incidence: 0.08 per 1,000,000
- Median age at diagnosis: 50
- Men: Women = 4:1
- Predilection for digits and toes
- Risk for metastasis: approx. 15%
- Treatment: Surgical resection

21M with mass on rt 5th finger

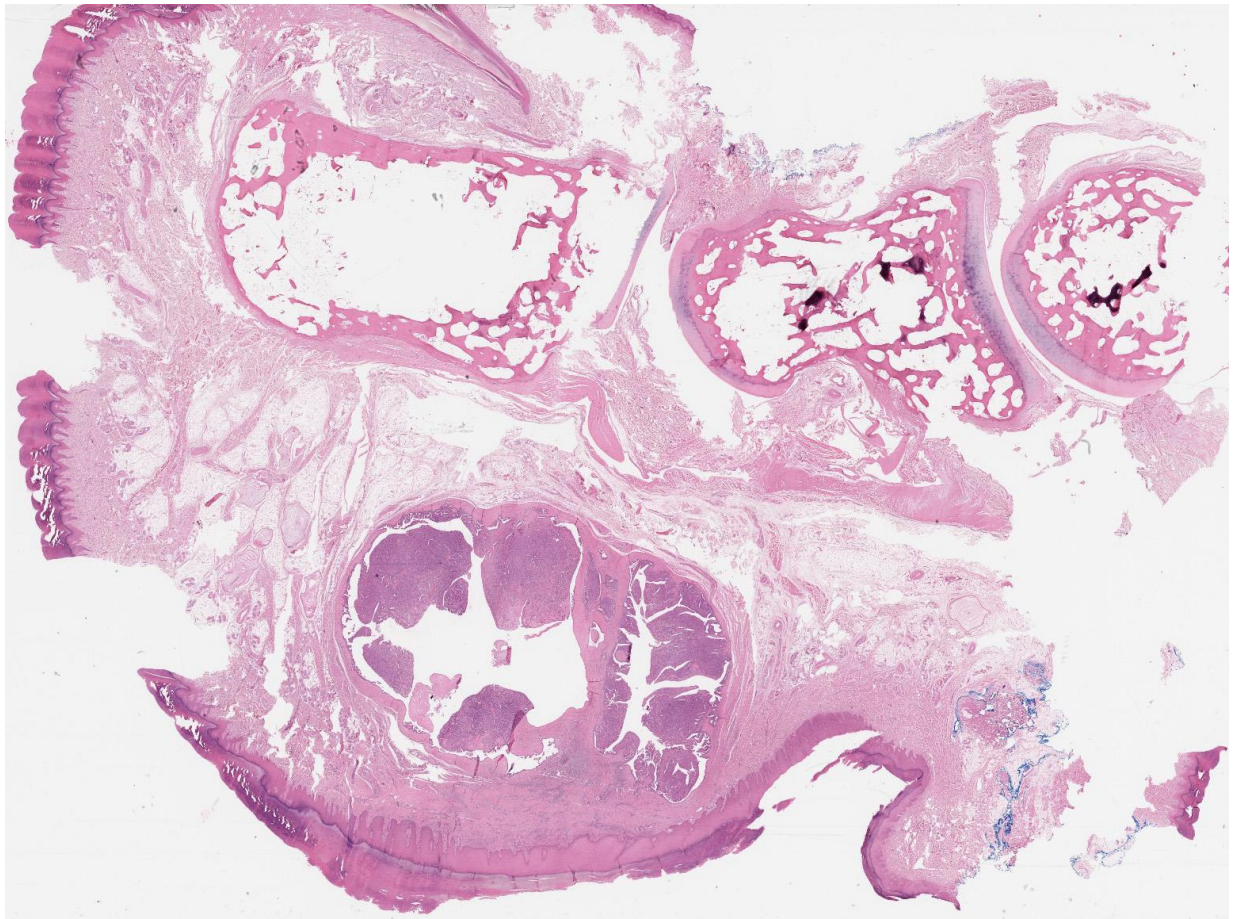





100 µm


100 µm

Digital Papillary Adenocarcinoma



Metastatic Digital Papillary Adenocarcinoma

DPAC – A Diagnostic Challenge

ORIGINAL ARTICLE

"Apocrine Hidrocystoma and Cystadenoma"–like Tumor of the Digits or Toes

A Potential Diagnostic Pitfall of Digital Papillary Adenocarcinoma

Ana-María Molina-Ruiz, MD, Mar Llamas-Velasco, MD,† Arno Rütten, MD,‡ Lorenzo Cerroni, MD,§ and Luis Requena, MD**

ORIGINAL ARTICLE

Clinicopathologic Characterization of Hidradenoma on Acral Sites

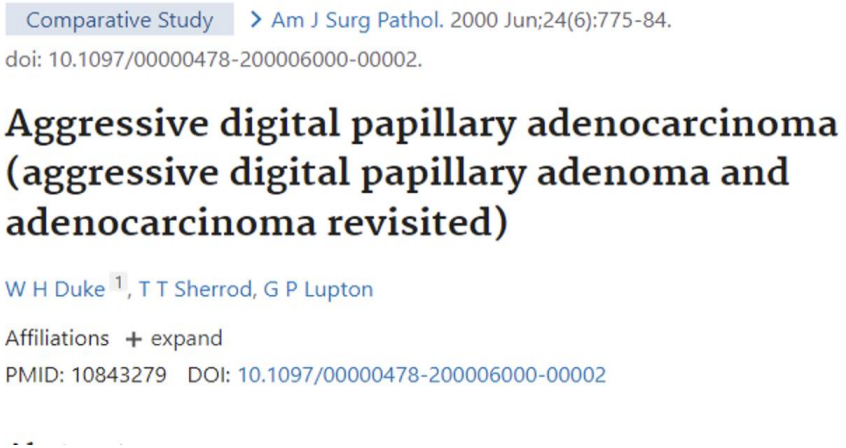
A Diagnostic Pitfall With Digital Papillary Adenocarcinoma

Katharina Wiedemeyer, MD,† Pavandeep Gill, MD,* Michelle Schneider, MD,* Peter Kind, MD,‡ and Thomas Brenn, MD, PhD, FRCPath*§‖*

Can be confused with a benign sweat gland tumor

DPAC - History

- Helwig in 1984: “aggressive papillary adenoma”
- Kao in 1998: series of “aggressive papillary digital adenoma” and “aggressive papillary digital adenocarcinoma”
- Duke in 2000:



Comparative Study > Am J Surg Pathol. 2000 Jun;24(6):775-84.
doi: 10.1097/00000478-200006000-00002.

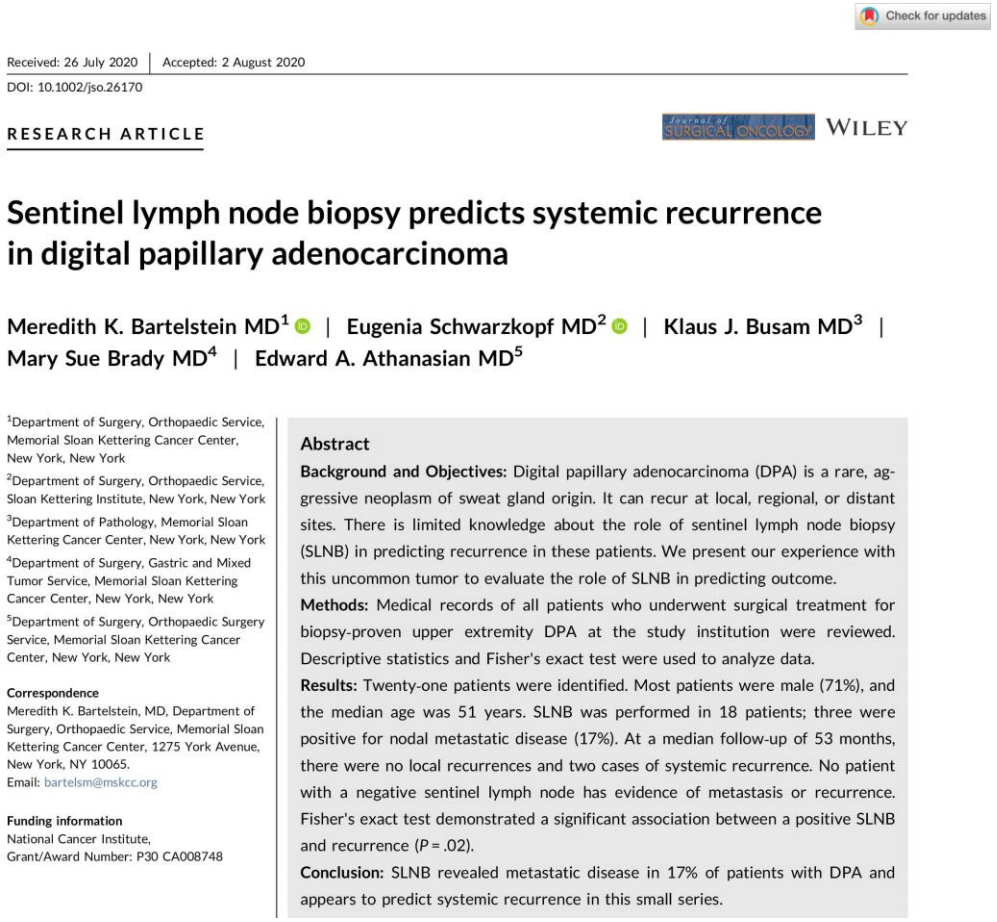
Aggressive digital papillary adenocarcinoma (aggressive digital papillary adenoma and adenocarcinoma revisited)

W H Duke [1], T T Sherrod, G P Lupton

Affiliations + expand

PMID: 10843279 DOI: 10.1097/00000478-200006000-00002

DPAC – Value of SLNbx for Prognosis



Received: 26 July 2020 | Accepted: 2 August 2020
DOI: 10.1002/jso.26170

RESEARCH ARTICLE

Journal of SURGICAL ONCOLOGY WILEY

Sentinel lymph node biopsy predicts systemic recurrence in digital papillary adenocarcinoma

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[2]Department of Surgery, Orthopaedic Service, Sloan Kettering Institute, New York, New York
[3]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York
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Meredith K. Bartelstein, MD, Department of Surgery, Orthopaedic Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065.
Email: bartelsm@mskcc.org

Funding information
National Cancer Institute, Grant/Award Number: P30 CA008748

Abstract

Background and Objectives: Digital papillary adenocarcinoma (DPA) is a rare, aggressive neoplasm of sweat gland origin. It can recur at local, regional, or distant sites. There is limited knowledge about the role of sentinel lymph node biopsy (SLNB) in predicting recurrence in these patients. We present our experience with this uncommon tumor to evaluate the role of SLNB in predicting outcome.

Methods: Medical records of all patients who underwent surgical treatment for biopsy-proven upper extremity DPA at the study institution were reviewed. Descriptive statistics and Fisher's exact test were used to analyze data.

Results: Twenty-one patients were identified. Most patients were male (71%), and the median age was 51 years. SLNB was performed in 18 patients; three were positive for nodal metastatic disease (17%). At a median follow-up of 53 months, there were no local recurrences and two cases of systemic recurrence. No patient with a negative sentinel lymph node has evidence of metastasis or recurrence. Fisher's exact test demonstrated a significant association between a positive SLNB and recurrence ($P = .02$).

Conclusion: SLNB revealed metastatic disease in 17% of patients with DPA and appears to predict systemic recurrence in this small series.

- 21 patients, 71% men, median age 51
- 17% had a pos SLN
- 2/21 had distant mets
- None of the patients with neg SLN had distant recurrence

Mutations said to be associated with DPAC

- Bell D et al. Ann Diagn Pathol. 2015;19(6):381-4.
  - NGS: 1/9 cases with *BRAFV600E* mutation

- Trager MH et al Am J Dermatopathol. 2021;43(1):57-59.
  - Single case report with BRAFV600E mutation

Report of BRAF Mutation in “DPAC”

Annals of Diagnostic Pathology 19 (2015) 381–384

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

Next-generation sequencing reveals rare genomic alterations in aggressive digital papillary adenocarcinoma☆,☆☆

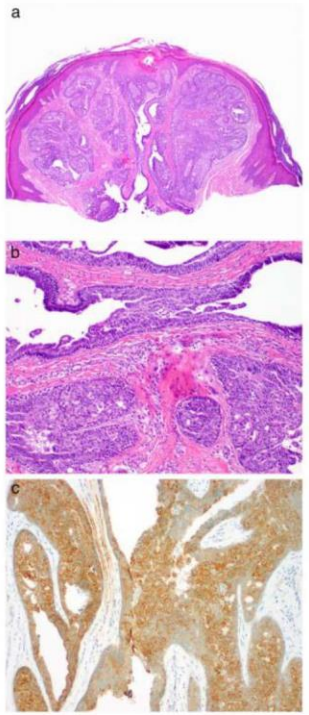
Diana Bell, MD *, Phyu P. Aung, MD, PhD, Victor G. Prieto, MD, PhD, Doina Ivan, MD

Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX

Table
Demographic, clinicopathologic, and molecular characteristics of 9 patients with ADPA

Case	Age (y)/sex	Location	SLN status	Follow-up (mo)	Sequenom
1	52/F	Third finger	Negative	NED, 36	No mutations
2	48/F	Ankle	Negative	NED, 48	No mutations
3	41/M	Index finger	Positive (2/5)	NED, 54 mo	No mutations
4	58/M	Fifth finger	Negative	NED, 6	No mutations
5	39/F	Heel	Positive (1/4)	NED, 18	No mutations
6	58/F	Fifth finger	Positive	NED, 6	No mutations
7	57/M	Third finger	N/A	NED, 36	No mutations
8	40/M	Third finger	N/A	DOD, lung metastasis	No mutations
9	31/F	Ankle	Negative	NED, 12	BRAF c.1799T>A p.V600E

Abbreviations: SLN, sentinel lymph node; NED, no evidence of disease; DOD, died of disease.



1 of 9 tumors with *BRAFV600E*

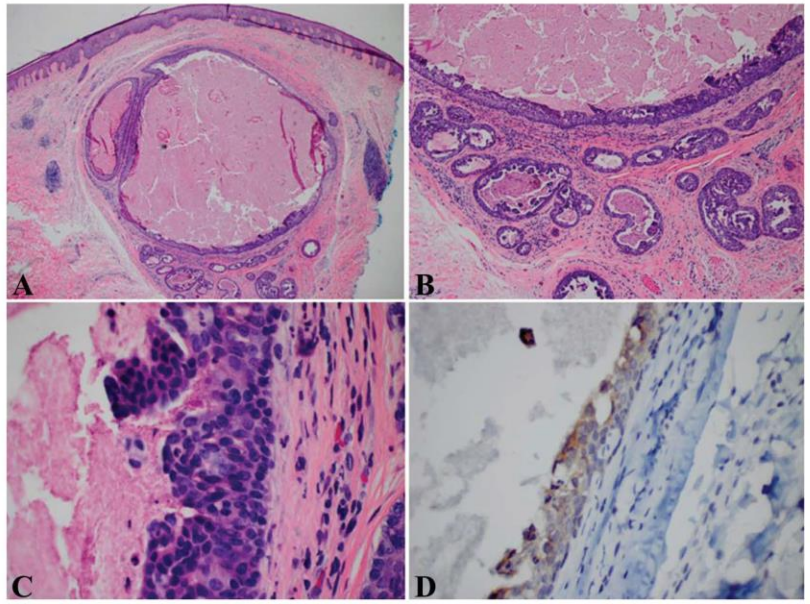
UNUSUAL CASE
- 31**F**
- **Ankle**
- NED (1yr)

Report of BRAF Mutation in “DPAC”

EXTRAORDINARY CASE REPORT

A Case Report of Papillary Digital Adenocarcinoma With BRAFV600E Mutation and Quantified Mutational Burden

Megan H. Trager, BA, Magdalena Jurkiewicz, MD, PhD,† Shaheer Khan, MD,‡ George W. Niedt, MD,§ Larisa J. Geskin, MD,¶ and Richard D. Carvajal, MD‡*



- 63 yo woman
- **Right forearm**
- “High TMB”

Tubulopapillary Adenomas harbor *BRAF* mutations

Human Pathology (2018) **73**, 59–65

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Human PATHOLOGY

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Original contribution

BRAF and *KRAS* mutations in tubular apocrine adenoma and papillary eccrine adenoma of the skin☆,☆☆

Jau-Yu Liau MD[a,b,*], Jia-Huei Tsai MD[a,b], Wen-Chang Huang MD[c], Jui Lan MD[d], Jin-Bon Hong MD[e], Chang-Tsu Yuan MD[a]

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Received 26 September 2017; revised 17 November 2017; accepted 1 December 2017

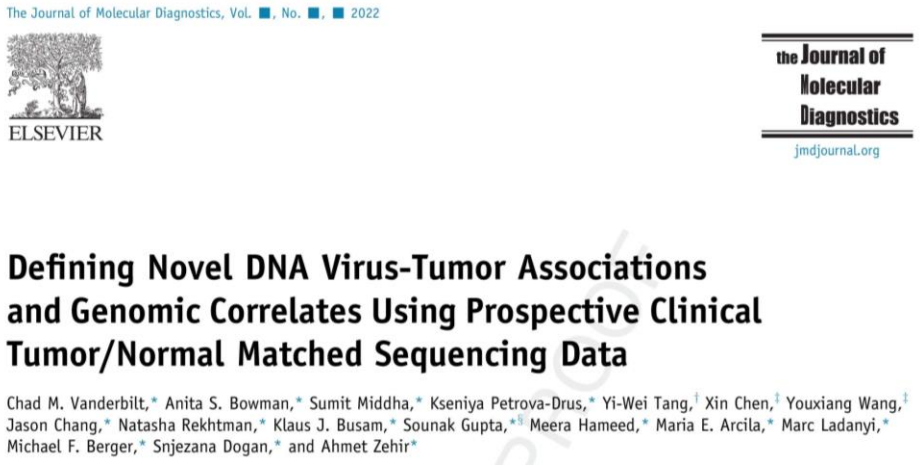
BRAFV600E Mutation:

- 9/15 (60%) of TAA
- 7/8 (78%) of PEA

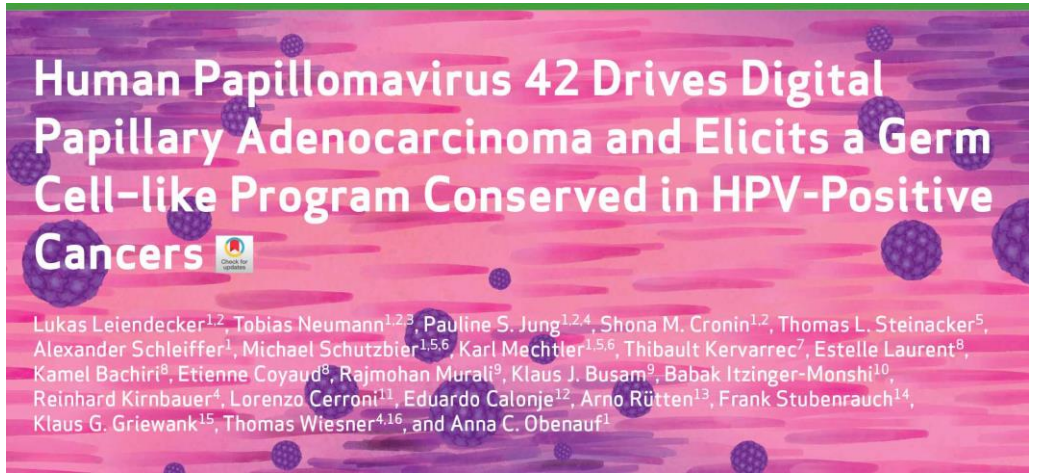
Next Generation Sequence Analysis of Tumors

- Searching for point mutations
- Searching for gene fusions
- Also permits search for potential non-human pathogens

NGS to Detect Virus-Tumor Associations



Chad Vanderbilt and colleagues



Thomas Wiesner and colleagues

Hybridization capture library enrichment

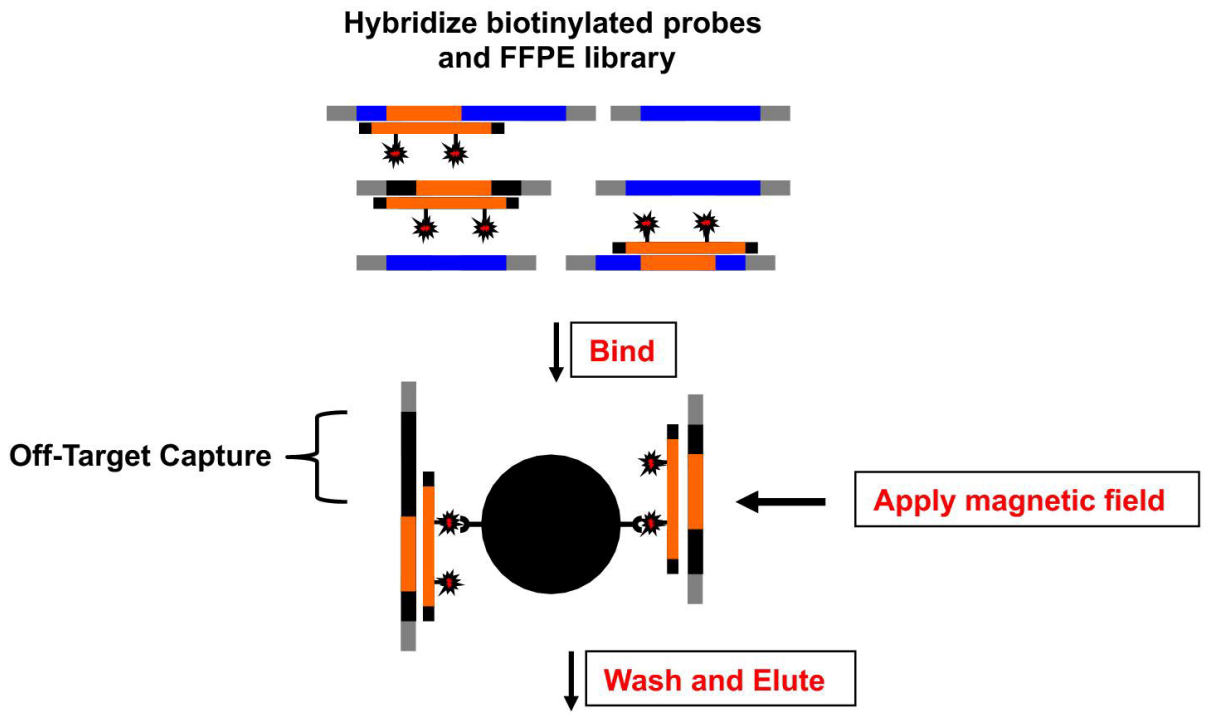
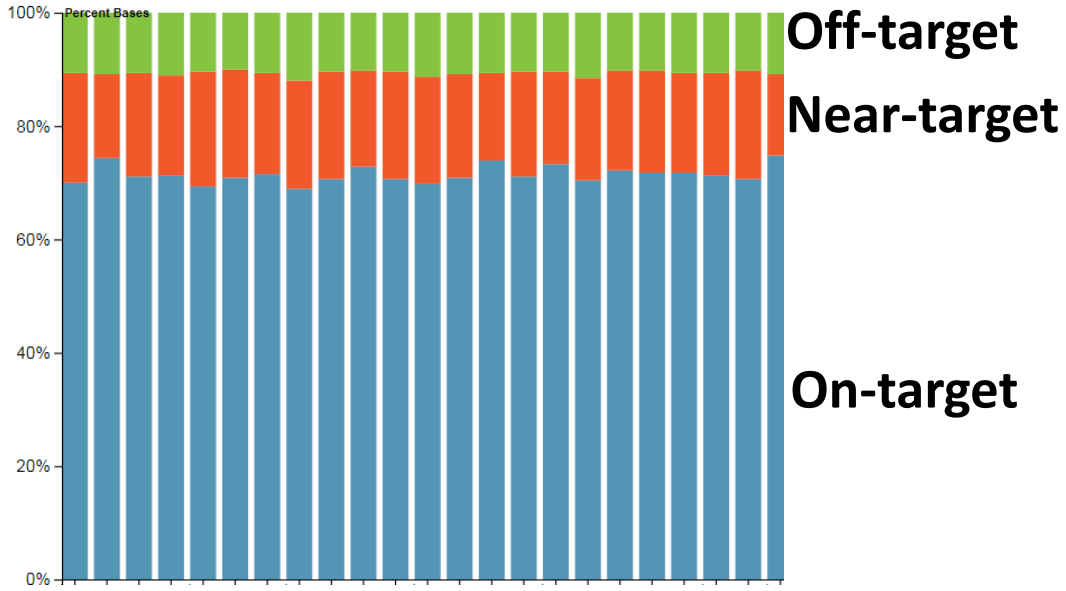
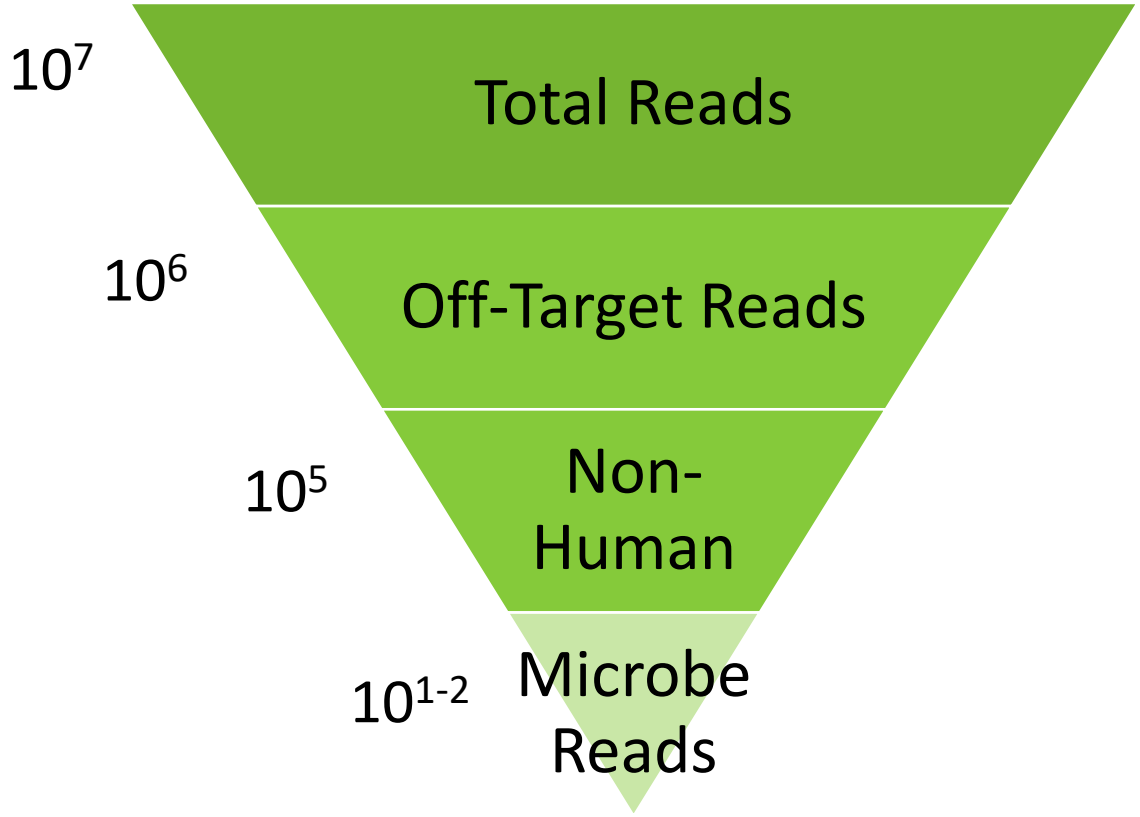


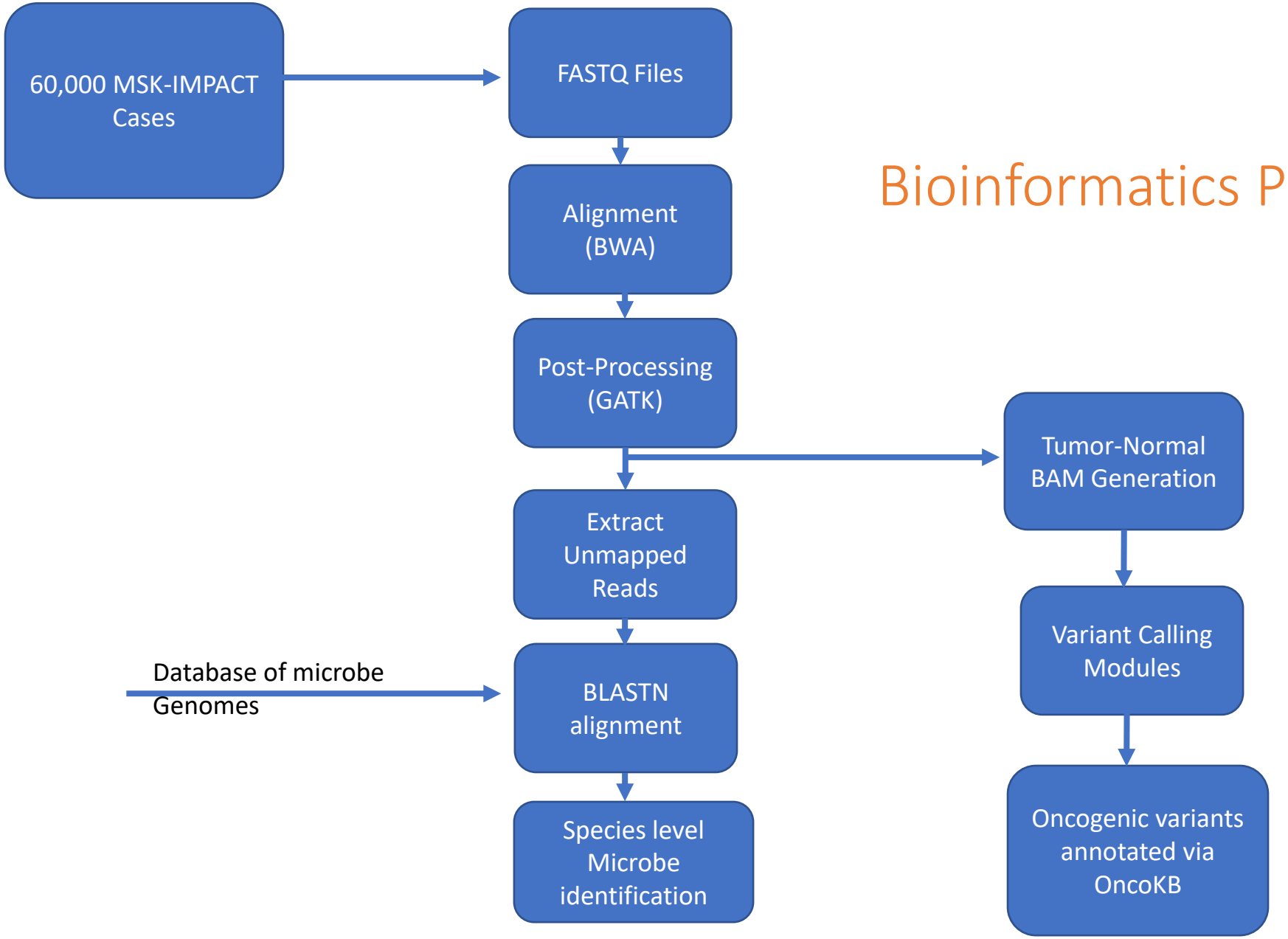
Image adapted from Duncavage et al. JMD. 2011

Off-targets enable identification of microorganisms



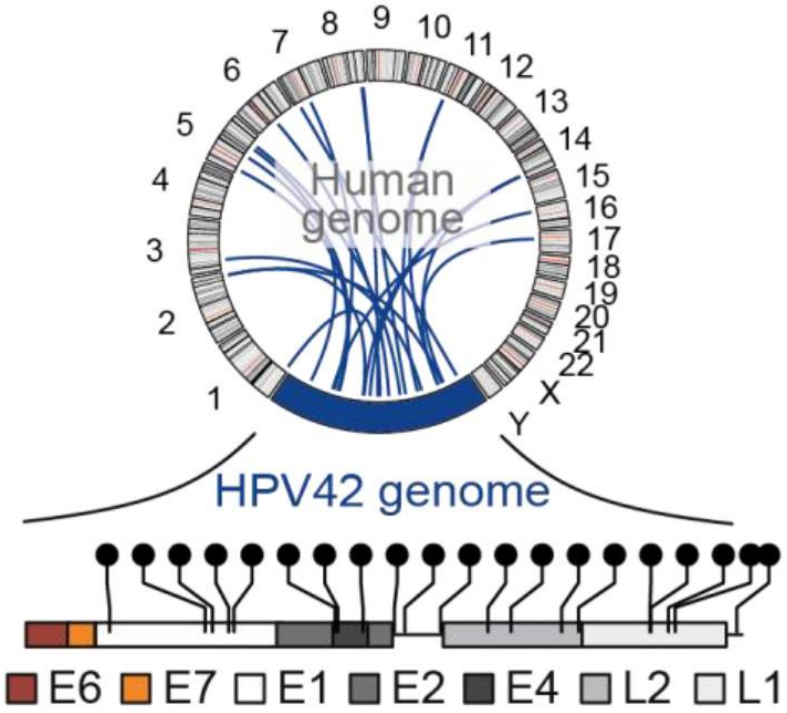


Bioinformatics Process

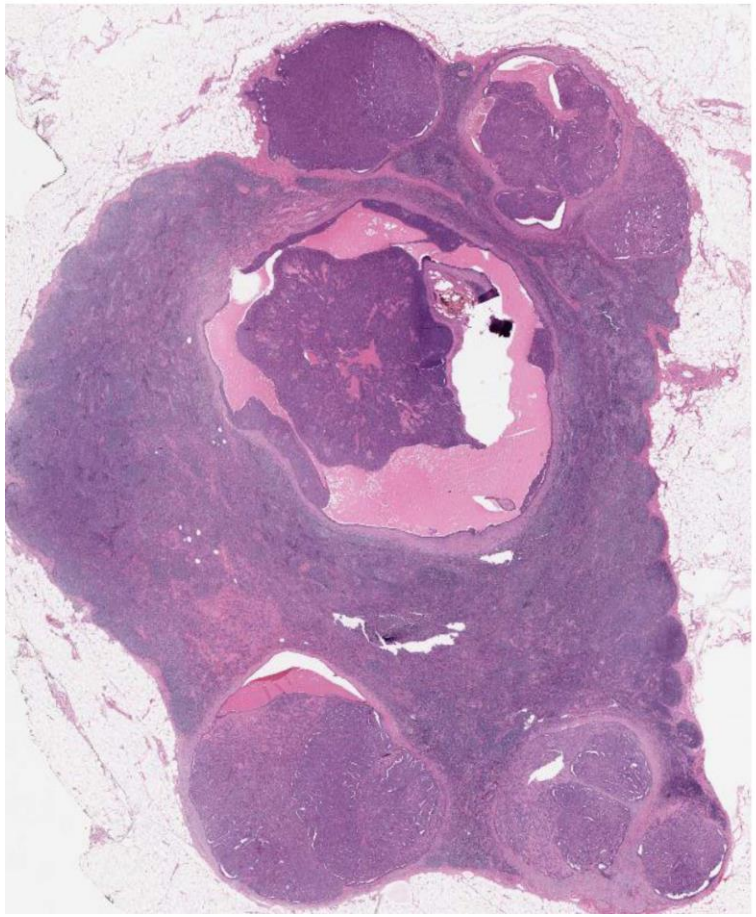


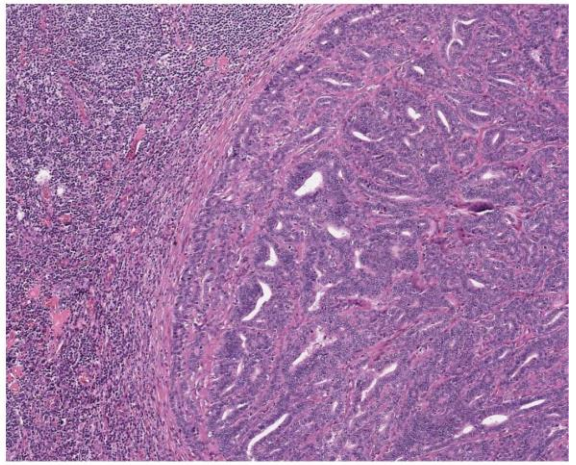
Sequence Analysis Detects HPV42 in DPAC

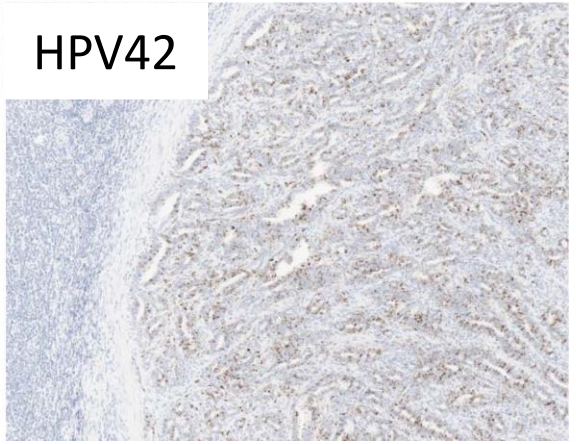
- 55,000 cases analyzed by MSK-IMPACT
- 4 skin tumors positive for HPV42
- All had been diagnosed as DPAC



HPV42 Detection in Metastatic DPAC







DPAC – Positive for HPV42

Acral Sites							
Case	Age (yrs)	Gender	Anatomic Site	Size (mm)	Growth	ISH HPV42	Metastasis
1	68	M	rt 3rd finger	17	nodular	POSITIVE	
2	36	M	rt 2nd finger	8	nodular	POSITIVE	LN, ST
3	60	M	rt 2nd finger	30	infiltrative	POSITIVE	
4	68	M	rt 3rd finger	5	nodular	POSITIVE	
5	31	M	rt 4th toe	13	nodular	POSITIVE	LN (4/10)
6	21	M	rt great toe	20	nodular	POSITIVE	
7	37	M	rt 5th finger	18	nodular	POSITIVE	
8	65	M	lt thumb	16	nodular	POSITIVE	LN
Non-Acral Sites							
9	80	M	scrotum	20	nodular	POSITIVE	
10	77	M	scrotum	8	nodular	POSITIVE	

USCAP

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ARTICLE

Check for updates

Association of HPV42 with digital papillary adenocarcinoma and the use of in situ hybridization for its distinction from acral hidradenoma and diagnosis at non-acral sites

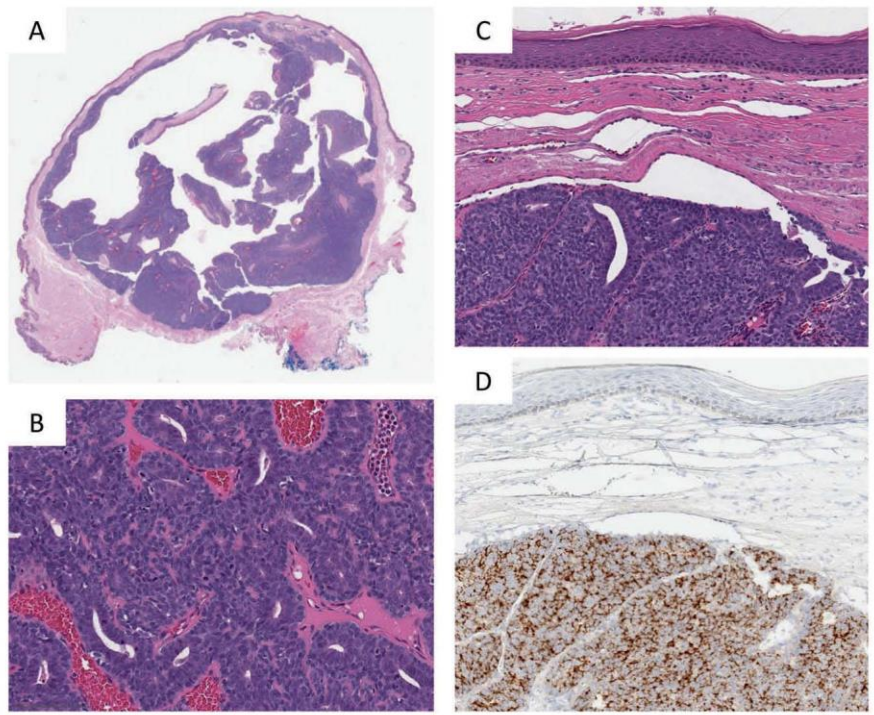
Chad Vanderbilt[1], Thomas Brenn[2], Andrea P. Moy[1], Gordon Harloe[3], Charlotte Ariyan[4], Edward Athanasian[4] and Klaus J. Busam[1]✉

ORIGINAL ARTICLE

Digital Papillary Adenocarcinoma in Nonacral Skin

Clinicopathologic and Genetic Characterization of 5 Cases

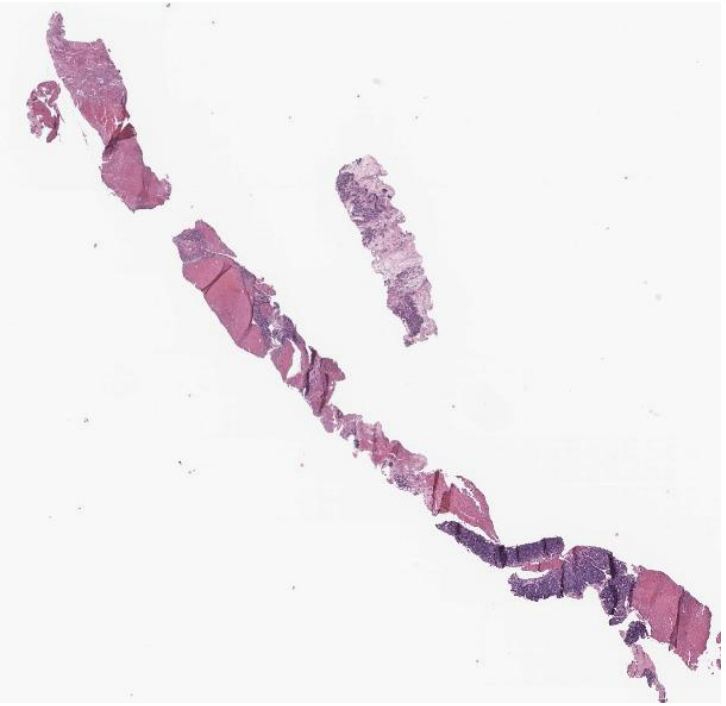
Thibault Kervarrec, MD, PhD,†‡ Sandrine Imbeaud, PhD,§ David Veyer, PharmD, PhD,§‖ Helene Pere, PharmD, PhD,§‖ Julien Puech,§ Agnes Pekár-Lukacs, MD,¶# Dorota Markiewicz, MD,# Michael Coutts, MD,** Anne Tallet, PharmD,†† Christine Collin, PhD,†† Patricia Berthon, PhD,† Ignacio G. Bravo, PhD,‡‡ Alice Seris,‡§§ Thomas Jouary, MD,‡§§ Nicolas Macagno, MD, PhD,‖‖¶¶ Antoine Touzé, PhD,† Bernard Cribier, MD, PhD,## Maxime Battistella, MD, PhD,*** and Eduardo Calonje, MD#*

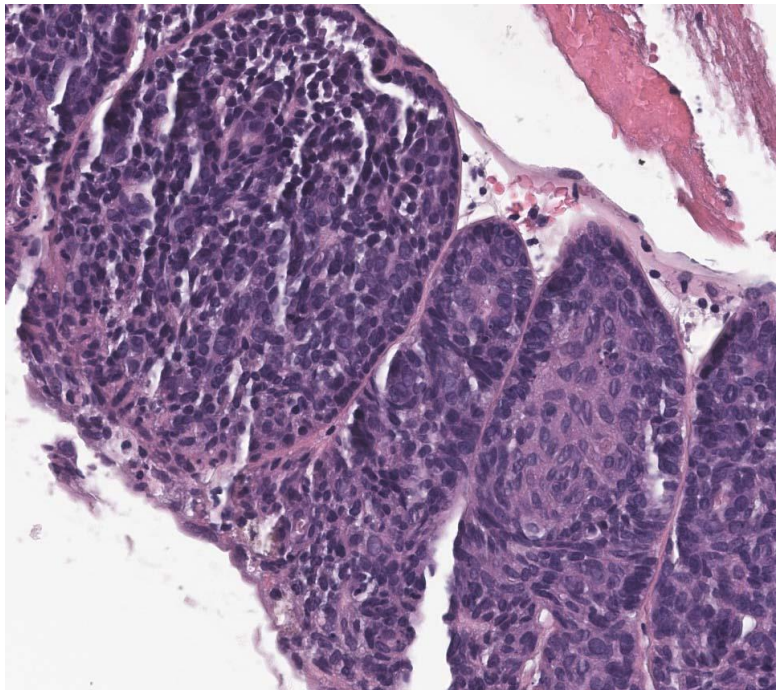


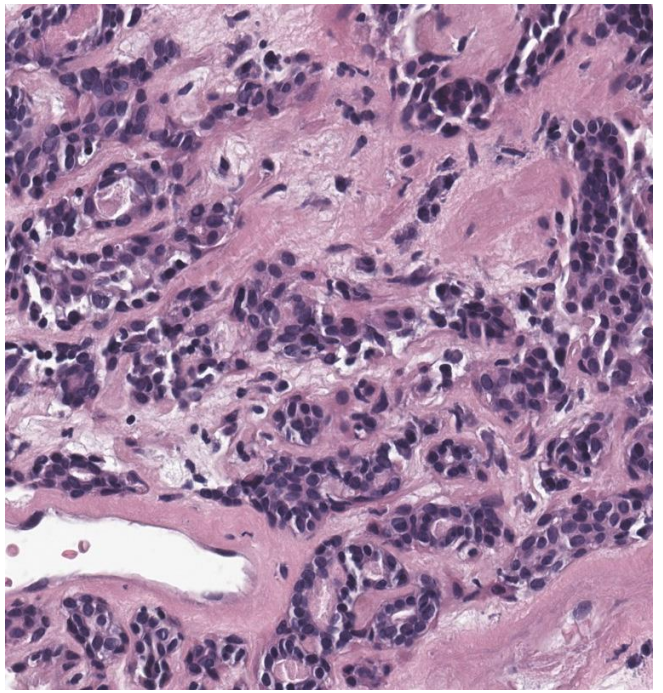
Potential Utility of ISH for HPV42

- Diagnosis of poorly differentiated primary DPAC
- Diagnosis of well-differential adenoma-like DPAC
- Diagnosis of DPAC at non-acral sites
- Diagnosis of metastatic DPAC

What is Your Diagnosis?

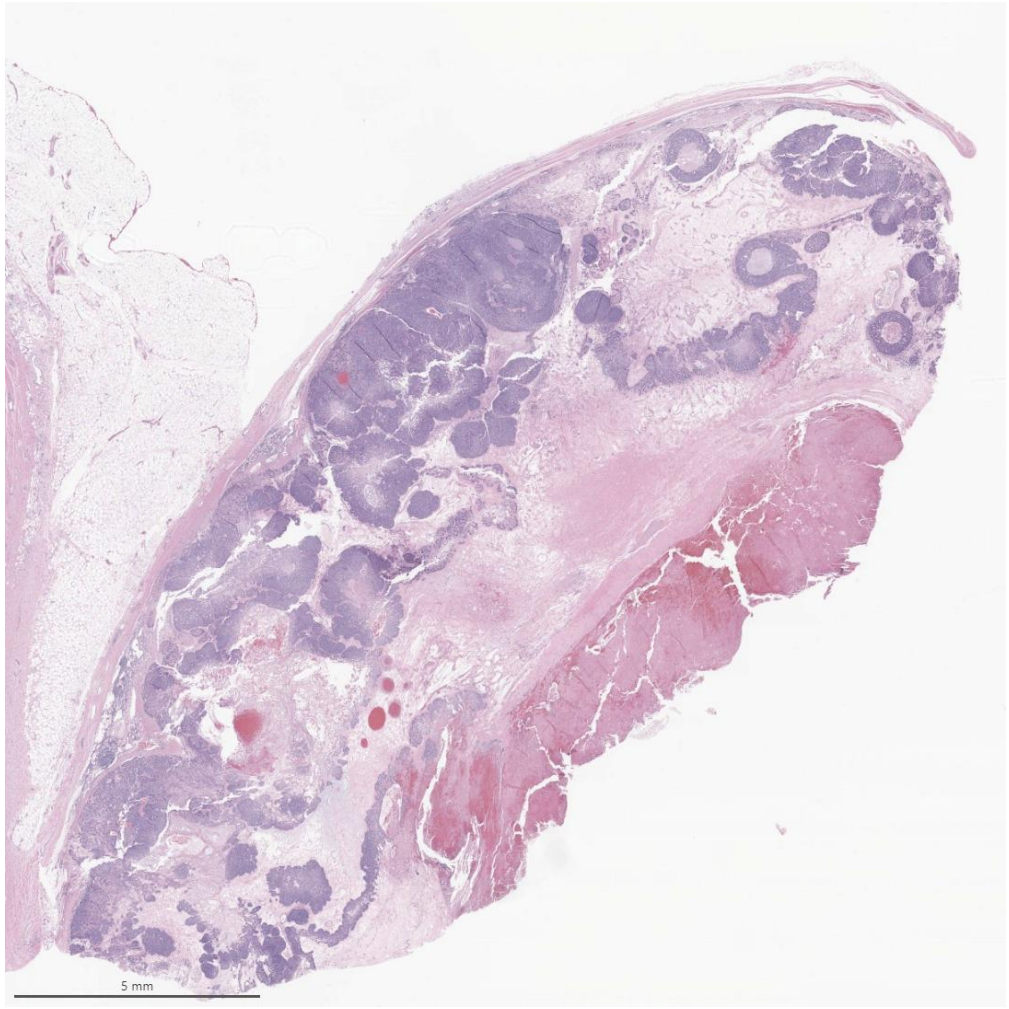


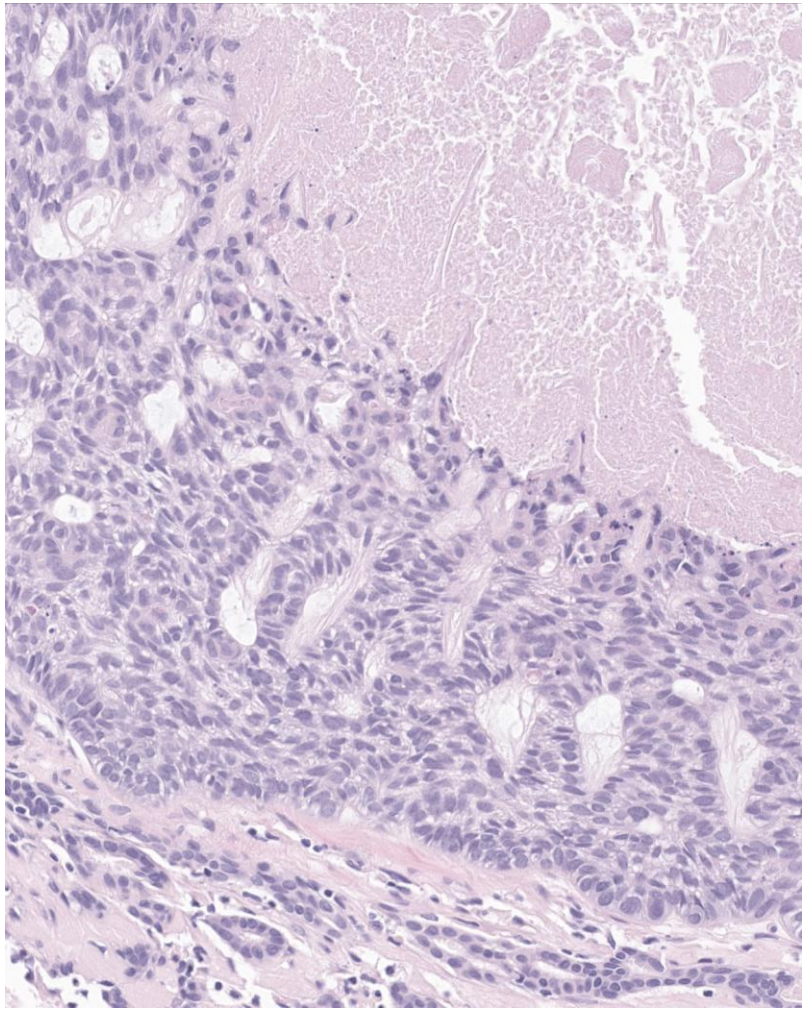




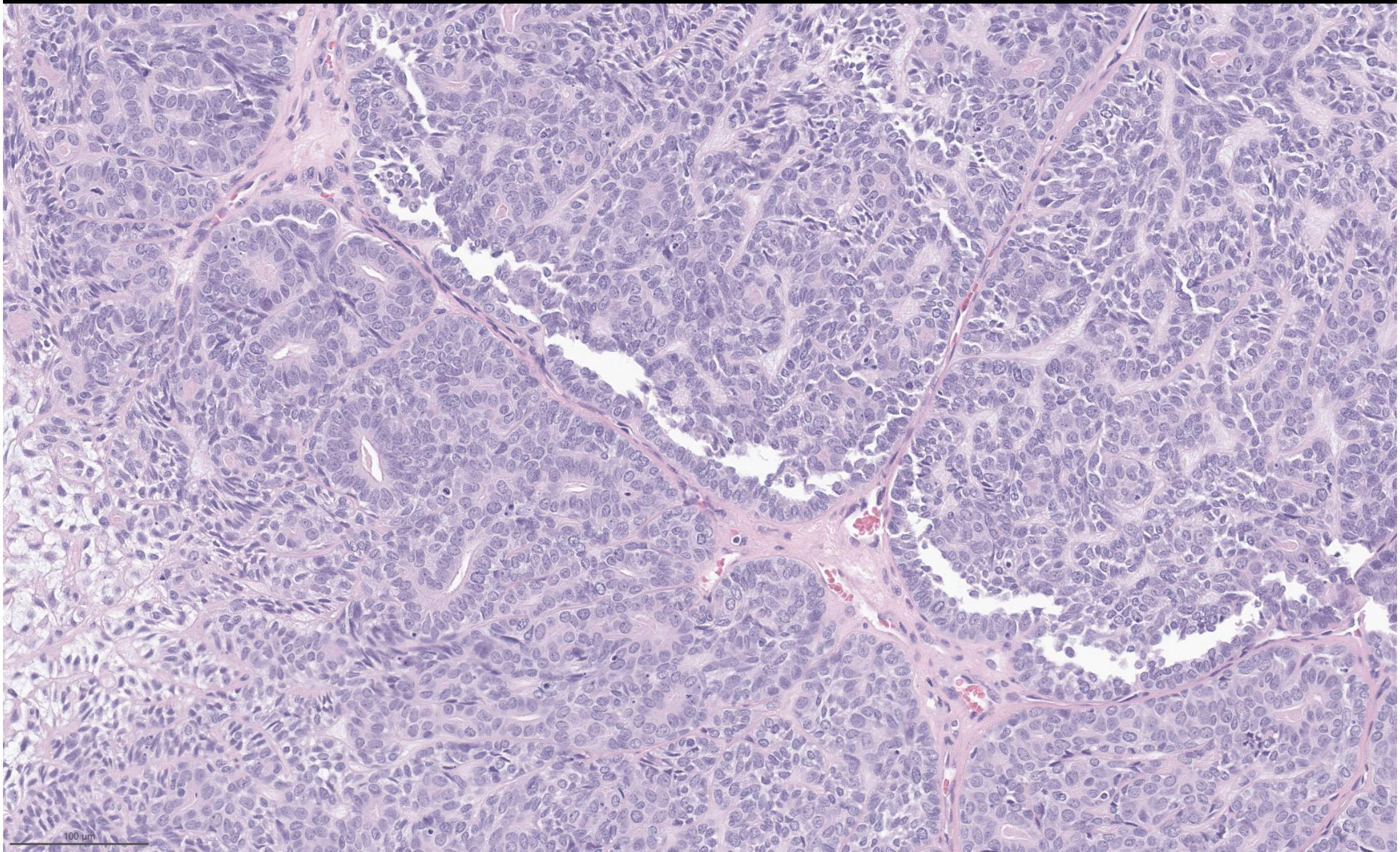
68 M with axillary mass

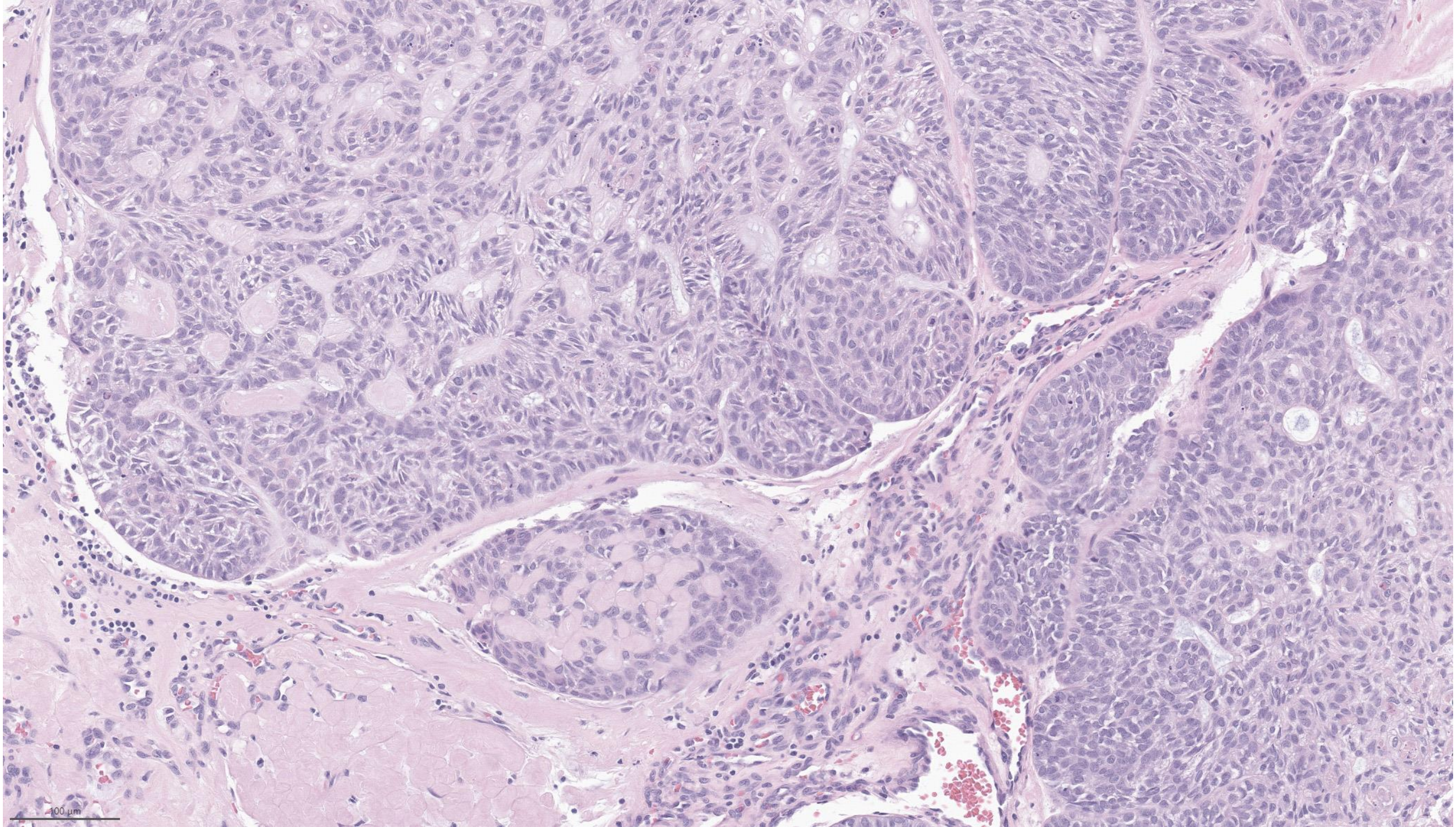
What is Your Diagnosis?





68 M with axillary mass


100 µm


100 µm

What is Your diagnosis?

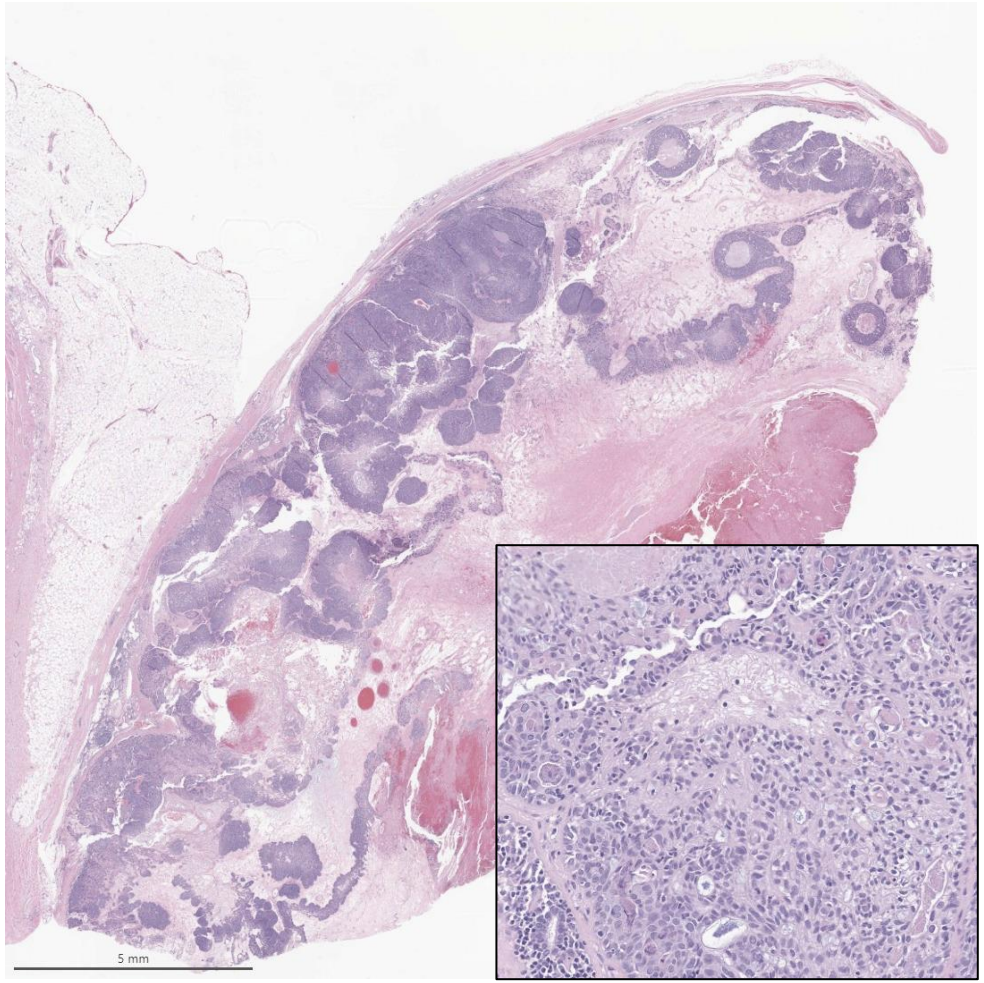
A. Adenoid cystic carcinoma

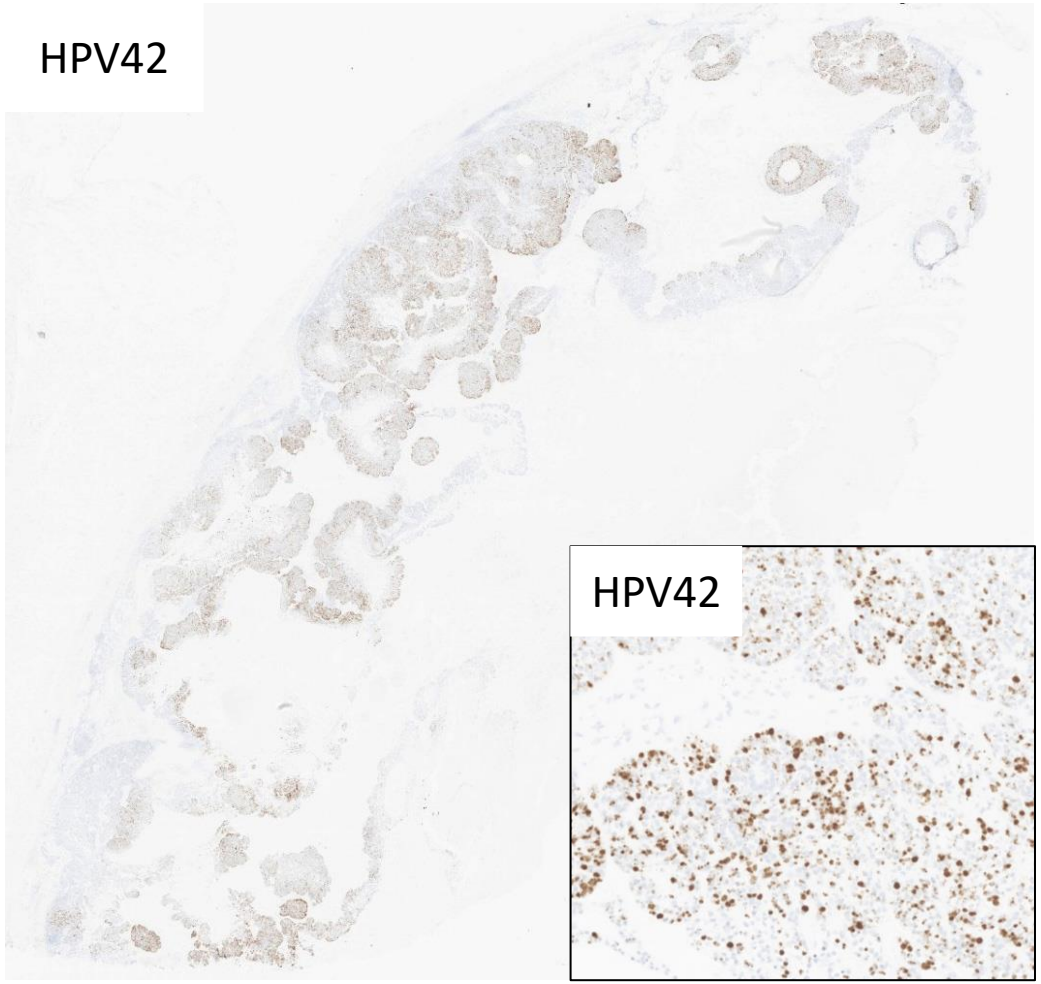
B. Spiradenocarcinoma

C. Cylindrocarcinoma

D. Other

Metastatic DPAC





Clinical History

- Prior diagnosis of ”benign” eccrine tumor in 2008; narrowly excised
- Recurred in 2010; excised with negative margin

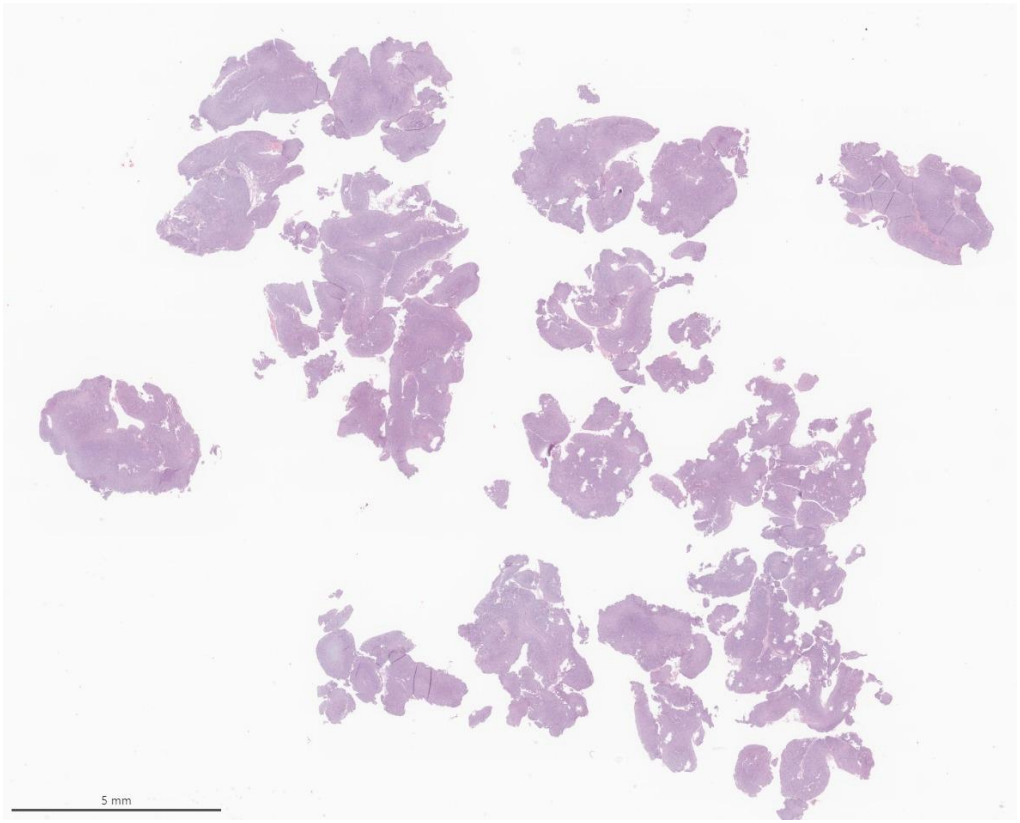
Final Anatomic Diagnosis

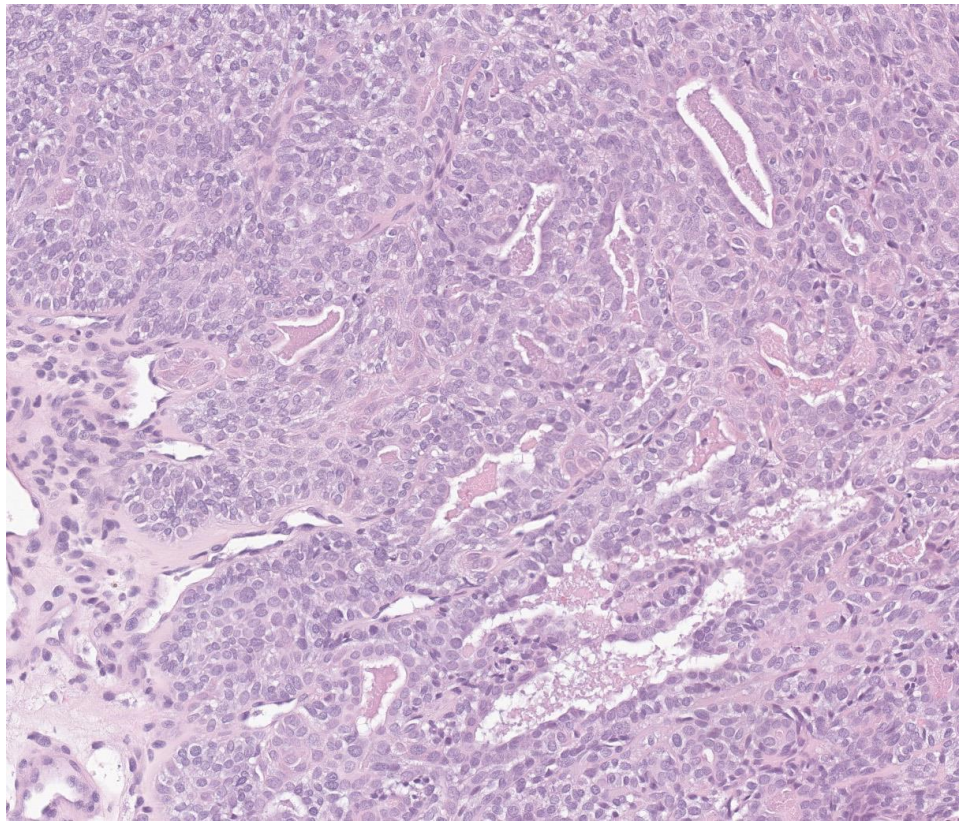
1. THUMB, SOFT TISSUE, LEFT
   Eccrine Acrospiroma (Eccrine Nodular Hidradenoma)
   FROZEN SECTION DIAGNOSIS: Epithelial lesion. Wait for permanent section for further classification (Dr. M. Bansal)
2. THUMB, SOFT TISSUE, LEFT
   Eccrine Acrospiroma (Eccrine Nodular Hidradenoma)

Comment on Case

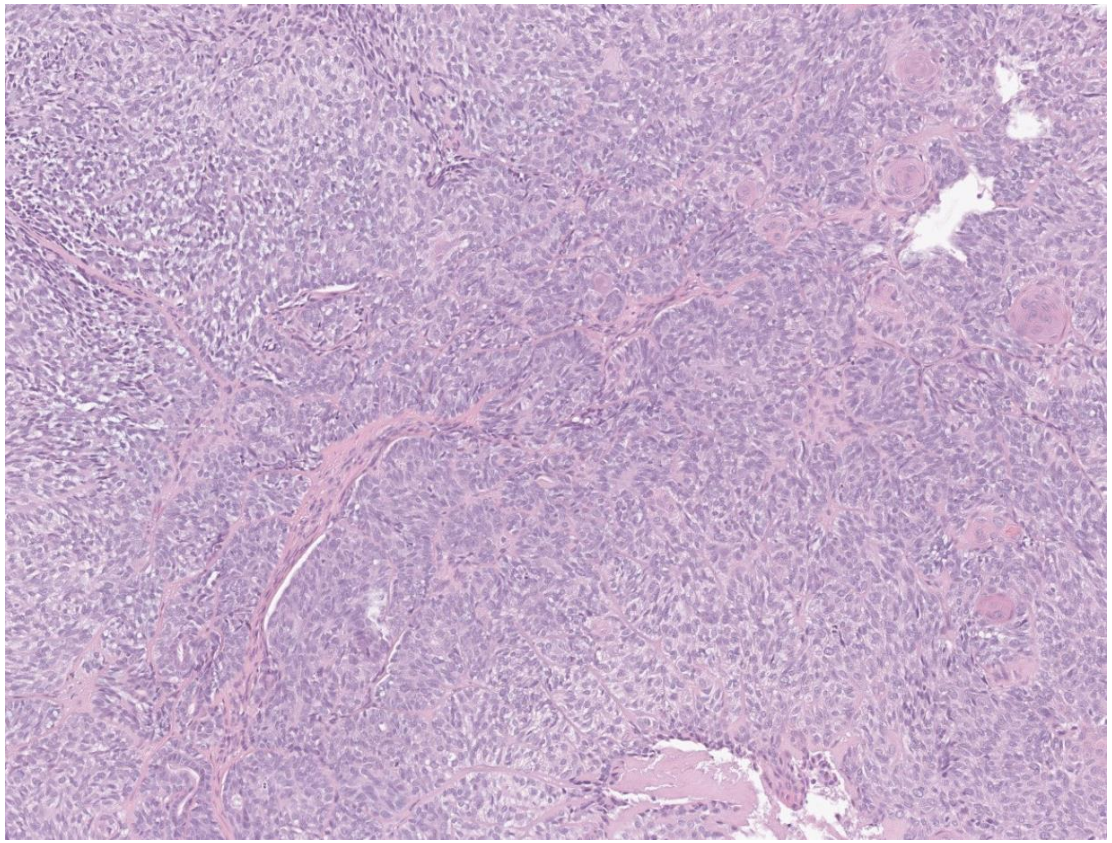
Although eccrine acrospiromas are benign tumors which do not exhibit a high rate of recurrence, close clinical follow-up is recommended due to the marginal excision of the tumor and the lack of clear margins of resection.

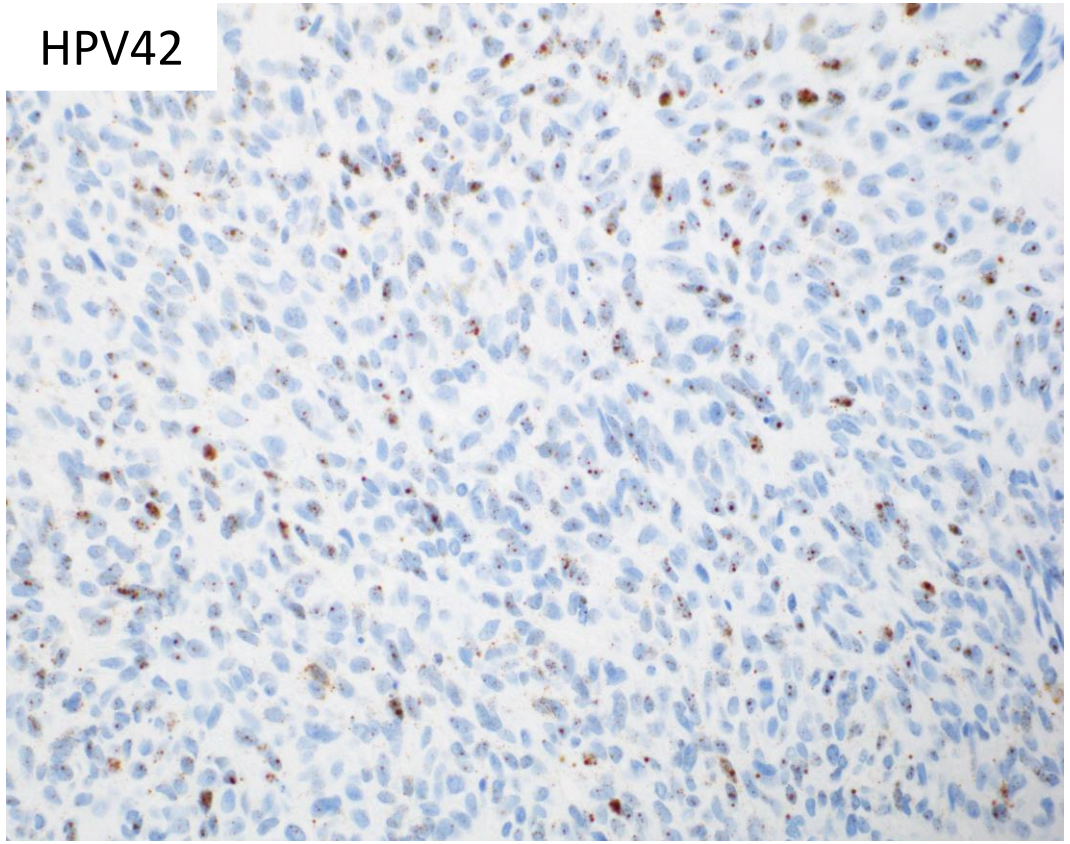
Biopsy from 2008

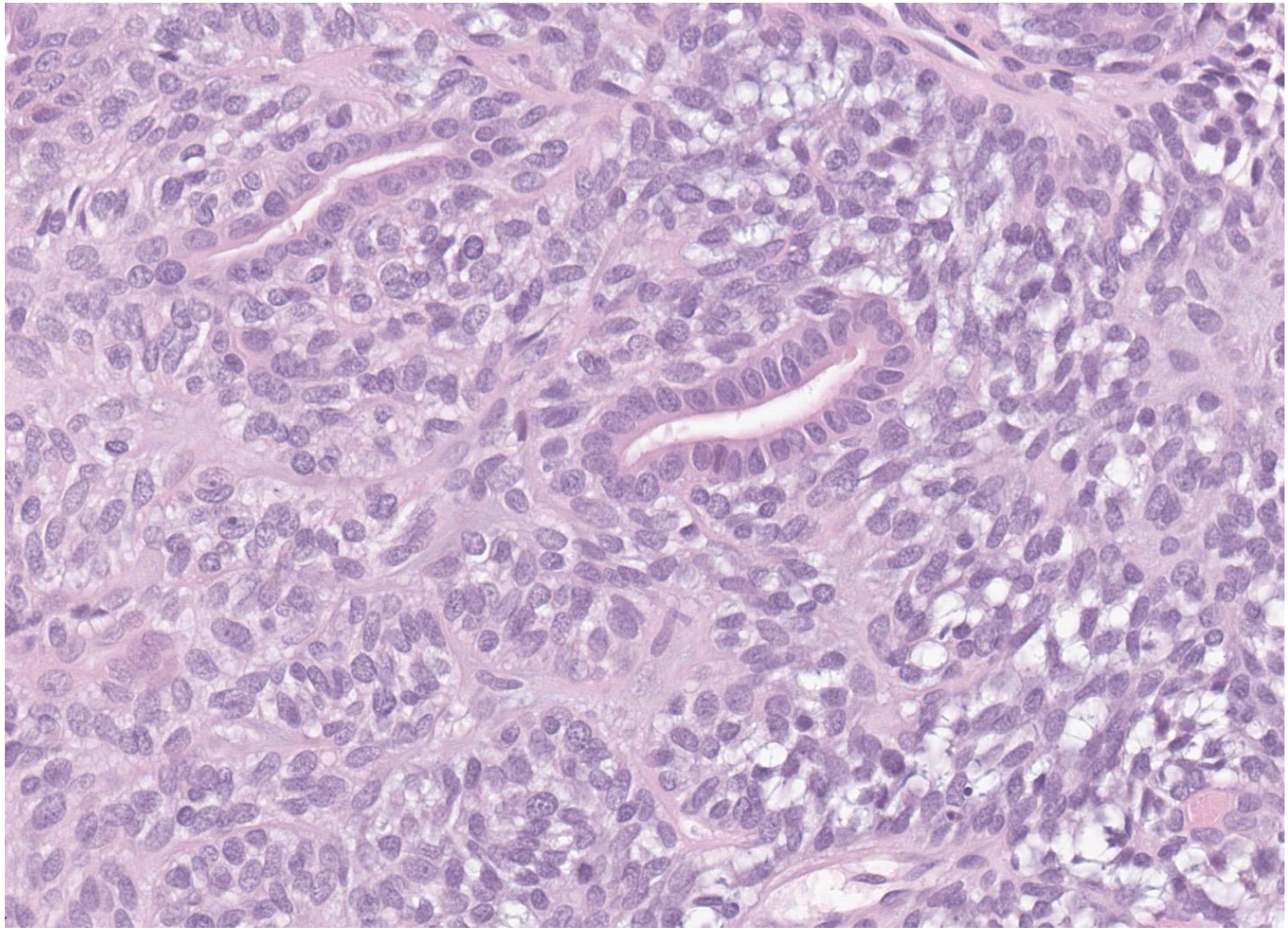




DPAC – Positive for HPV42







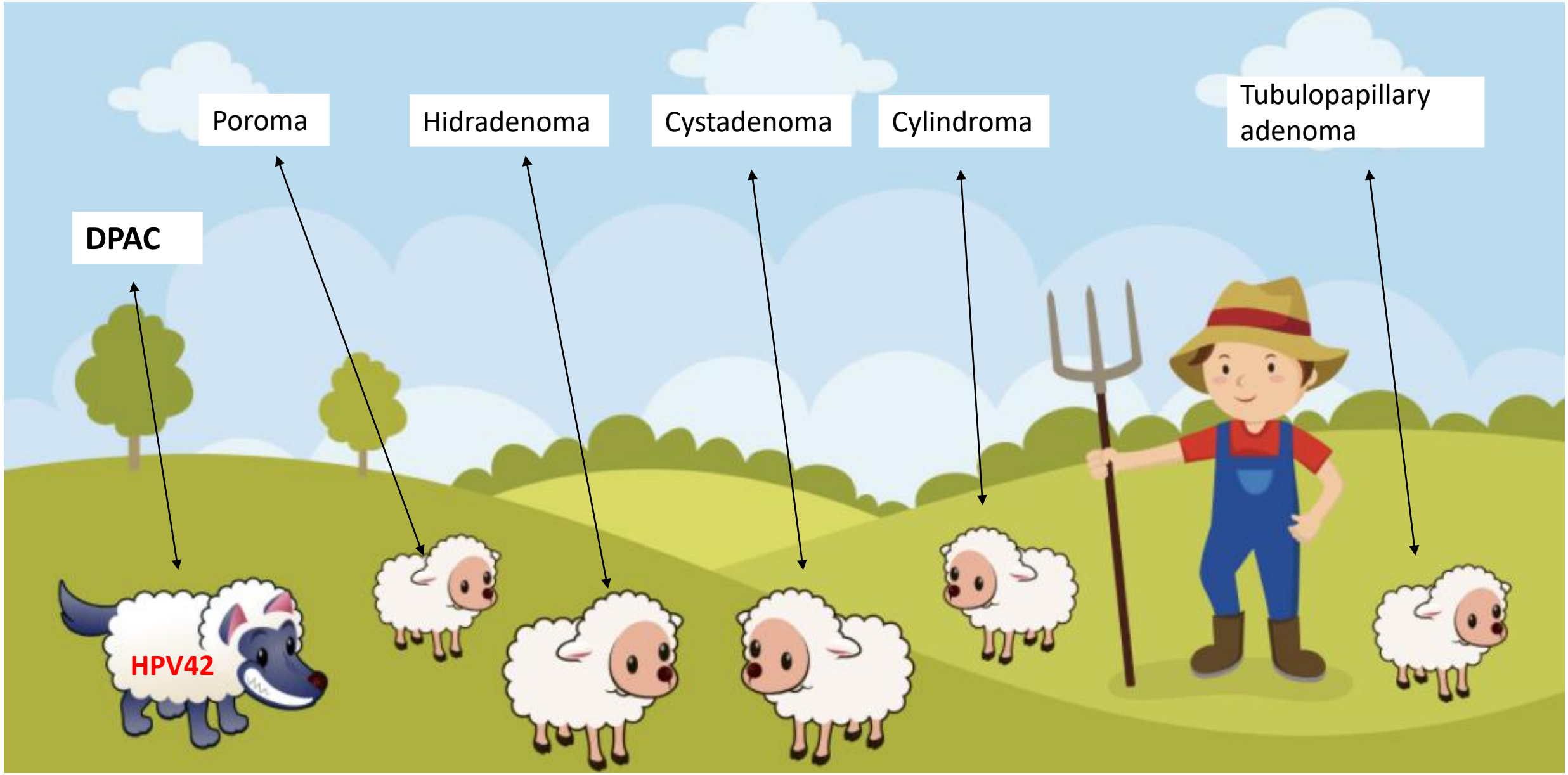
Digital Papillary Adenocarcinoma

- Scientific advances have helped improve the classification of sweat gland carcinoma
- DPAC can be confused with other sweat gland tumors
- HPV42 is associated with DPAC
- In situ hybridization of HPV42 can help support the diagnosis of DPAC and distinguish it from histologic mimics

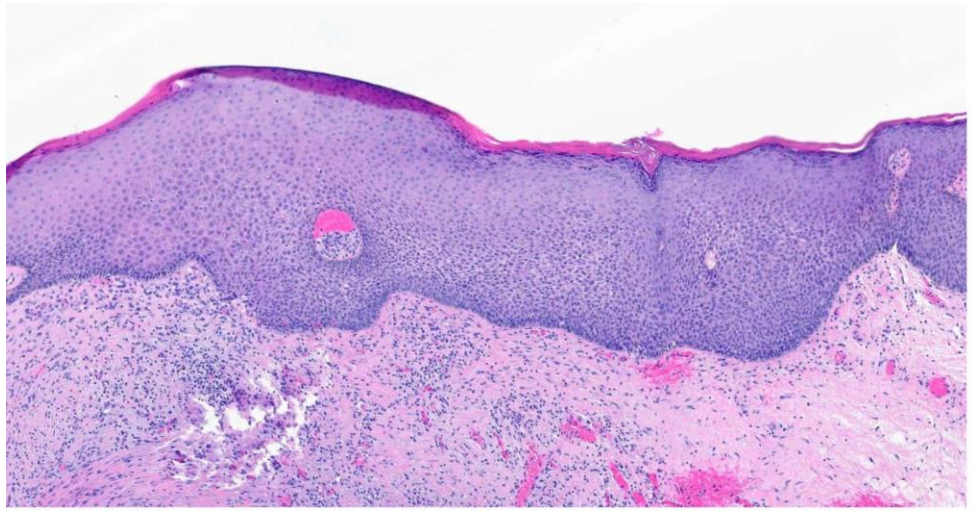
Virus-Associated Malignant Solid Skin Tumors

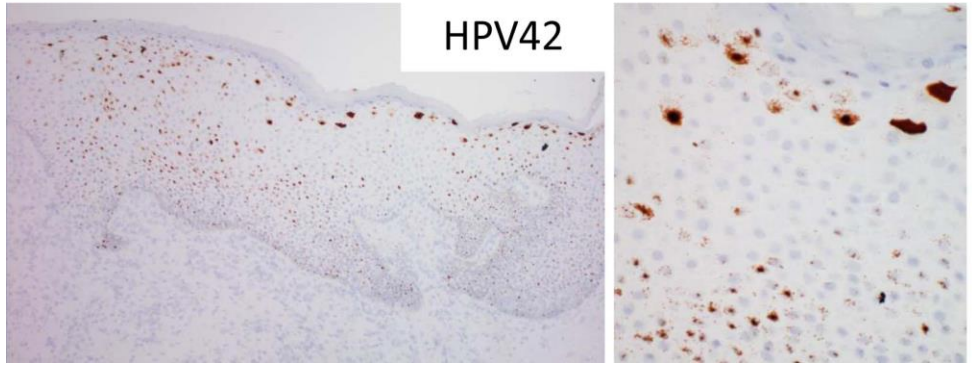
- Squamous cell carcinoma (HPV)
- Kaposi sarcoma (HHV8)
- Merkel cell carcinoma (MCPyV)
- DPAC (HPV42)

ISH for HPV42 helps to recognize DPAC



HPV42-associated SK-like lesion





Seborrheic Keratosis-like Lesions of the Cervix and Vagina

Report of a New Entity Possibly Related to Low-risk Human Papillomavirus Infection

Karen L. Talia, FRCPA, MBBS and W. Glenn McCluggage, FRCPath†*

Am J Surg Pathol 2017; 41:517-24

International Journal of Gynecological Pathology
41:649–654, Lippincott Williams & Wilkins, Baltimore

Case Report

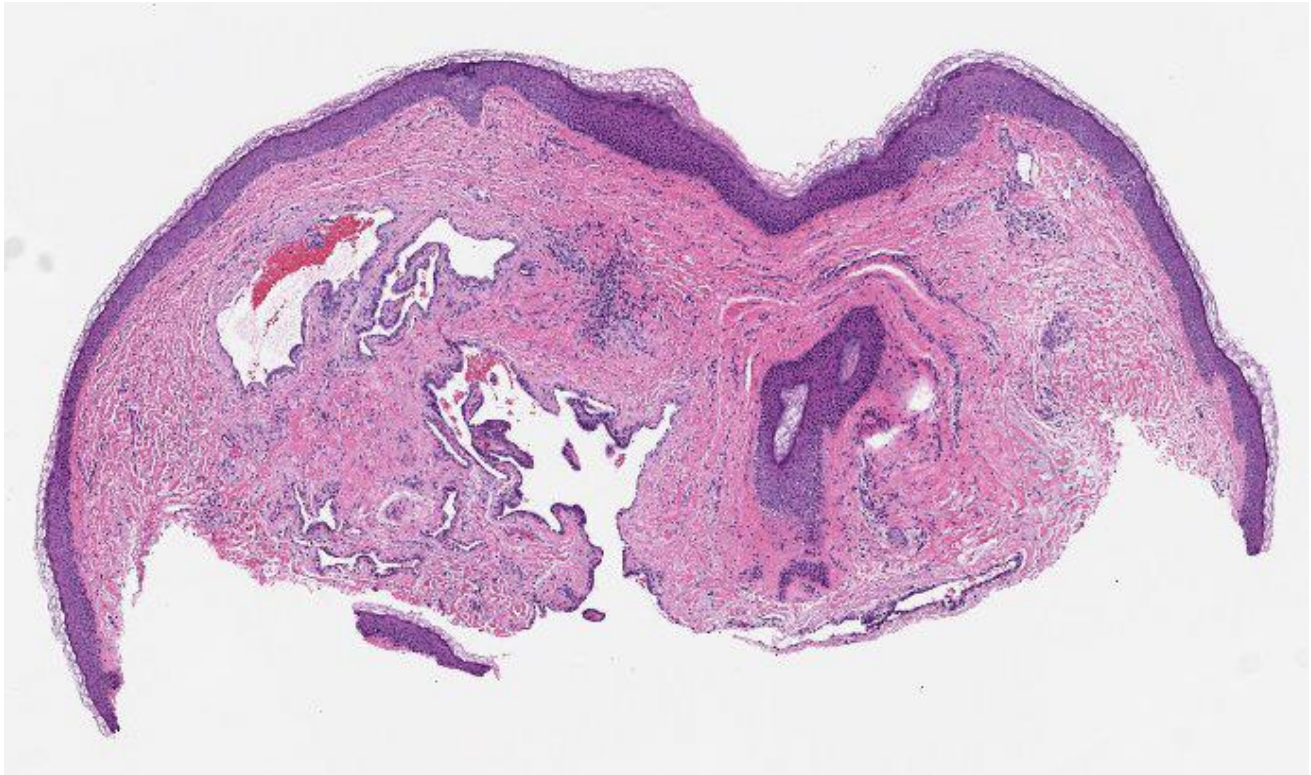
HPV42-associated Seborrhoeic Keratosis-like Lesion of the Cervix: First Reported Case With High-grade Morphology

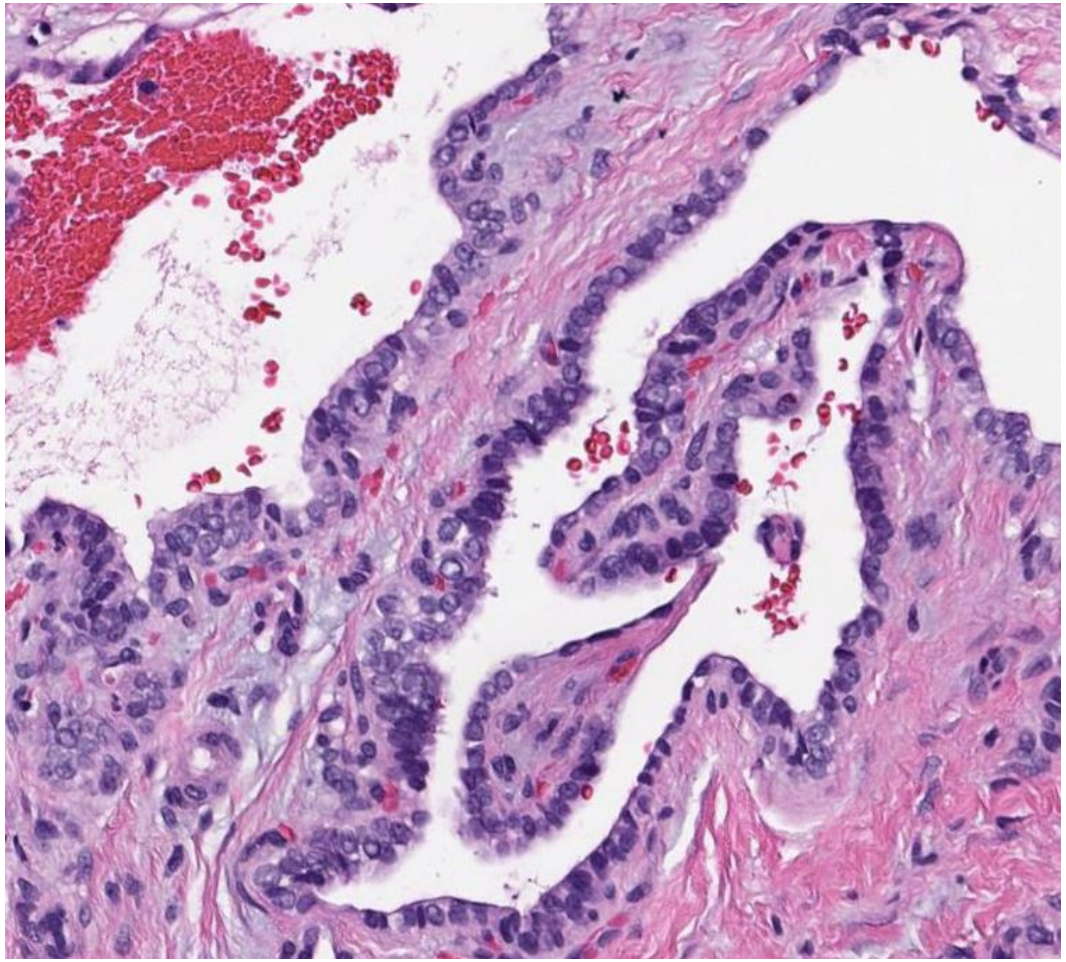
Karen L. Talia, F.R.C.P.A., Siavash Rahimi, F.R.C.Path., David Hawkes, Ph.D., and W. Glenn McCluggage, F.R.C.Path.

Adenocarcinoma - primary or metastatic?

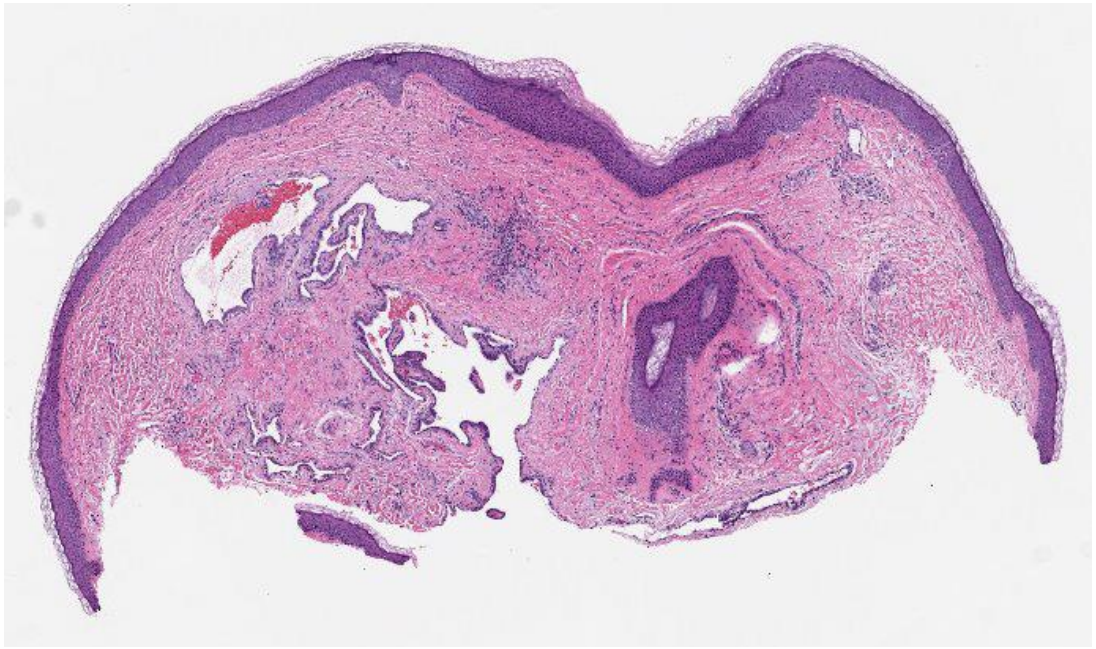
- Is there an associated adenoma?
- Does the carcinoma have distinct features that reveal its stage?
- Does the patient have a history of prior carcinoma?

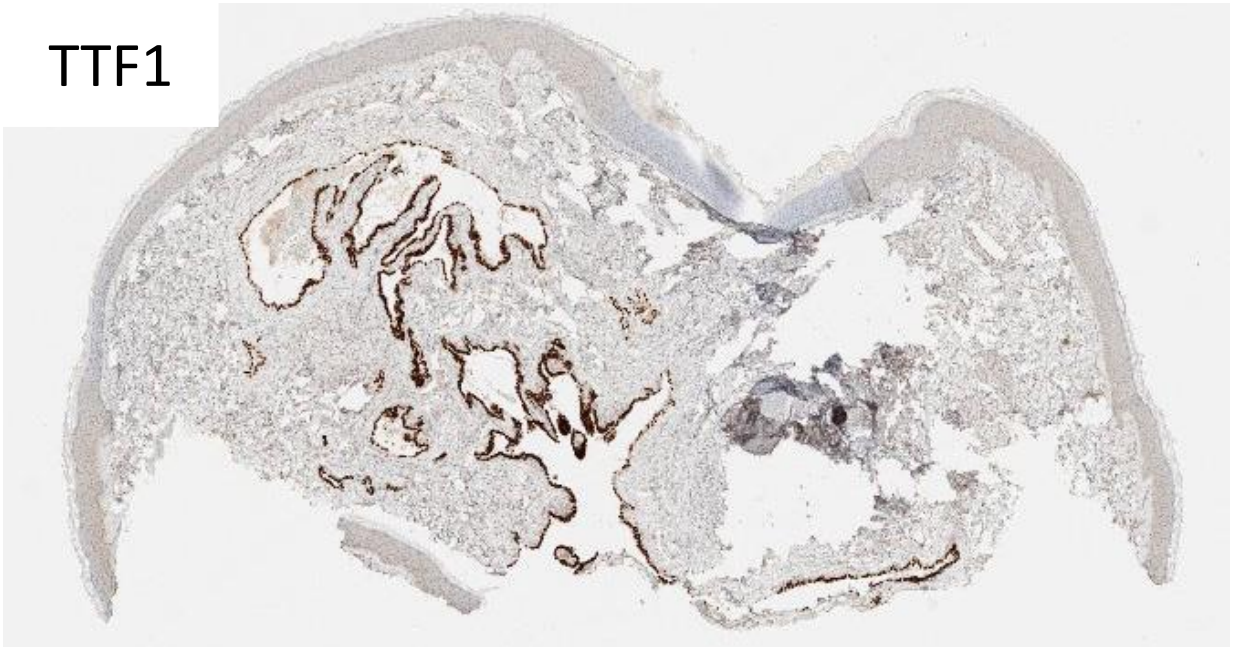
Primary neoplasm or metastatic?





Metastasis with Distinct IHC

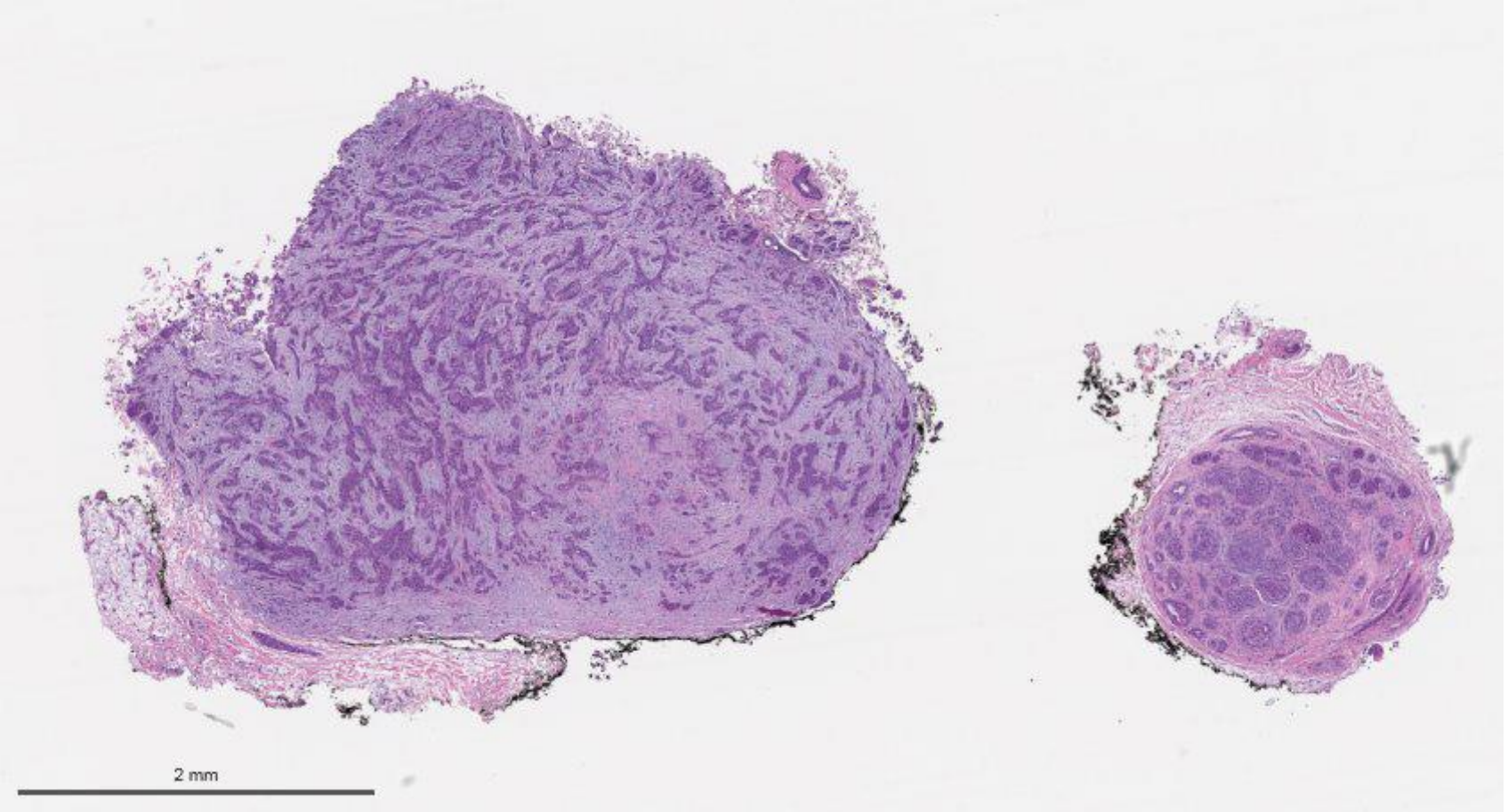




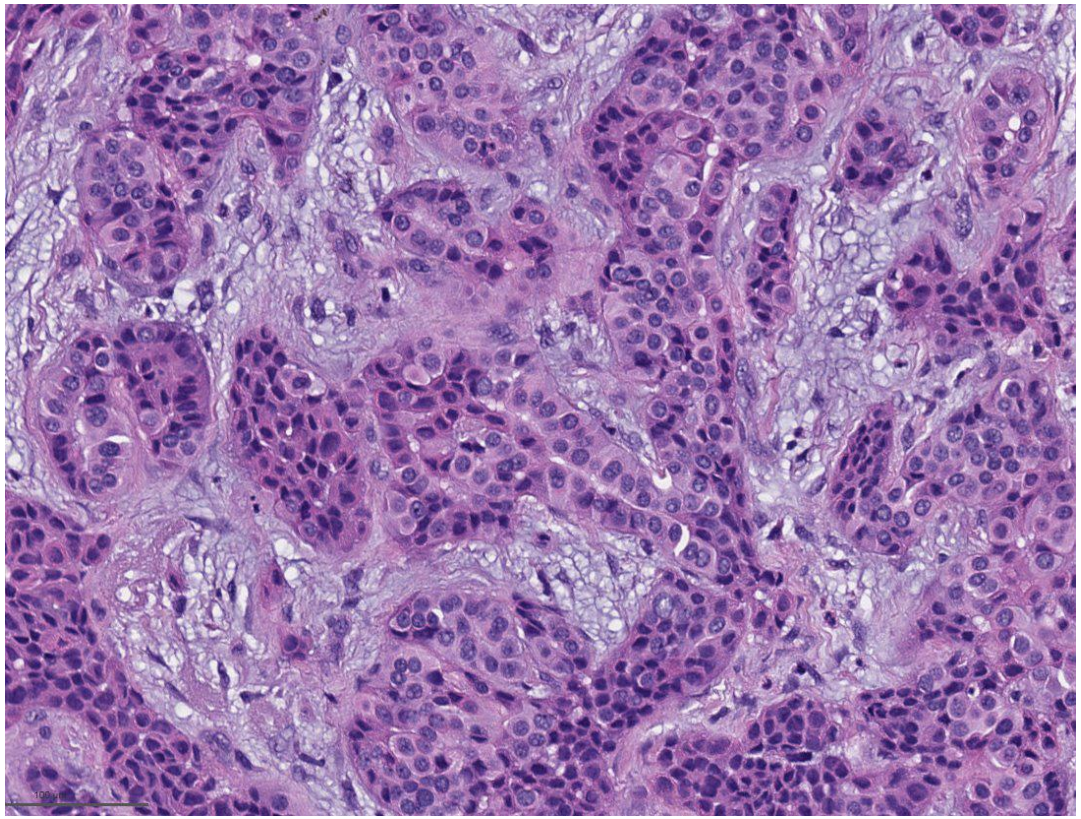
Metastatic Thyroid Carcinoma

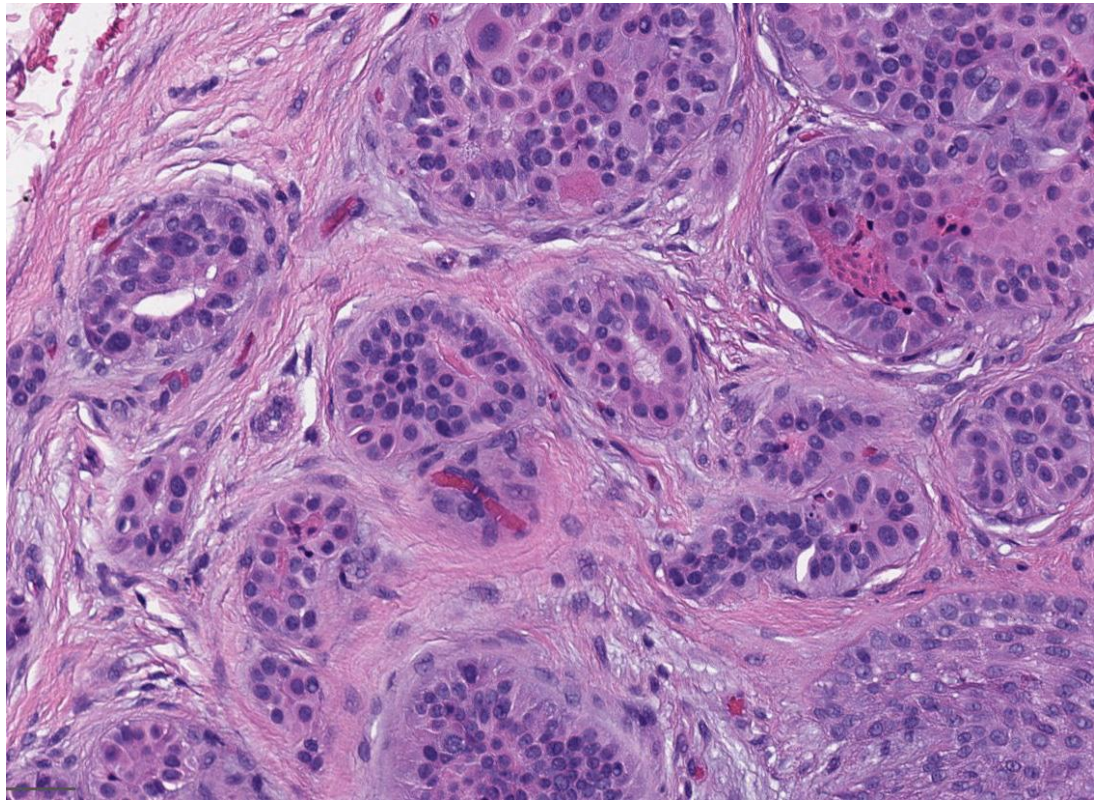
What is Your Diagnosis?

76M
Scalp



What is Your Diagnosis?





Original Pathology Interpretation

CLINICAL INFORMATION:
A. SKIN.Right vertex scalp: Patient with hepatocellular carcinoma and 1 cm exophytic white dermal nodule of unclear duration on right vertex of scalp. I expected cyst but it is not cystic shelled out DDX: CARTILAGINOUS MIXED TUMOR/ECCRINE? PEN/SCHWANNOMA. D48.5 - **Please check margins**

DIAGNOSIS:
A. SKIN.Right vertex scalp:
-MODERATELY DIFFERENTIATED ADENOCARCINOMA, POSSIBLY REPRESENTING AN ADENOCARCINOMA, ARISING IN A PRE-EXISTING CHONDROID SYRINGOMA/MIXED TUMOR.

Diagnosis: Metastatic Cholangiocarcinoma

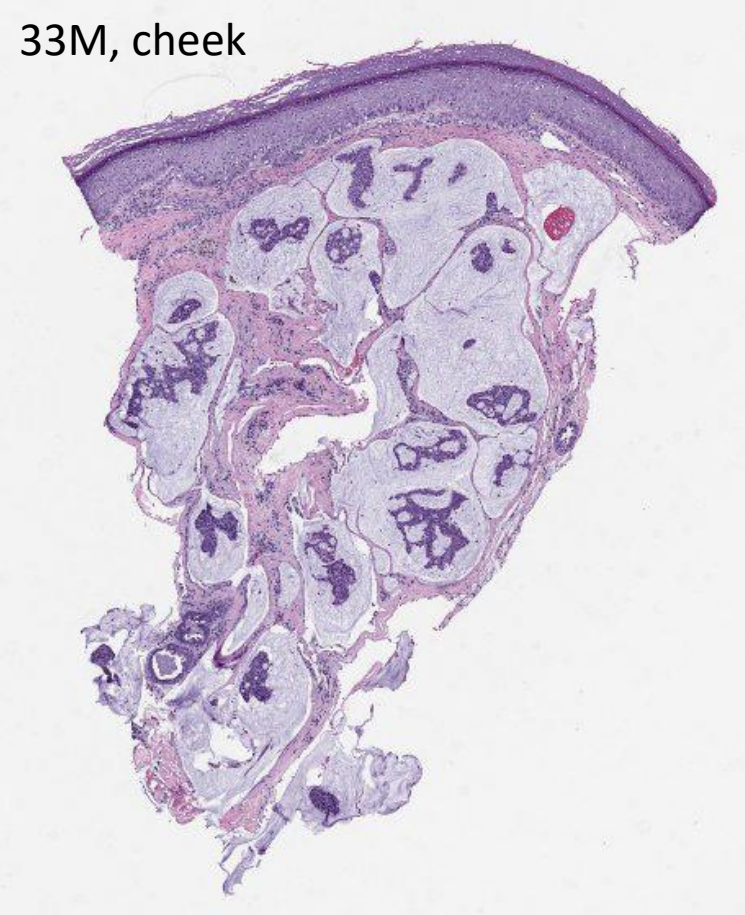
CYTOLOGIC DIAGNOSIS:

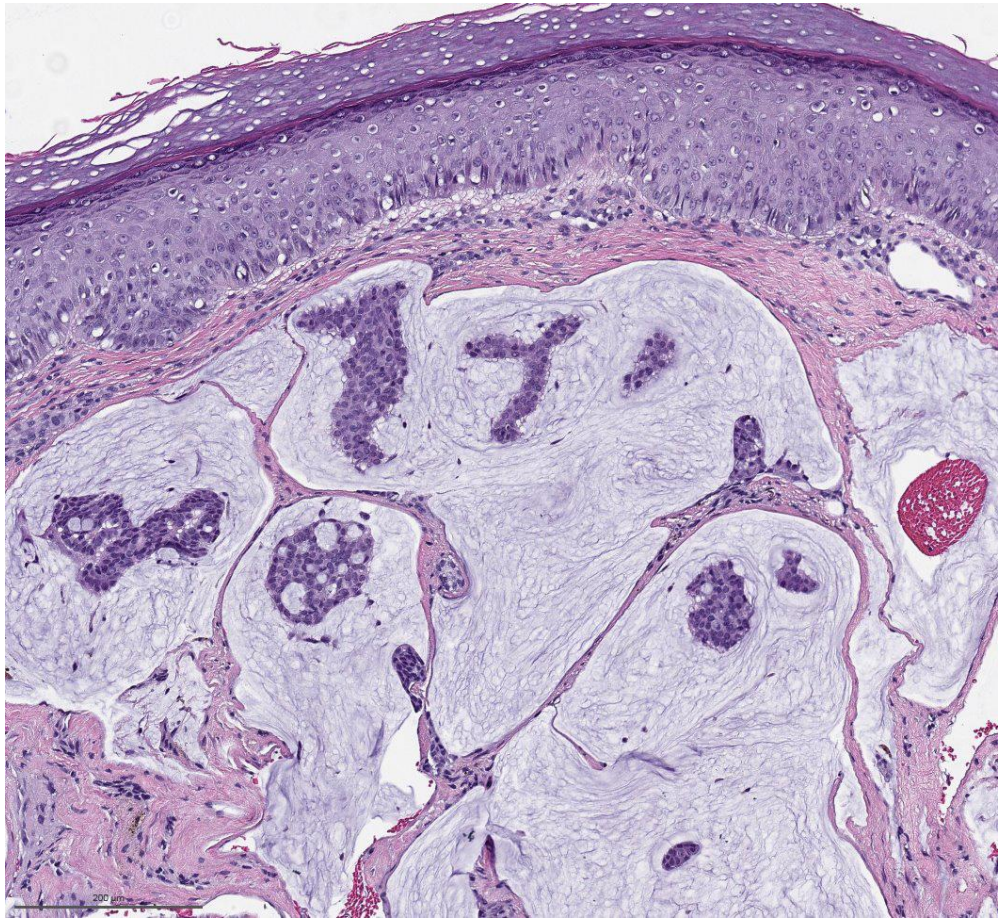
1. Common hepatic duct stricture, Brushing
Positive for malignant cells. Poorly differentiated carcinoma.
Immunocytochemical stain(s) pending.

Work-up of Adenocarcinoma in Dermis

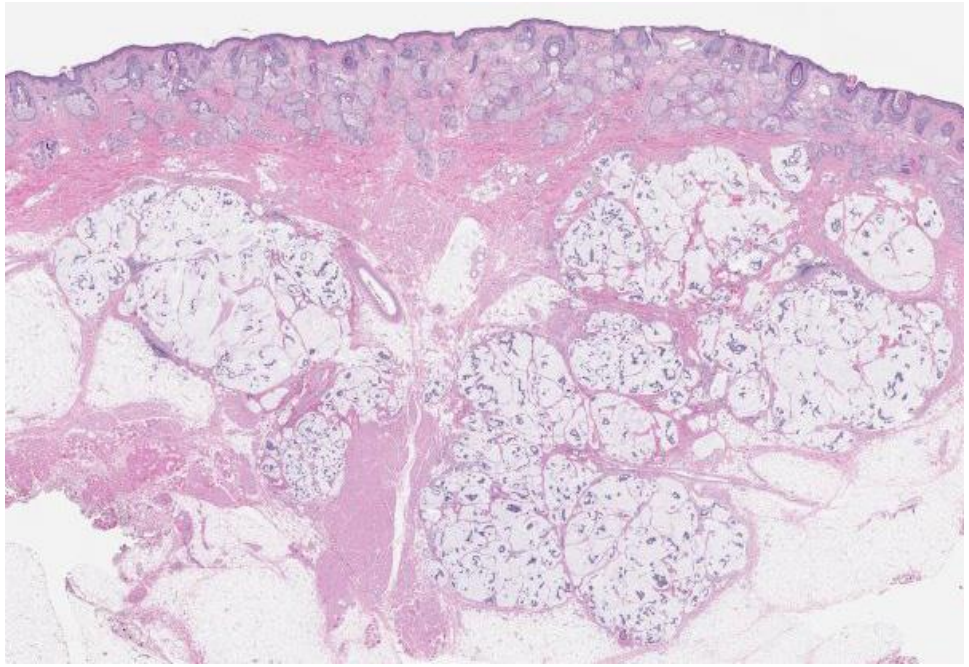
- Clinical history is paramount
- Review of entire tumor may provide clues (e.g., associated adenoma)
- Ancillary studies can help, but not always
- Tumors with features that do not fit a known entity may be mets
- Comparative pathology (H&E, IHC, molecular) is important

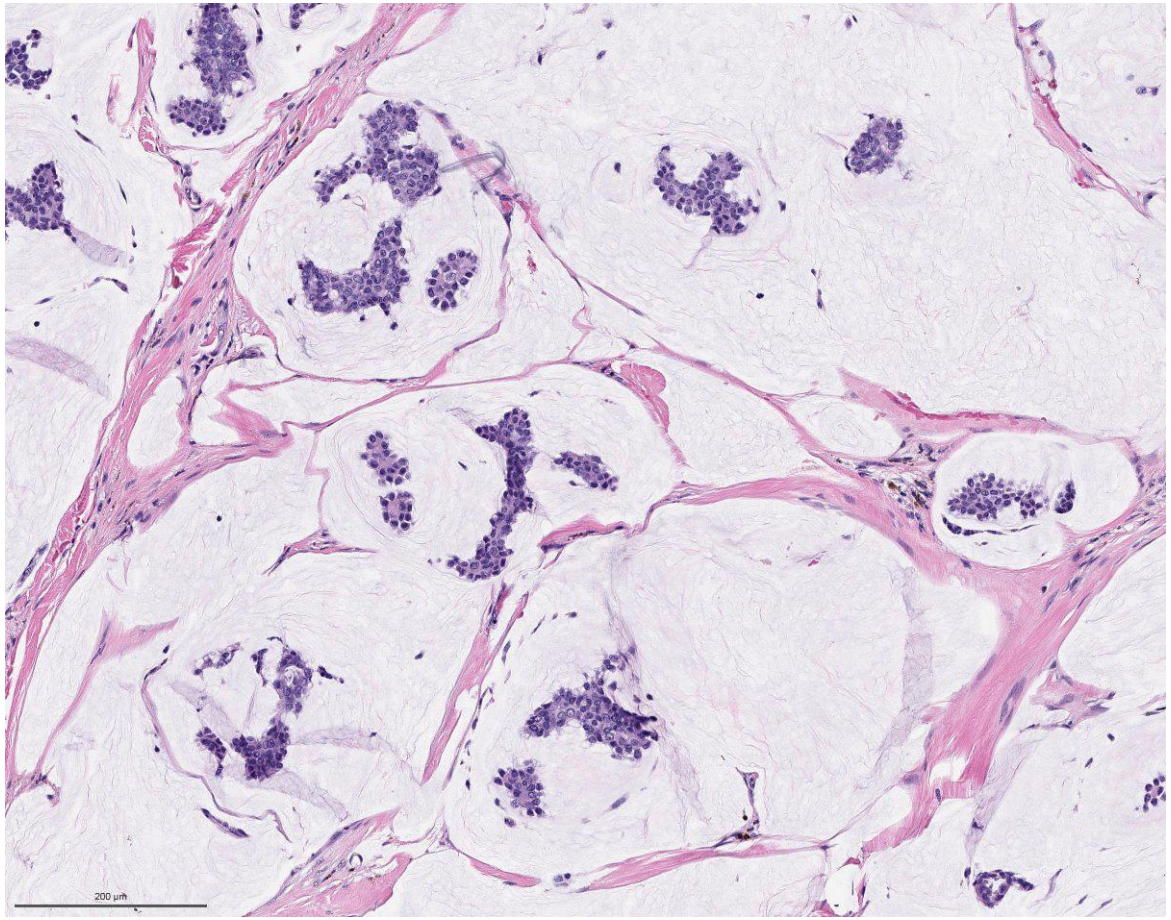
Mucinous Carcinoma



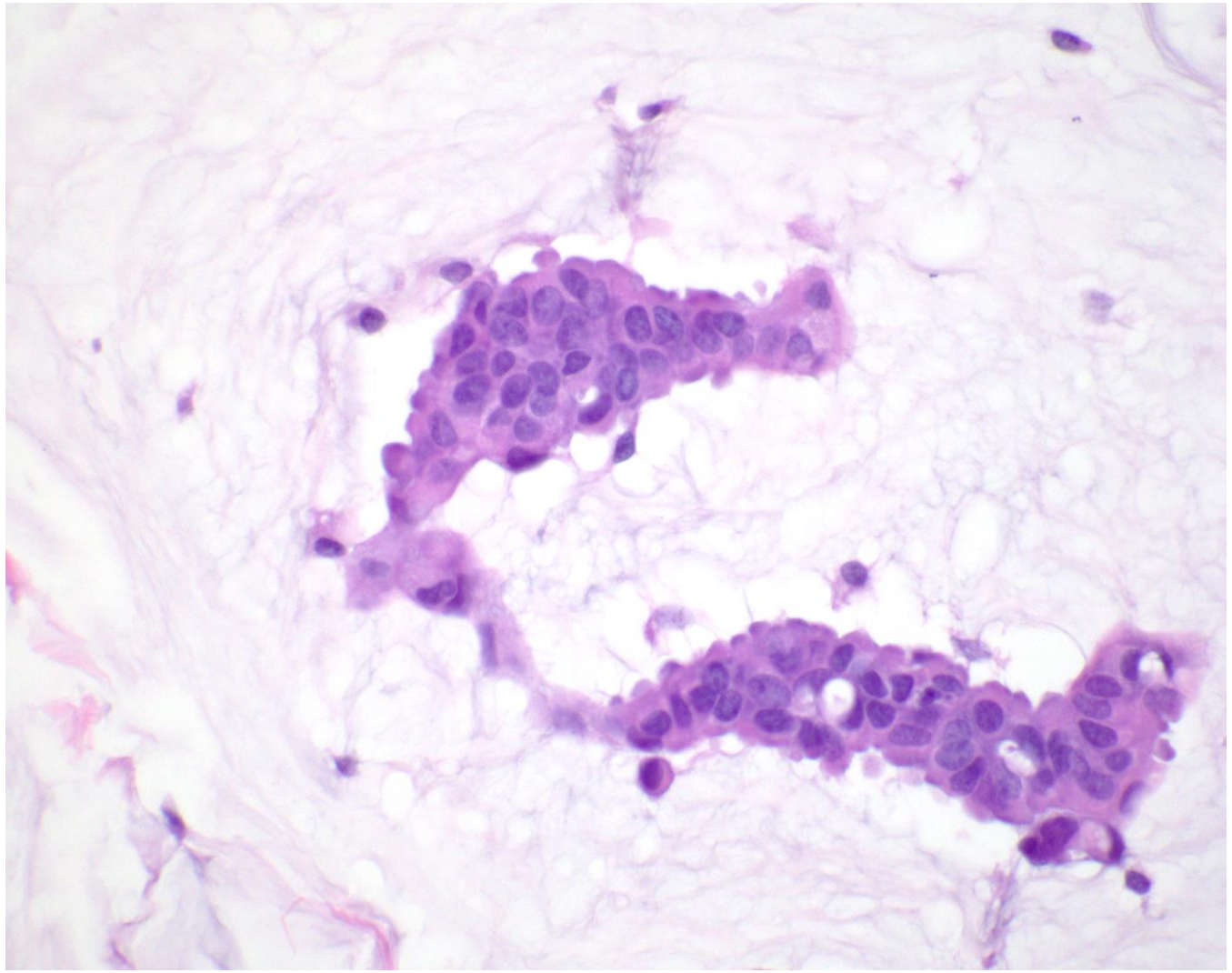


Primary Cutaneous Mucinous Carcinoma

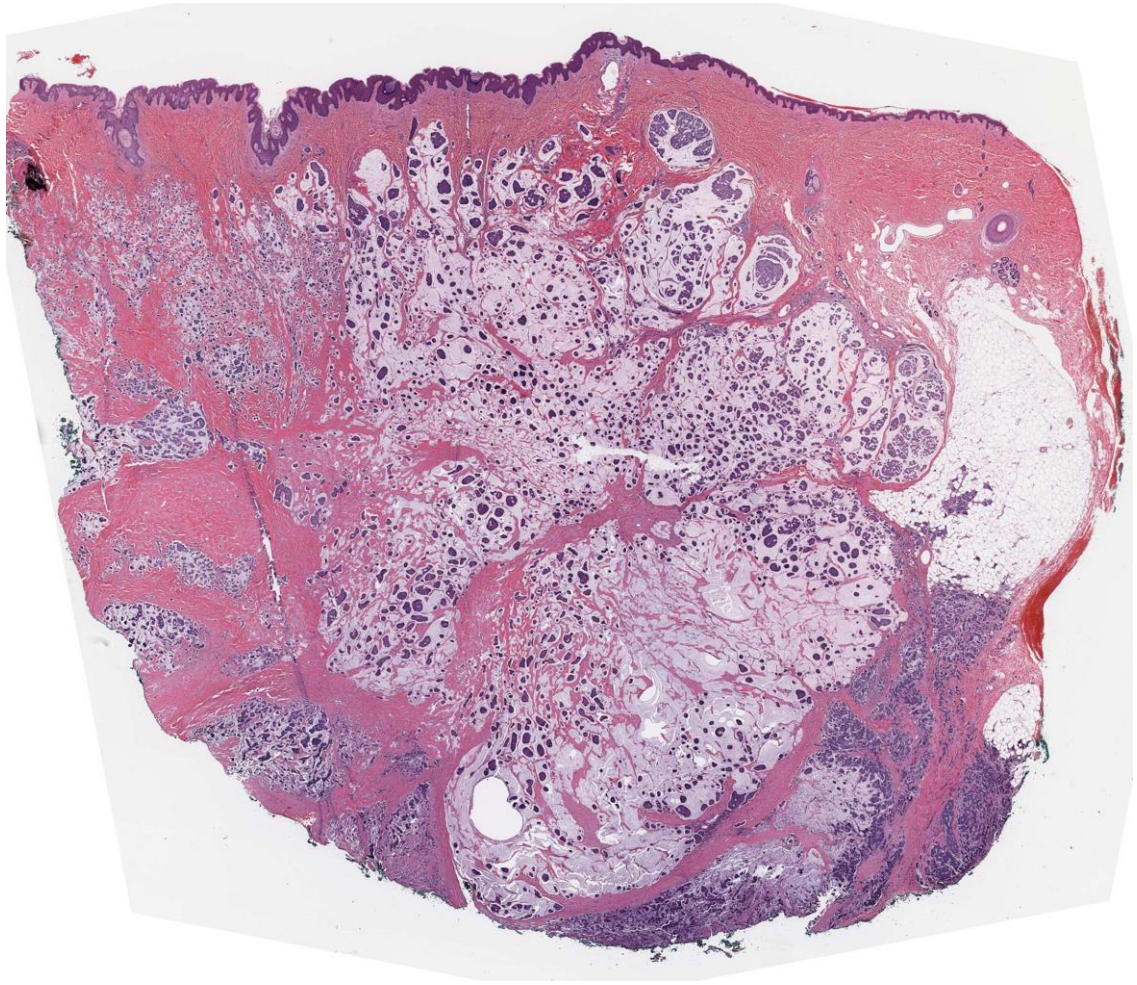


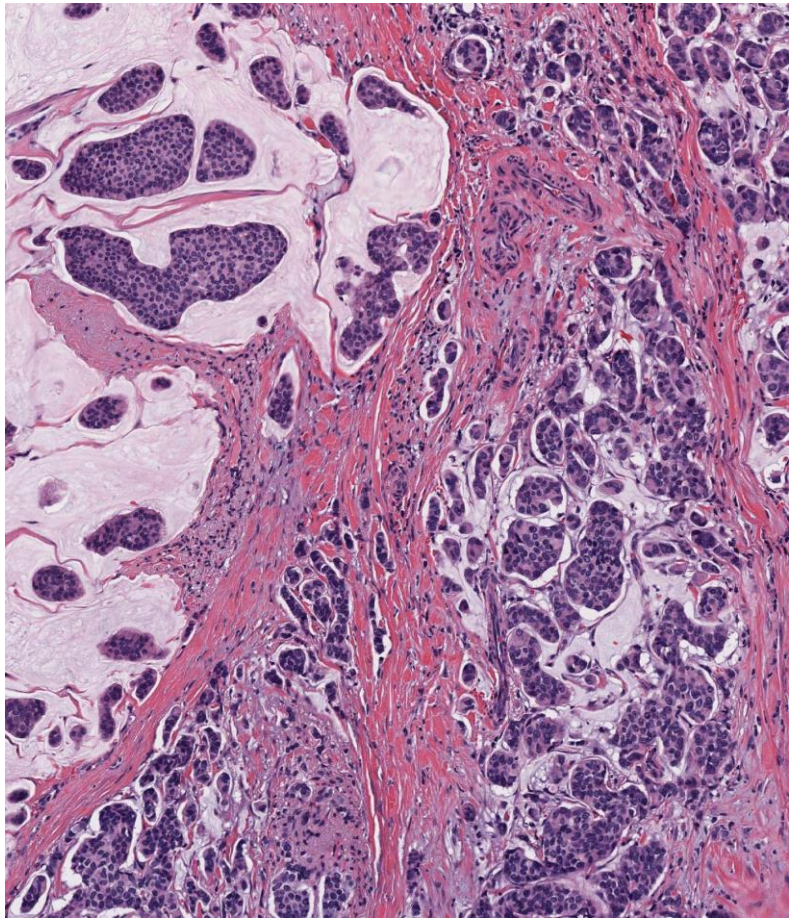


Mucinous Carcinoma - Cytology



Mixed Mucinous Carcinoma





Mucinous Carcinoma

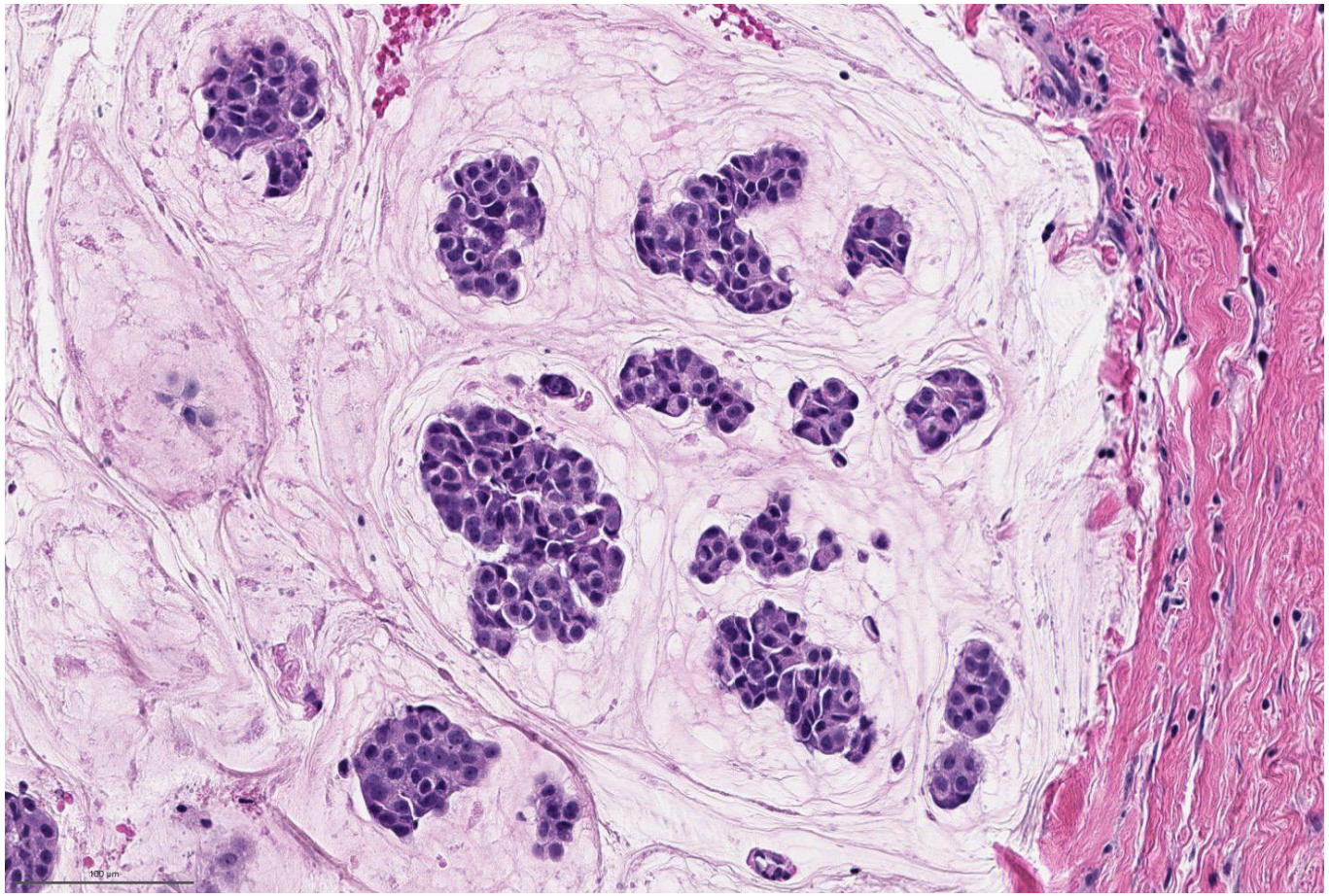
- First report by Lennox et al J Pathol Bacteriol 1952; 74: 865-80

- Requena&Sangueza (Cutaneous Adnexal Neoplasms; Springer, 2017):
  - Reviewed 287 cases of reported mucinous carcinoma
  - 80% of patients are between 50-60 yrs of age
  - Predilection for head and neck area, especially eyelids
  - Associated metastases
    - 21/287 (7.3%) with regional LN metastasis
    - 9/287 (3.1%) with distant metastasis

Mucinous Carcinoma – Primary vs Metastatic

- Requena & Sangueza in Cutaneous Adnexal Neoplasms, 2017; p326:
  - “The majority of the mucinous carcinomas involving the skin are metastatic”
  - “In any patient with mucinous ca of the skin, it is important to r/o metastasis”
- MSKCC Experience
  - Pure “low grade” mucinous carcinomas tend to be primary cutaneous
  - Most metastatic carcinomas to the skin are mixed mucinous carcinomas or adenocarcinomas with mucinous features

Mucinous (Colloid) Mammary Carcinoma



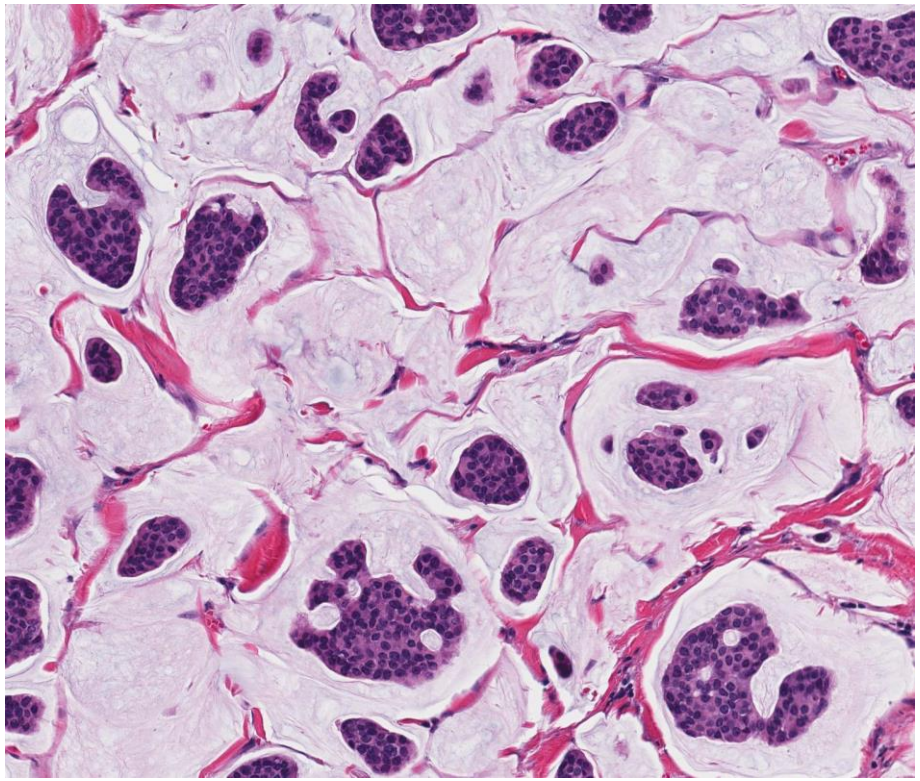
MSKCC Experience

- 849 patients with mucinous mammary carcinoma
- 159 metastasized (15%)
- Most common sites of metastasis
  - Lung
  - Lymph node

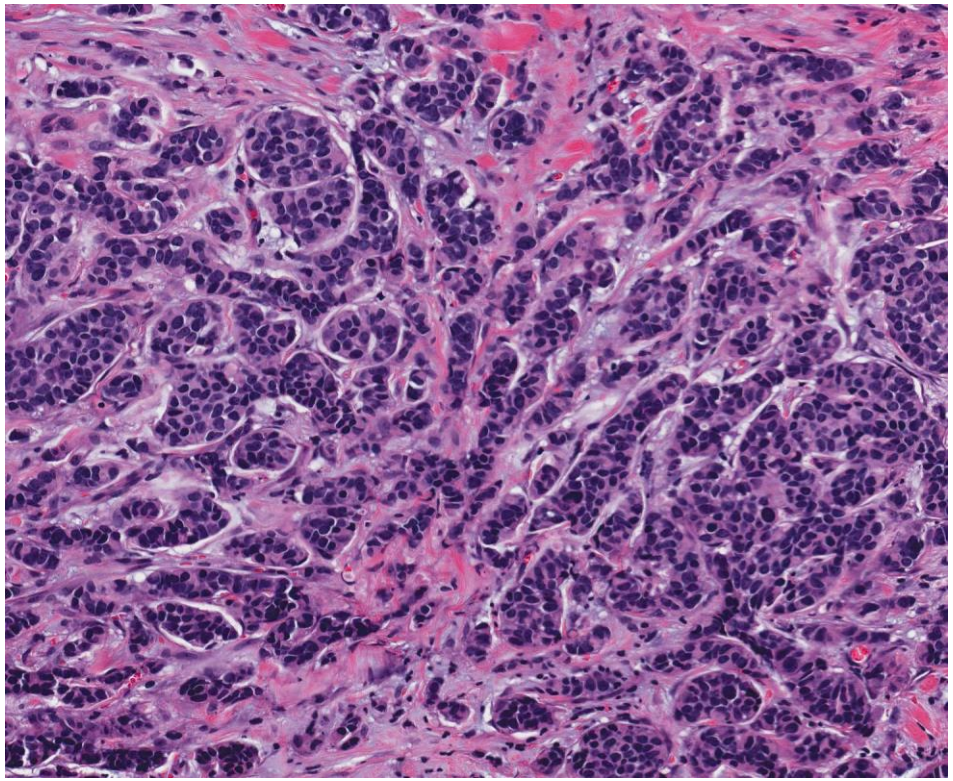
- **First metastasis to skin very rare**

Mixed Mucinous Carcinoma

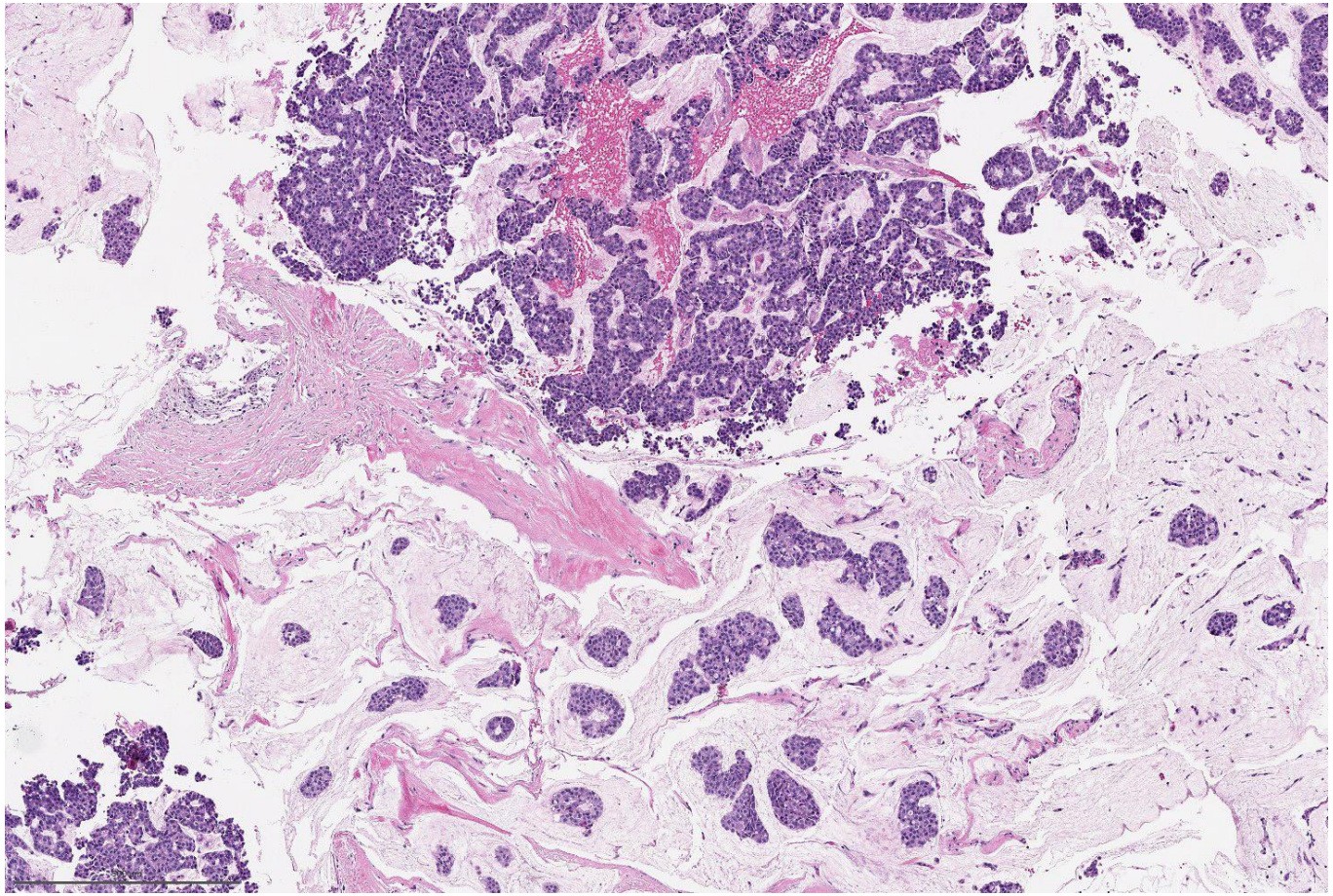
Stroma-Rich, Cell-Poor



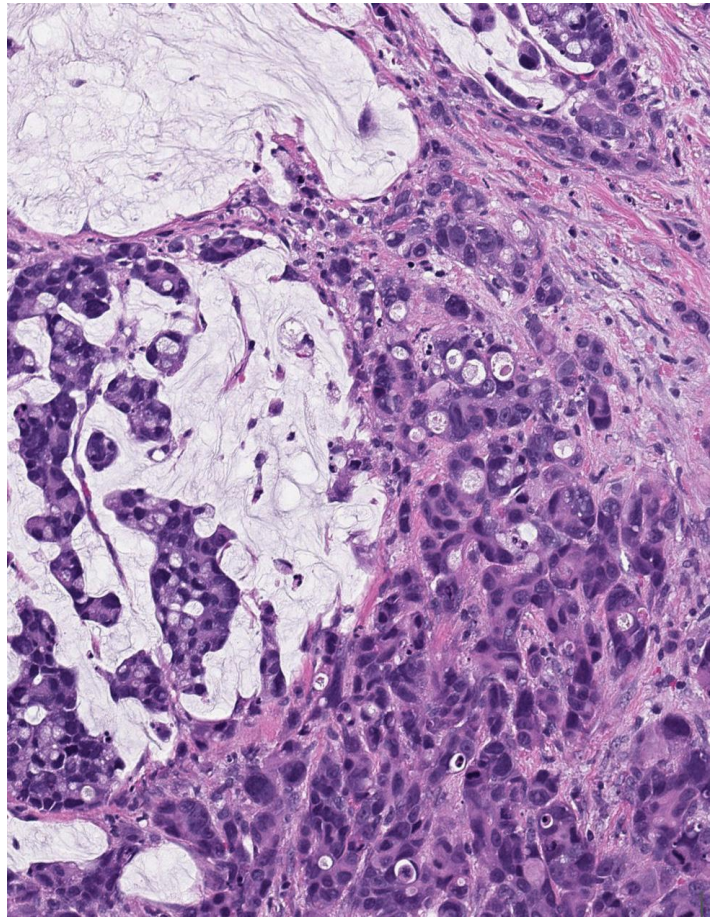
Stroma-Poor, Cell-Rich

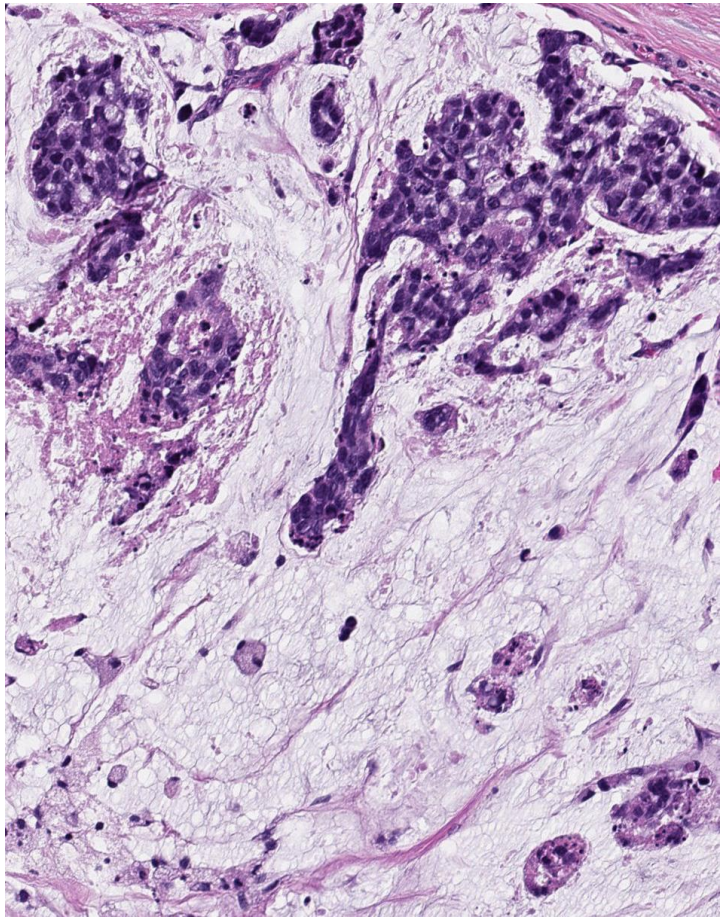


Metastasizing Mucinous Mammary Carcinoma

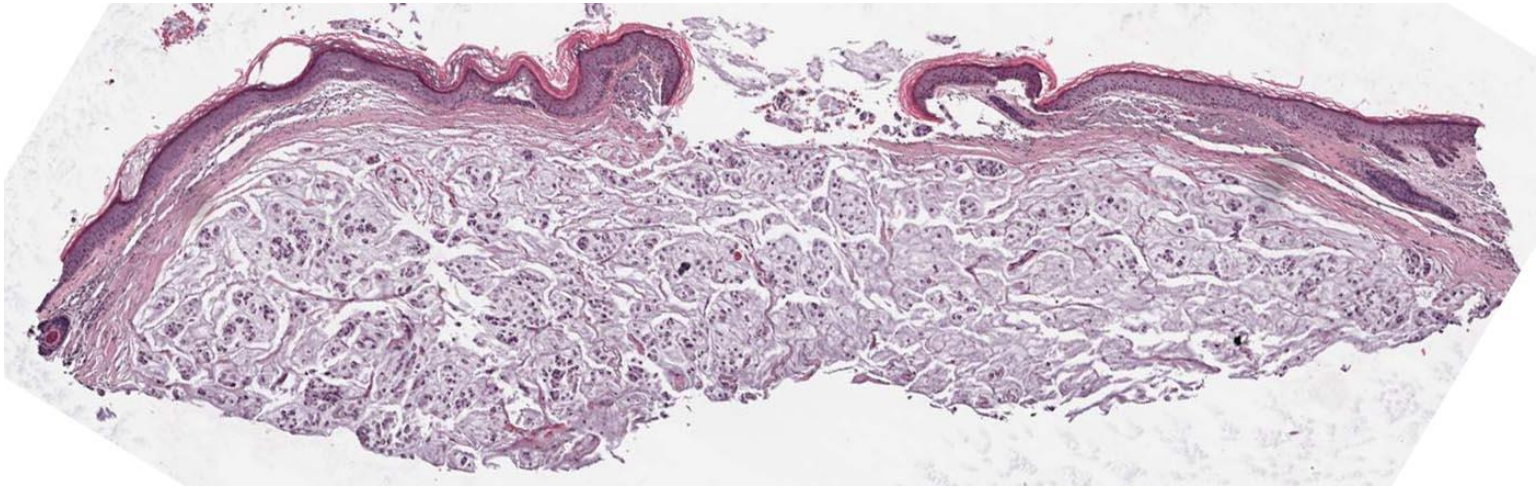


Metastatic AdenoCA with Mucinous Features

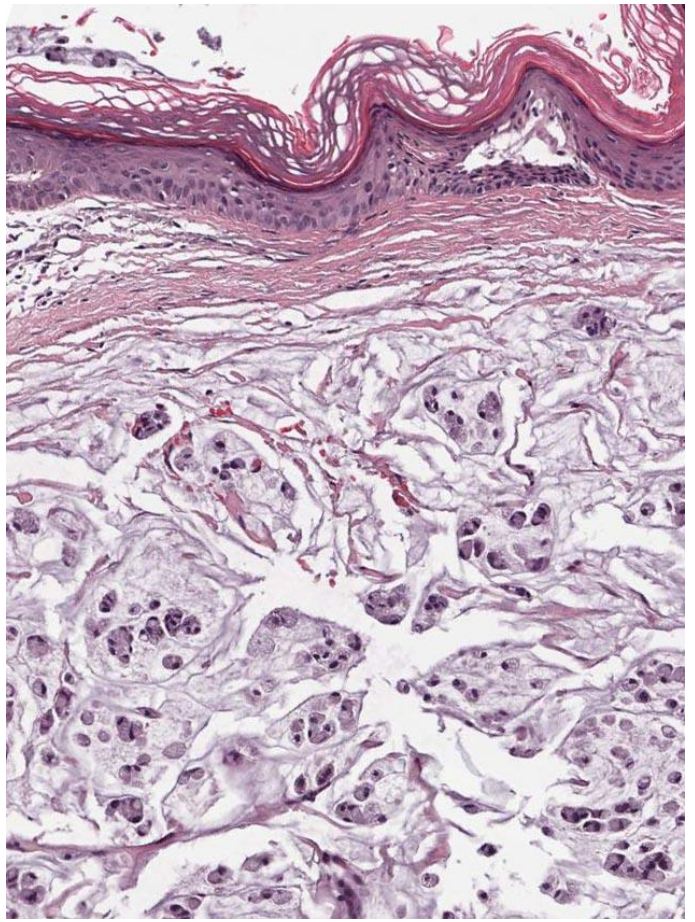




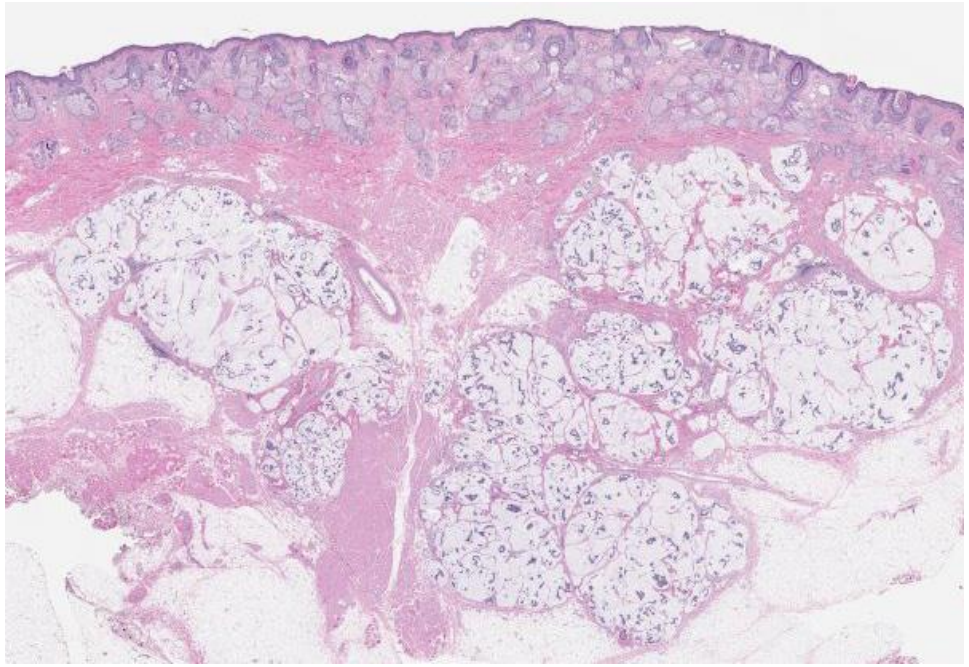
Mucinous Signet Ring Cell Carcinoma

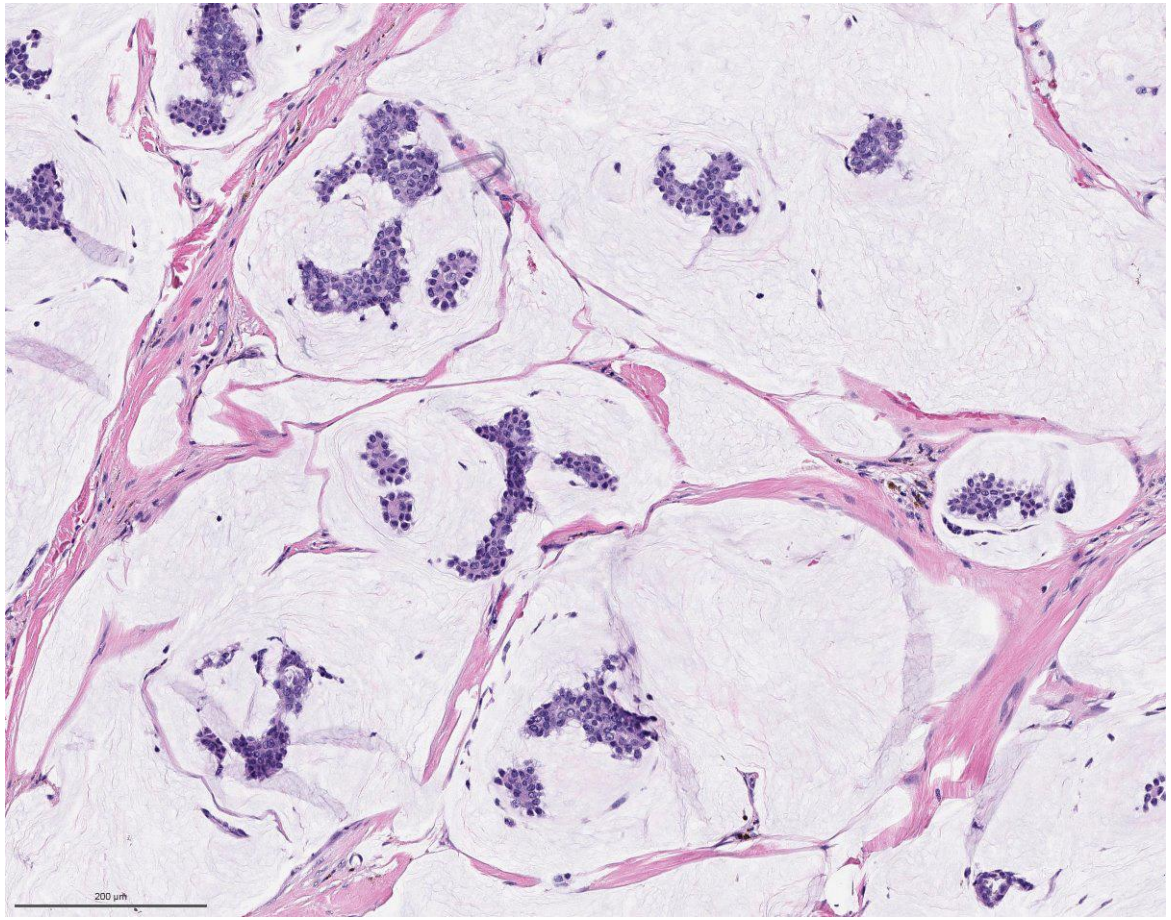


Metastatic Coloreactal Signet Ring Cell Carcinoma

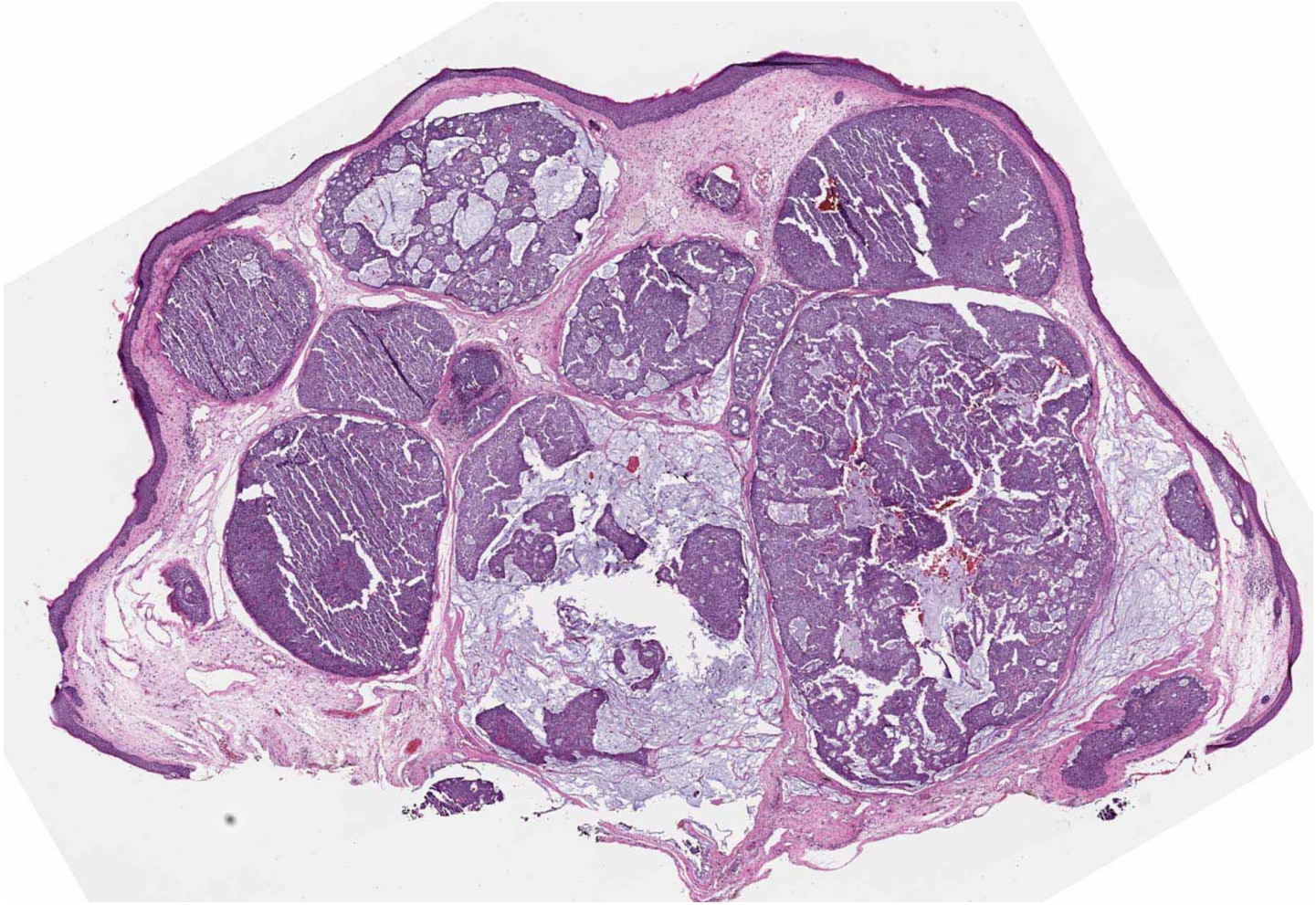


Primary Cutaneous Mucinous Carcinoma

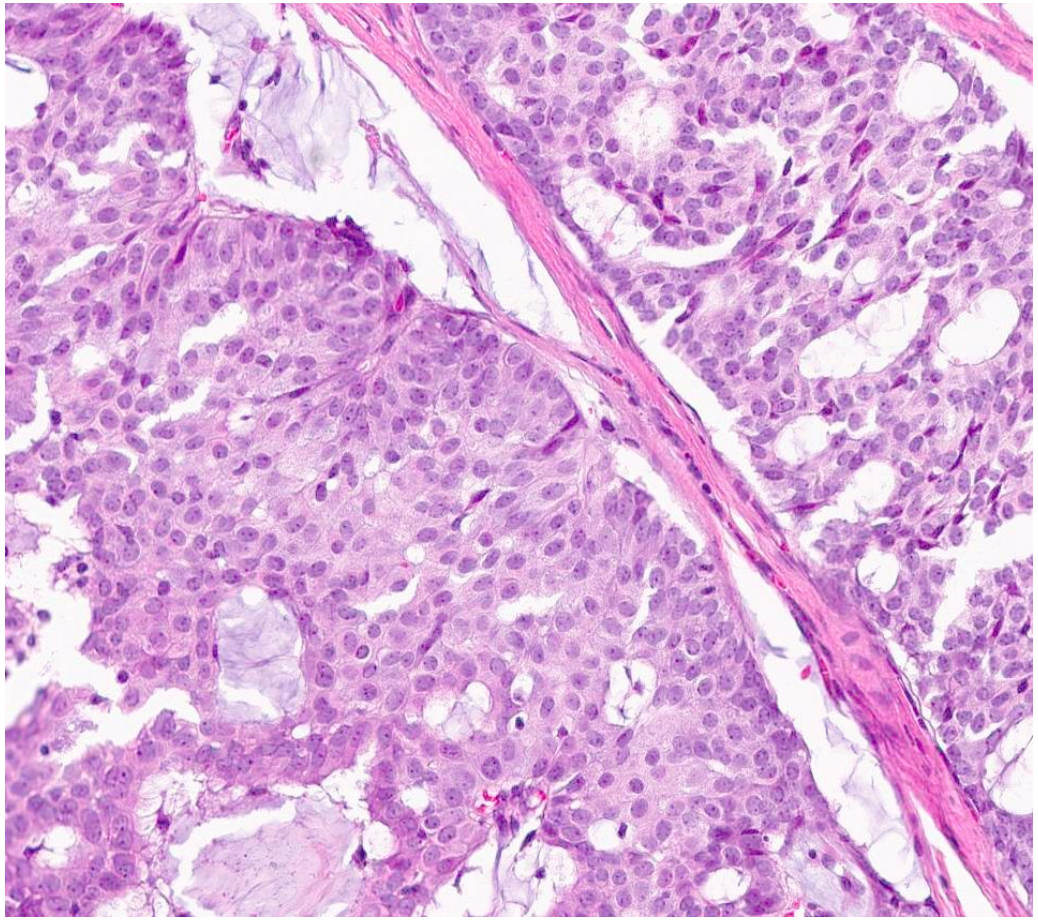




Endocrine Mucin-Producing Sweat Gland Carcinoma



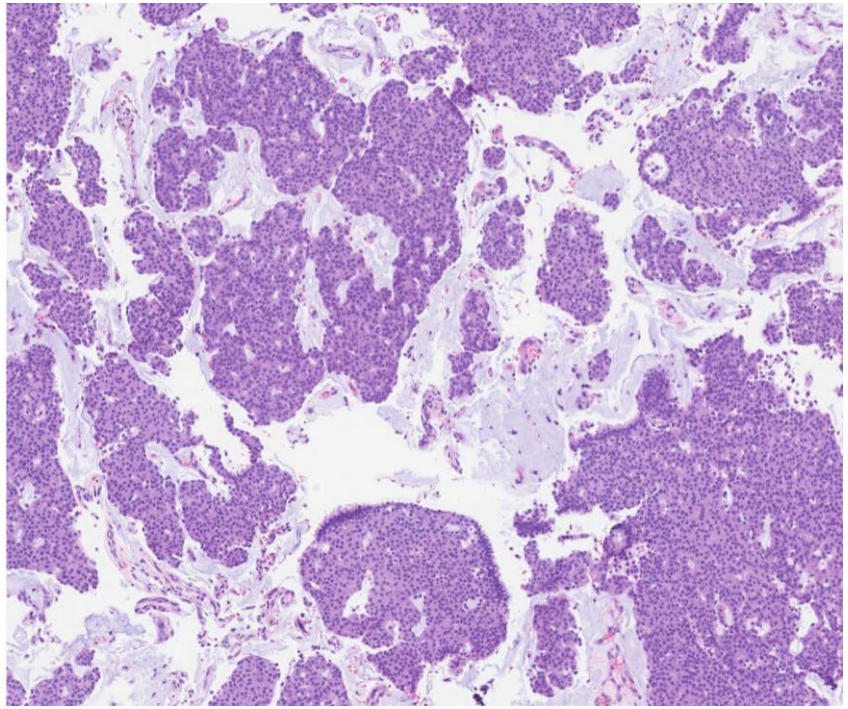
Endocrine Mucin-Producing Sweat Gland Carcinoma

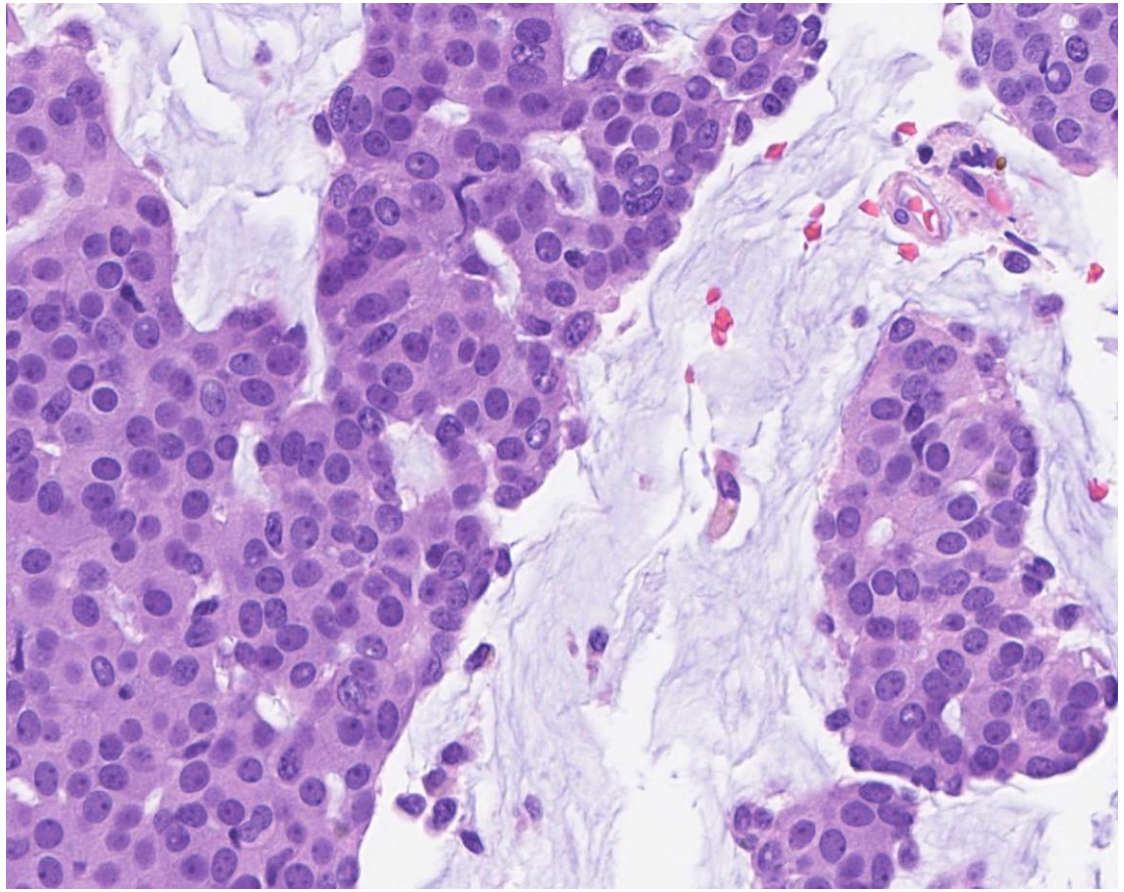


- Clinical
  - Typically periocular
  - Low grade neoplasm
- Histopathology
  - Intra- and peritumoral mucin
  - Solid and cribriform growth
  - Low nuclear grade
- IHC
  - CK7, ER, PR, INSM1,chromo, synaptophysin

What is Your Diagnosis?

- 75F with scalp nodule
- R/o cyst





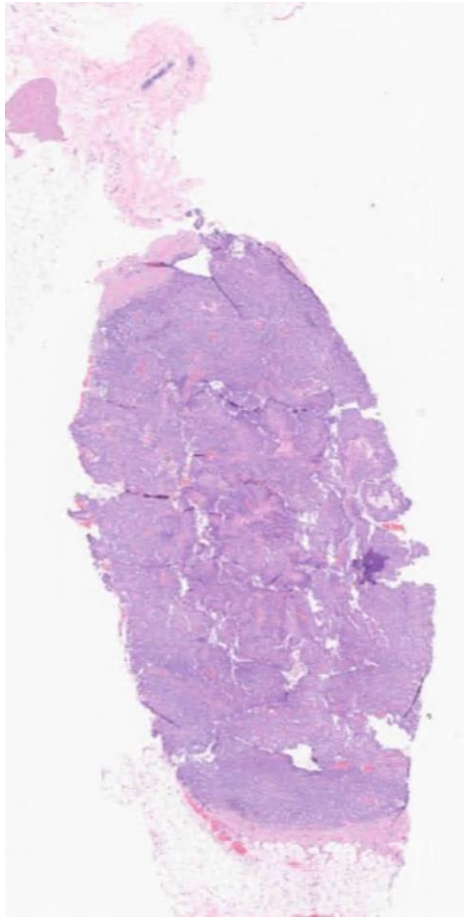
What is Your Diagnosis?

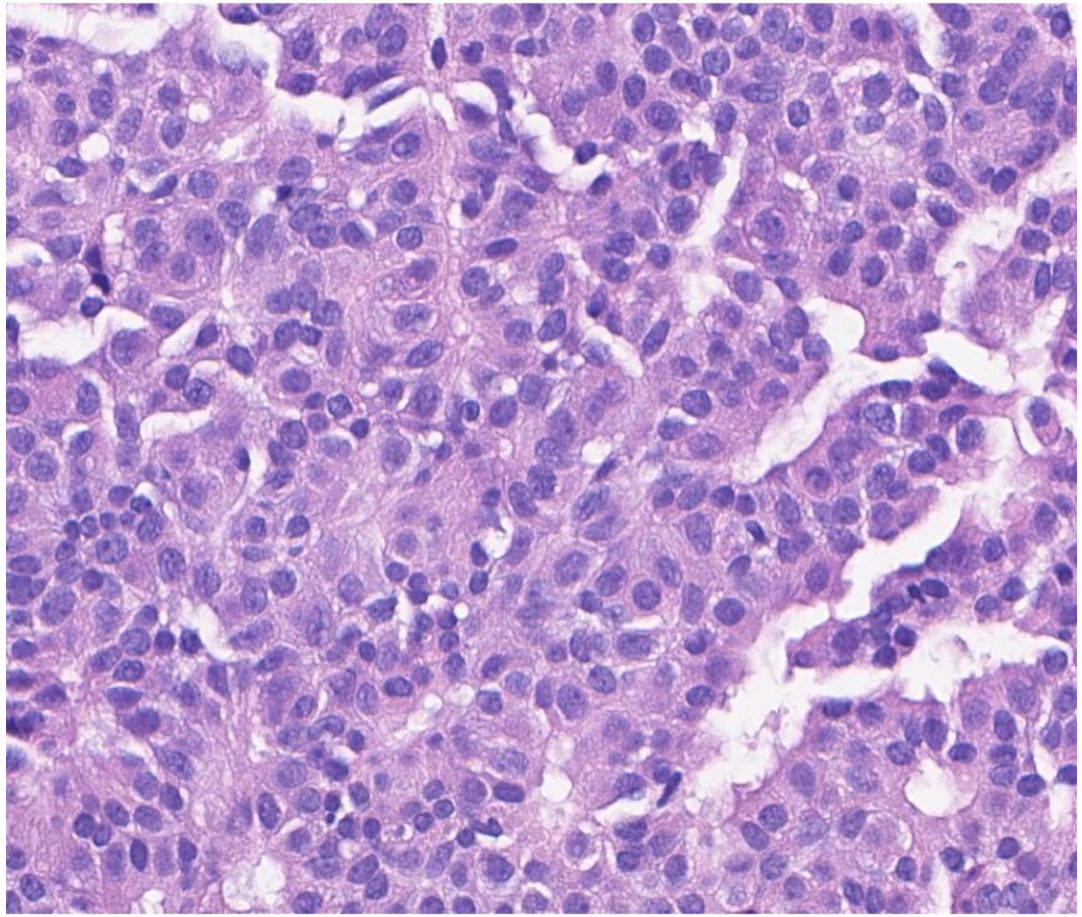
A. Endocrine mucin-producing sweat gland carcinoma

B. Primary mucinous carcinoma of the skin

C. Metastatic adenocarcinoma with mucinous features

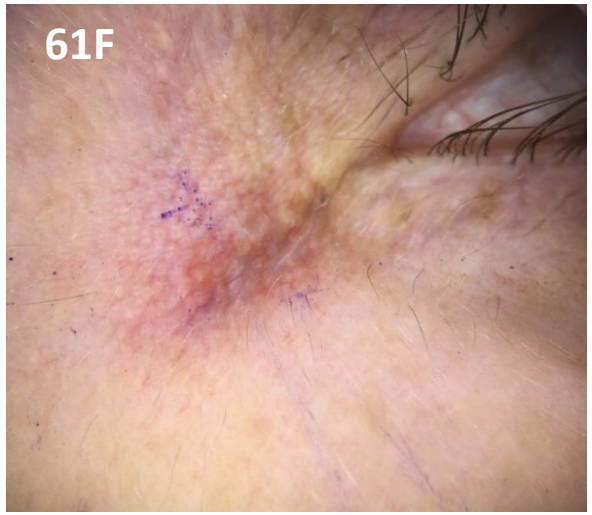
Mammary Carcinoma





Challenging Case – Primary or Metastatic?

- History of breast cancer, metastatic to LNs
- S/p chemo, XRT + tamoxifen
- Dark fleck along right lateral eye
- Dermatologist took 1 mm punch biopsy x2:
  - Prelim report: foreign body reaction
  - Addendum: c/w metastatic breast cancer



Outside Pathology Report

Clinical Information

Morphology: linear bluish grey dermal macule
DDX: Neoplasm of uncertain behavior vs melanoma
Notes: 2 pieces

Final Diagnosis

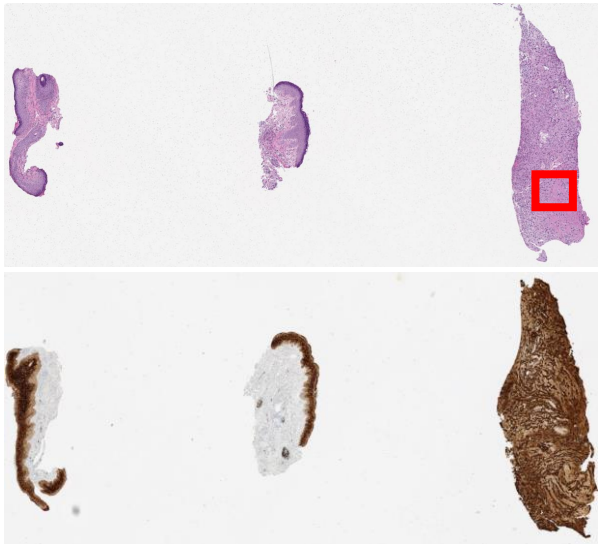
Skin, right lateral canthus, punch biopsy

- Consistent with metastatic mammary carcinoma. See note

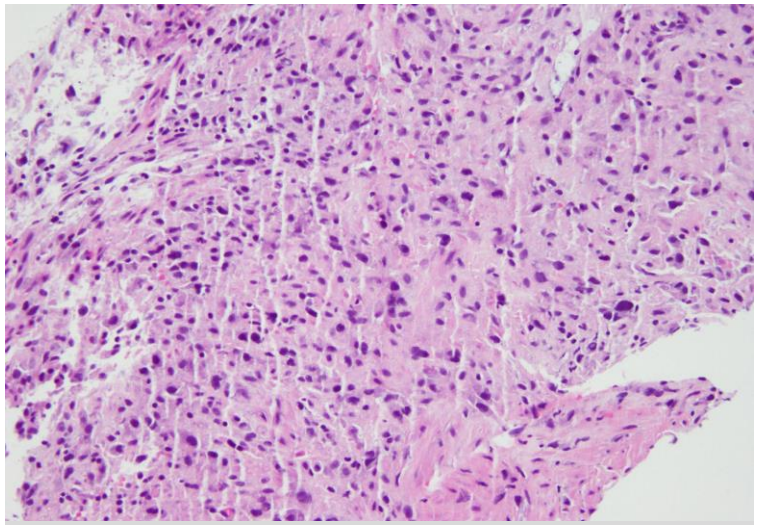
Note: The neoplastic cells show strong immunoreactivity with AE1.3 and GATA 3. There is also focal positive staining with ER. Patient's past medical history of a lobular carcinoma [redacted] is also noted.

Polarizable foreign material and nonpolarizable pigmented foreign materil present. Initial and deeper sections have been analyzed. PAS stain fails to reveal fungal elements. AFB stain fails to reveal mycobacteria.The atypical cells are negative for S-100. HMB45, CD68, TTF1, PAX 8 and Melan A.

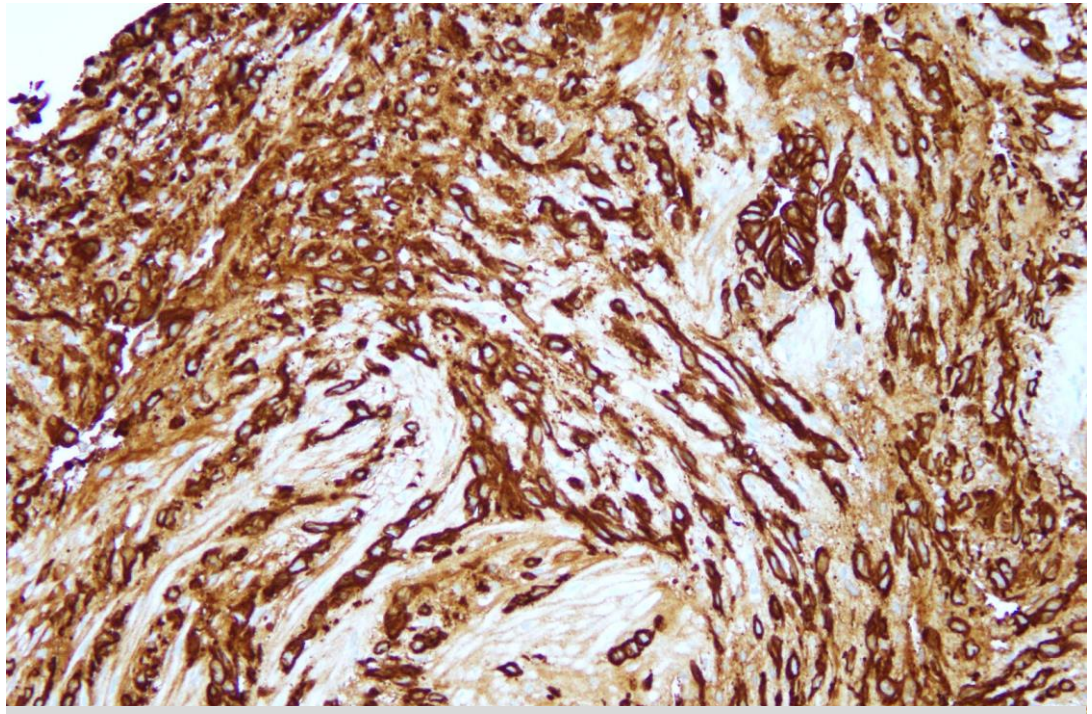
Pathology



CKAE1/3



Right lateral canthus
Poorly differentiated carcinoma



Right lateral canthus; Keratin (AE1/AE3)
Poorly differentiated carcinoma

MSK Breast Pathology

DIAGNOSIS:
1. Skin, right lateral canthus; punch biopsy

   - Poorly differentiated carcinoma. See note

Note: The submitted IHC stains show the carcinoma cells positive for AE1/3 and GATA3, while negative for PAX8, melan-A and ER. S100 and CD68 show non-specific staining. In the context of the patient's history of invasive lobular carcinoma, this may represent metastatic lobular carcinoma when other primary sites have been excluded.

What is Your Diagnosis?

A. Metastatic mammary carcinoma

B. Primary sweat gland carcinoma

C. Poorly differentiated sebaceous carcinoma

D. Metastatic carcinoma from another site

E. Other

What is the next best step?

A. Chemotherapy

B. Additional immunostains for TTF1, GATA3, Pax8, Other

C. Test for ER, PR, Her2Neu

D. Genetic test to determine anatomic site of origin

E. Other

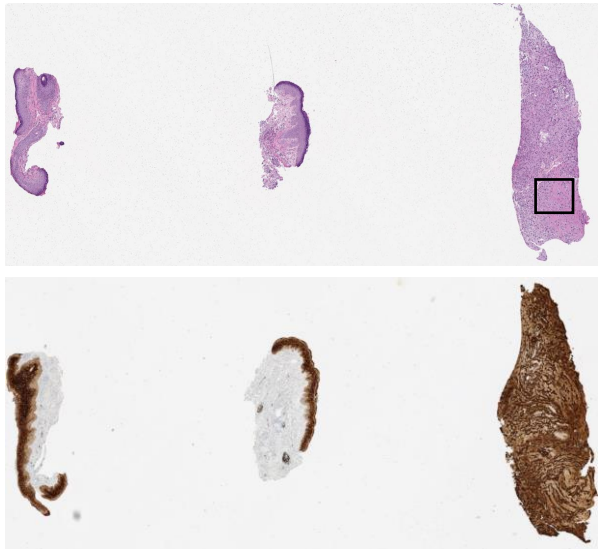
Clinical History

- Patient seen by Breast Onc survivorship
- Started on Letrozole (Femara)
- Sent to Derm for exc of breast met
- Clinically, no lesion left

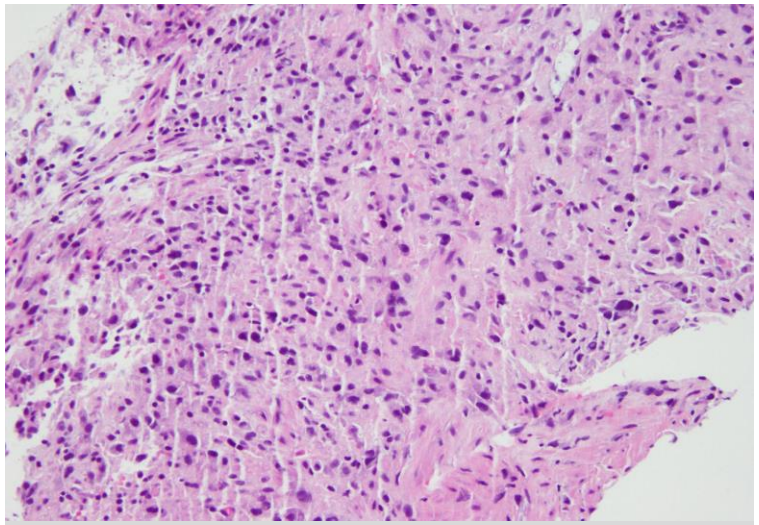
Next best step – further diagnostic work-up

- Review prior mammary carcinoma for comparison
- Re-review slides and pathology reports
- Consider additional tumor tissue sampling for further analysis

Pathology



CKAE1/3



Right lateral canthus
Poorly differentiated carcinoma

What is wrong with this picture?

Outside Pathology Report

Clinical Information

Morphology: linear bluish grey dermal macule
DDX: Neoplasm of uncertain behavior vs melanoma
Notes: 2 pieces

Final Diagnosis

Skin, right lateral canthus, punch biopsy

- Consistent with metastatic mammary carcinoma. See note

Note: The neoplastic cells show strong immunoreactivity with AE1.3 and GATA 3. There is also focal positive staining with ER. Patient's past medical history of a lobular carcinoma [redacted] is also noted.

Polarizable foreign material and nonpolarizable pigmented foreign materil present. Initial and deeper sections have been analyzed. PAS stain fails to reveal fungal elements. AFB stain fails to reveal mycobacteria.The atypical cells are negative for S-100. HMB45, CD68, TTF1, PAX 8 and Melan A.

Outside Pathology Report

Surgical Pathology Final Report

Clinical Information

Morphology: linear bluish grey dermal macule
DDX: Neoplasm of uncertain behavior vs melanoma
Notes: 2 pieces

Final Diagnosis

Skin, right lateral canthus, punch biopsy
- Consistent with metastatic mammary carcinoma. See note

Note: The neoplastic cells show strong immunoreactivity with AE1.3 and GATA 3. There is also focal positive staining with ER. Patient's past medical history of a lobular carcinoma is also noted.
Polarizable foreign material and nonpolarizable pigmented foreign materil present. Initial and deeper sections have been analyzed. PAS stain fails to reveal fungal elements. AFB stain fails to reveal mycobacteria The atypical cells are negative for S-100, HMB45, CD68, TTF1, PAX 8 and Melan A.

Gross Description

The specimen is received in formalin and the specimen container is labeled: **Right lateral canthus**. It consists of two minute skin punches biopsies each measuring 0.1 x 0.1 cm. in diameter and taken to a depth of 0.1cm . The epidermis is tan-white and soft. The specimen is entirely submitted in one cassette.

Gross Description

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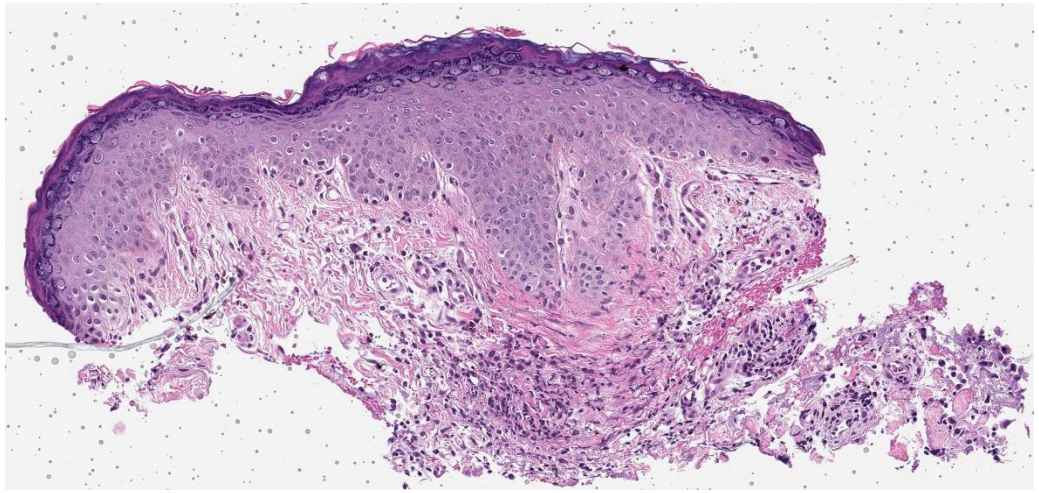
Punch biopsy

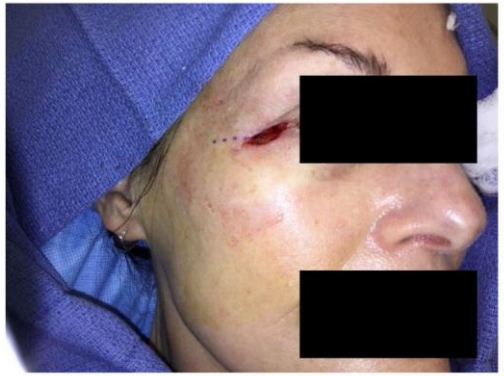


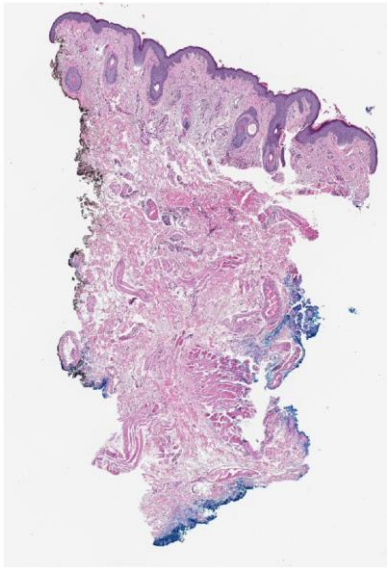
What is wrong?

There are 3 pieces!!

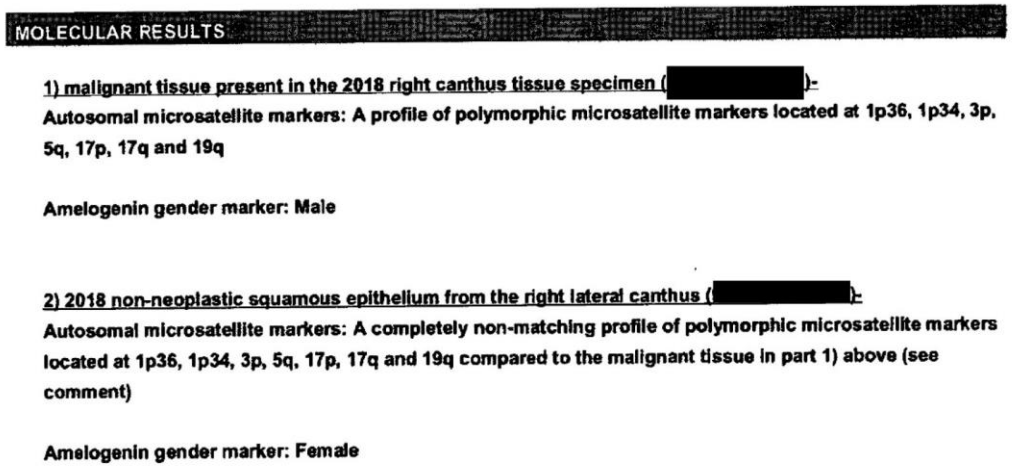
Where does the 3rd big piece come from?

Excisional biopsy: no tumor seen





Molecular Tests for Specimen ID



MOLECULAR RESULTS

1) malignant tissue present in the 2018 right canthus tissue specimen ([redacted])-
Autosomal microsatellite markers: A profile of polymorphic microsatellite markers located at 1p36, 1p34, 3p, 5q, 17p, 17q and 19q

Amelogenin gender marker: Male

2) 2018 non-neoplastic squamous epithelium from the right lateral canthus ([redacted])-
Autosomal microsatellite markers: A completely non-matching profile of polymorphic microsatellite markers located at 1p36, 1p34, 3p, 5q, 17p, 17q and 19q compared to the malignant tissue in part 1) above (see comment)

Amelogenin gender marker: Female

Primary or Metastatic Carcinoma?

No carcinoma at all

Acknowledgements

- Chad Vanderbilt and colleagues from Molecular Pathology, MSKCC
- Members of the Dermpath Team at MSKCC
- IHC Team, Pathology, MSKCC
- A Obenauf & T Wiesner, Vienna
- My family

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Thank You!