



Appendageal skin tumors

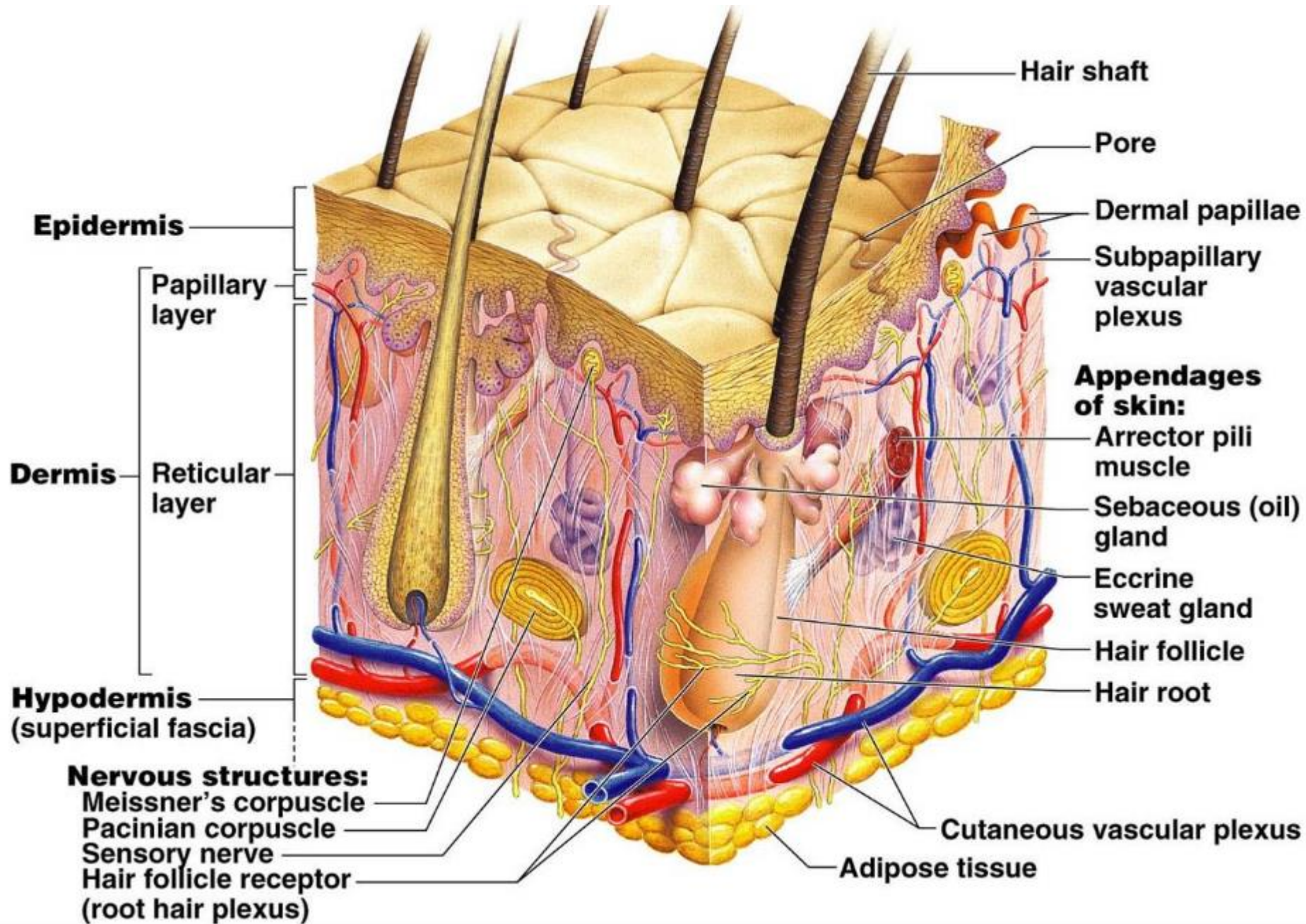
Ibrahim Khalifeh, M.D.

Associate Professor

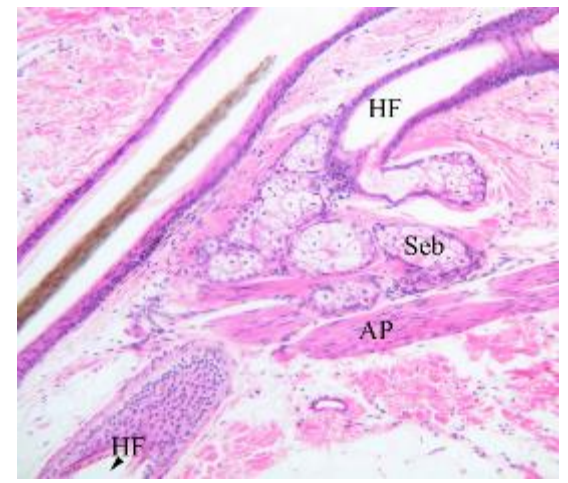
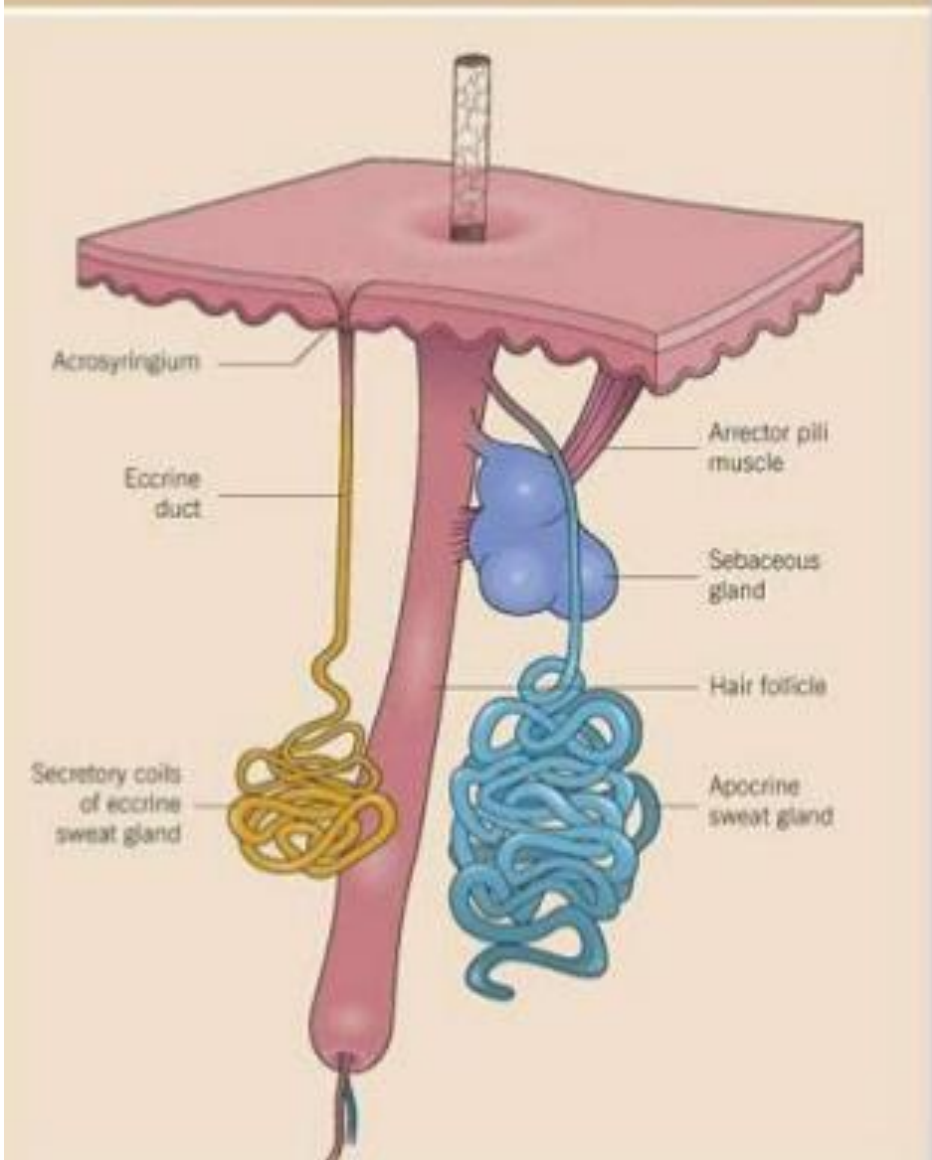
Department of Pathology

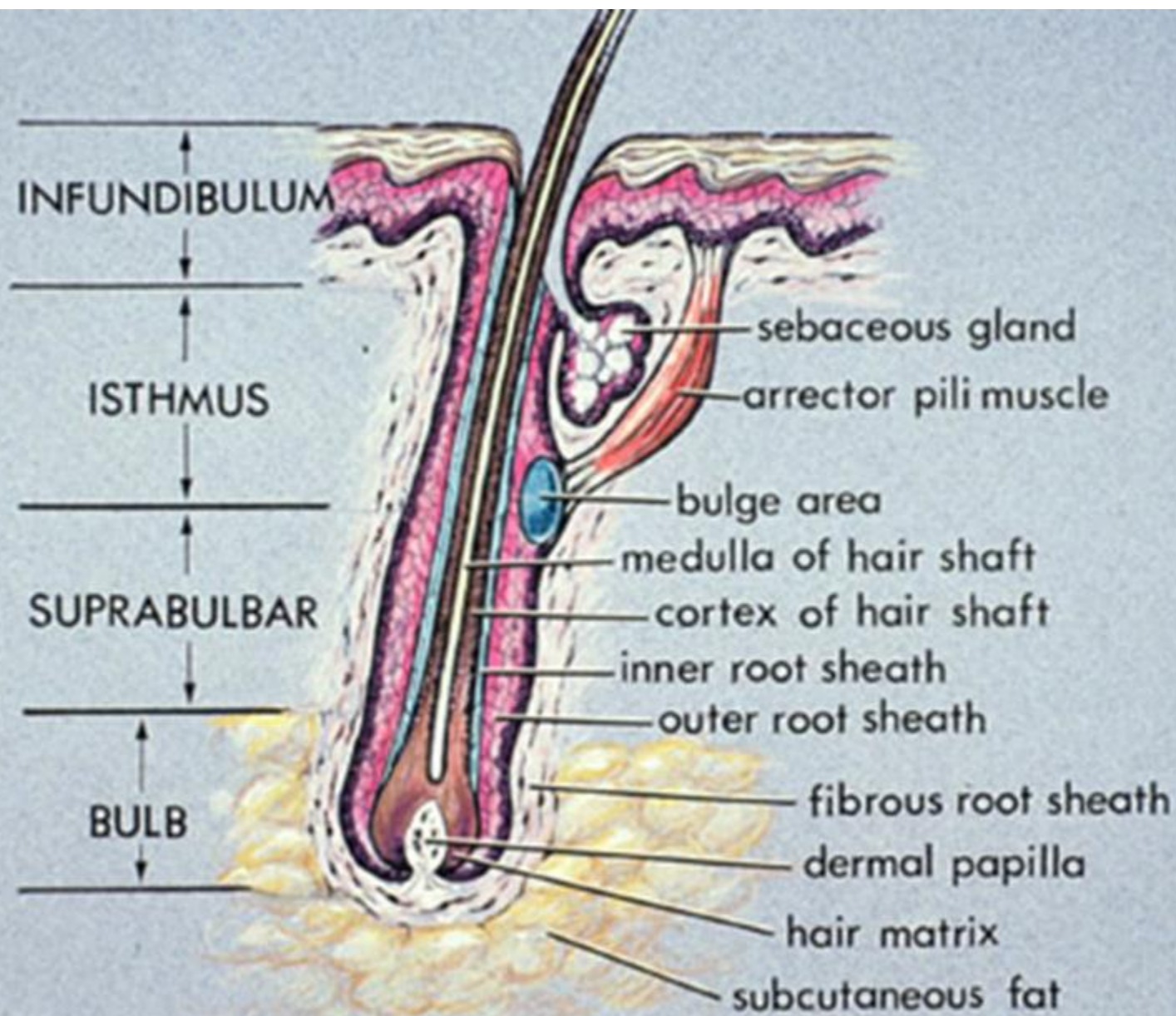
American University of Beirut Medical Center

Beirut, Lebanon



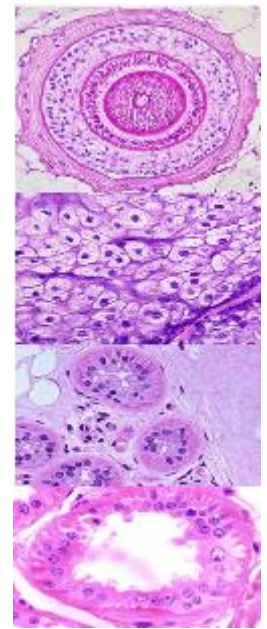
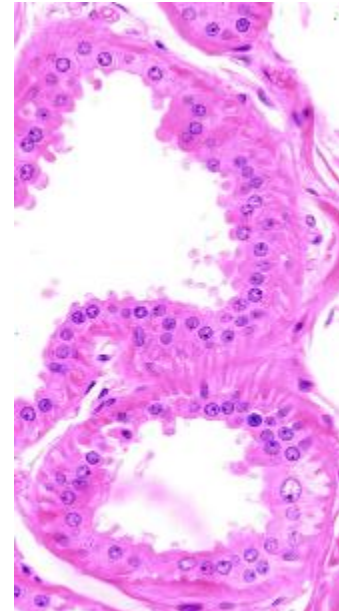
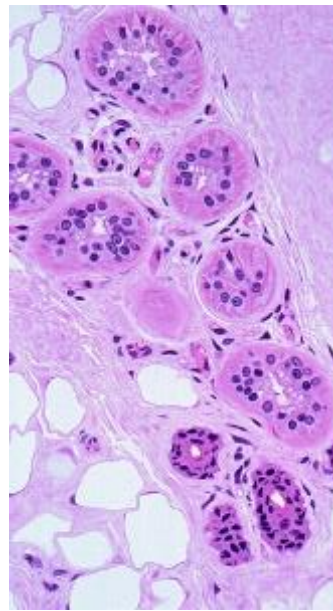
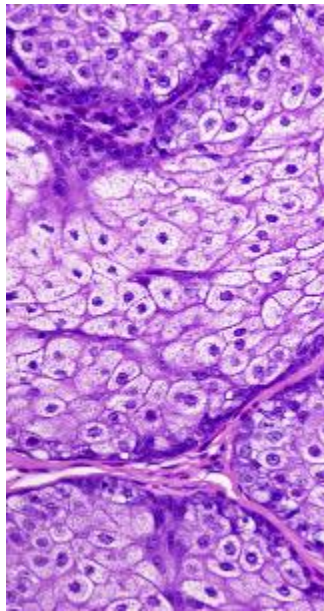
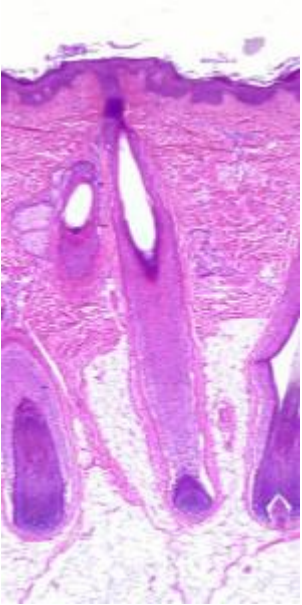
PILOSEBACEOUS UNIT WITH APOCRINE AND ECCRINE SWEAT GLANDS





Appendageal tumors

Neoplasms whose differentiation is toward one or more of the adnexal structures of the skin



WHO histological classification of appendageal tumours

Tumours with apocrine and eccrine differentiation

Malignant tumours

Tubular carcinoma	8211/3
Microcystic adnexal carcinoma	8407/3
Porocarcinoma	8409/3
Spiradenocarcinoma	8403/3
Malignant mixed tumour	8940/3
Hidradenocarcinoma	8400/3
Mucinous carcinoma	8480/3
Digital papillary carcinoma	8408/3
Adenoid cystic carcinoma	8200/3
Apocrine carcinoma	8401/3
Paget disease of breast	8540/3
Extramammary Paget disease	8542/3

Benign tumours

Hidrocystoma	8404/0
Syringoma	8407/0
Poroma	8409/0
Syringofibroadenoma	8392/0
Hidradenoma	8402/0
Spiradenoma	8403/0
Cylindroma	8200/0

Tubular adenoma	8211/0
Tubular papillary adenoma	8263/0
Syringocystadenoma papilliferum	8406/0
Hidradenoma papilliferum	8405/0
Mixed tumour (chondroid syringoma)	8940/0

Tumours with follicular differentiation

Malignant tumours

Pilomatrical carcinoma	8110/3
Proliferating tricholemmal tumour	8103/1

Benign tumours

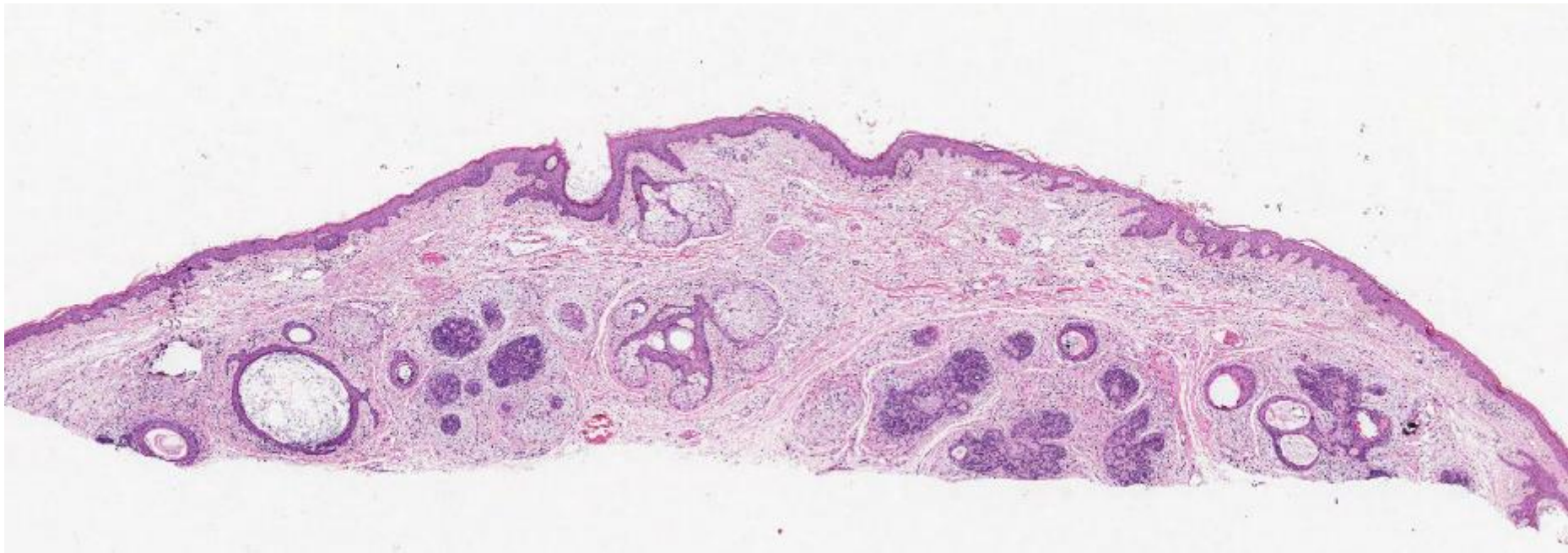
Trichoblastoma	8100/0
Pilomatricoma	8110/0
Tricholemmoma	8102/0
Multiple tricholemmomas	8102/0
Trichofolliculoma	8101/0
Fibrofolliculoma / trichodiscoma	8391/0

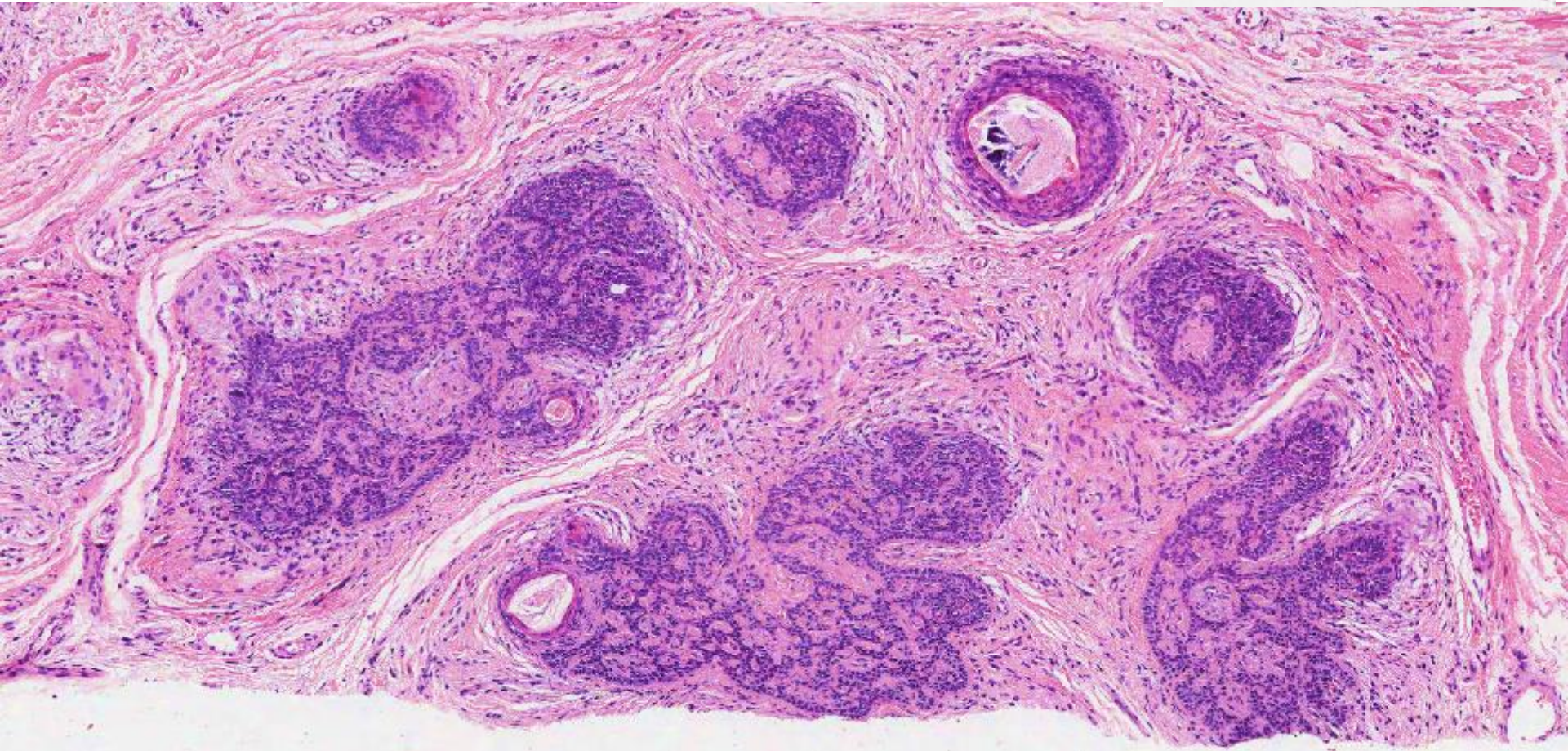
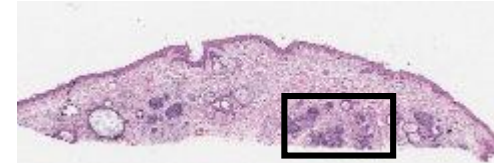
Tumours with sebaceous differentiation

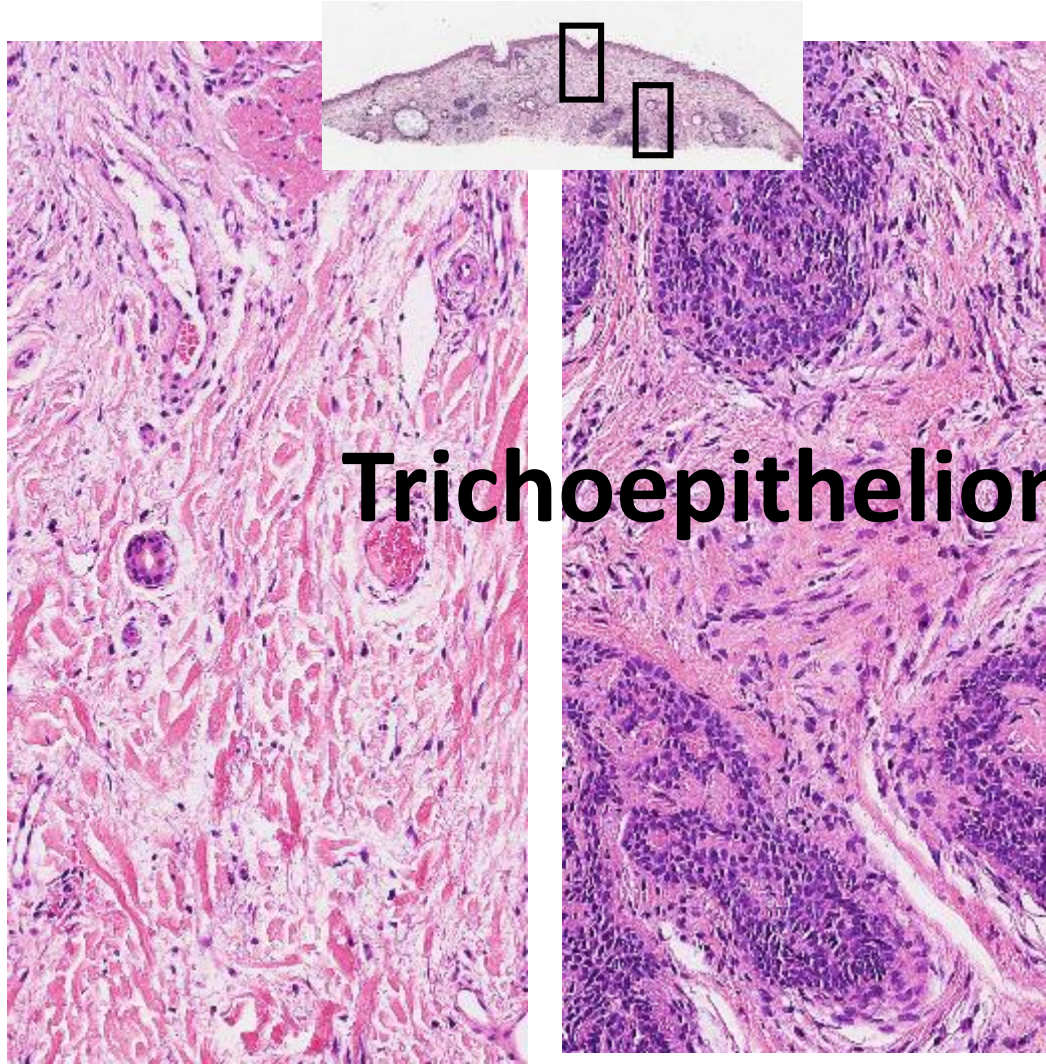
Sebaceous carcinoma	8410/3
Sebaceous adenoma	8410/0
Sebaceoma	8410/0
Cystic sebaceous tumour	8410/0

¹ Morphology code of the International Classification of Diseases for Oncology (ICD-O) [786] and the Systematized Nomenclature of Medicine (<http://snomed.org>). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

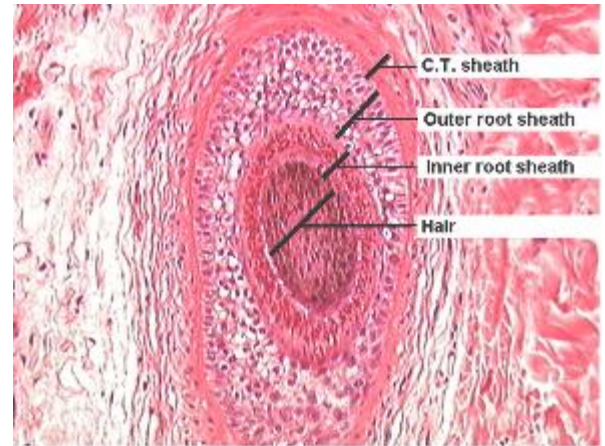
Nasal lesion in 47 Y man



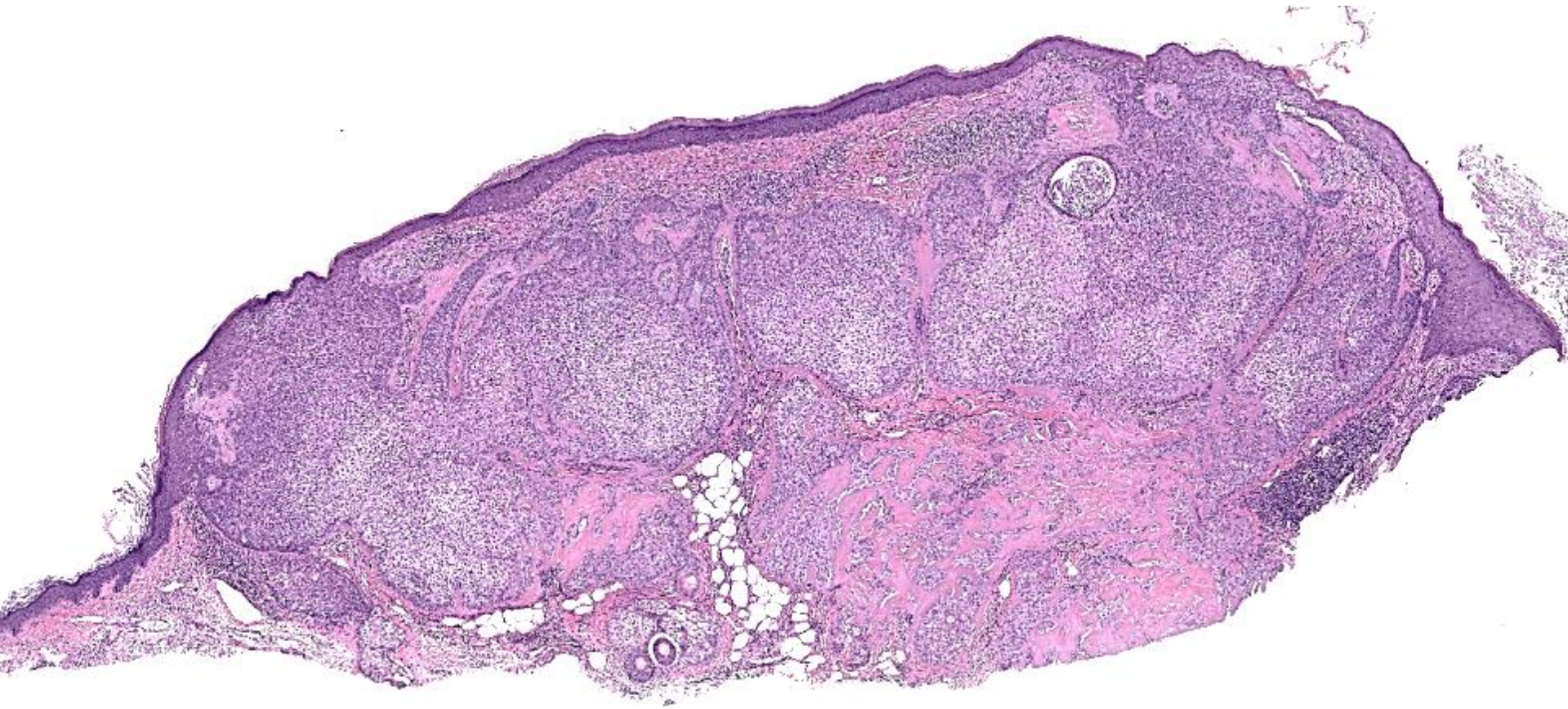


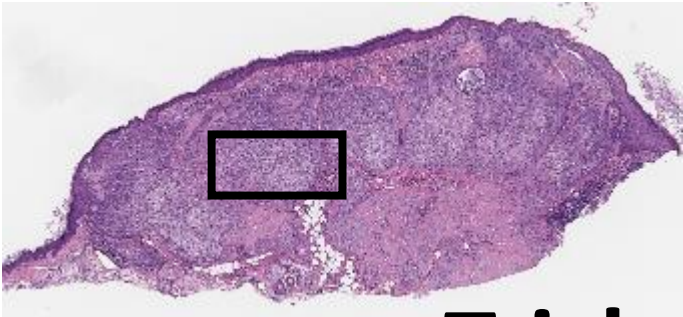


Trichoepithelioma

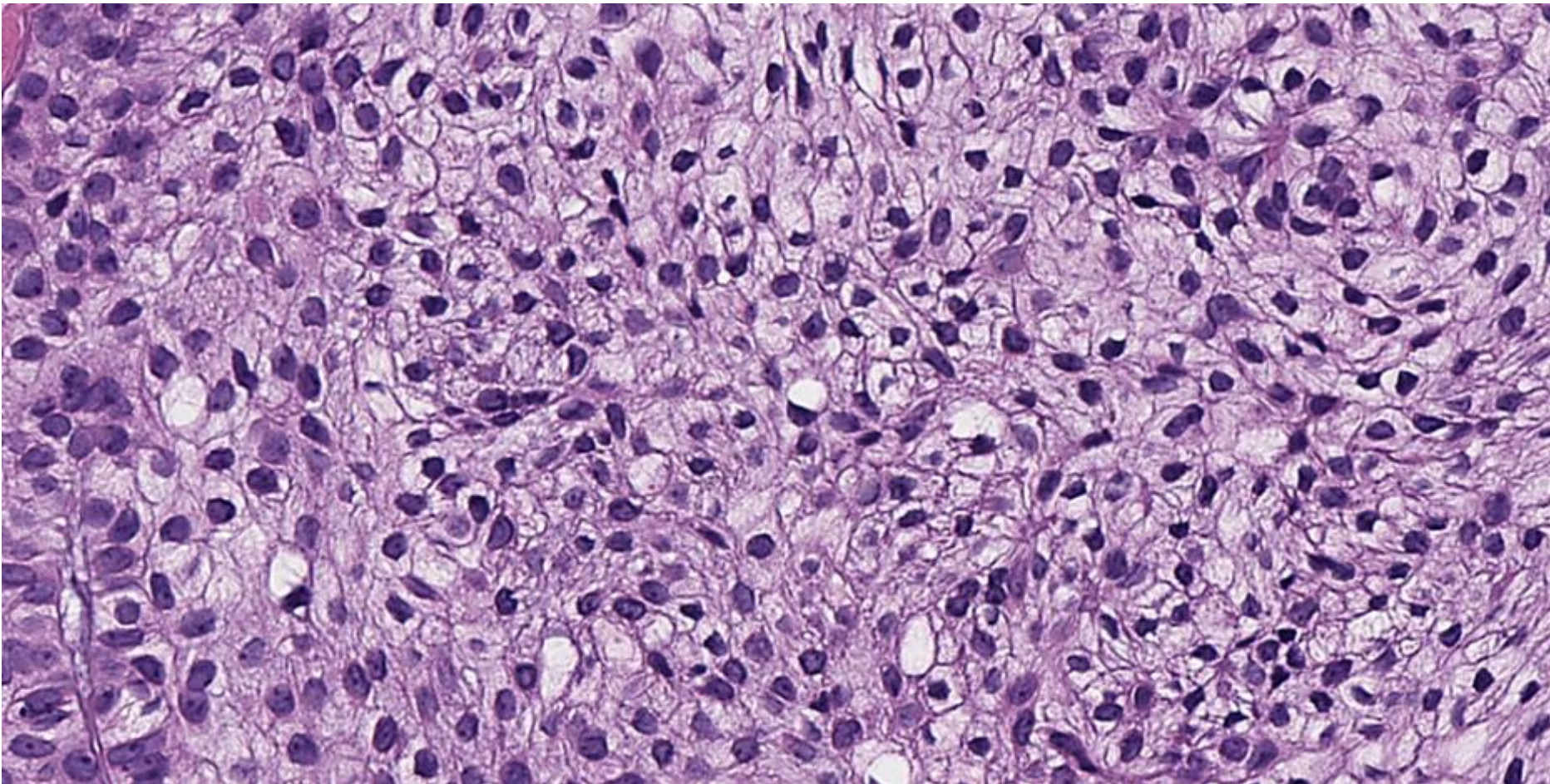
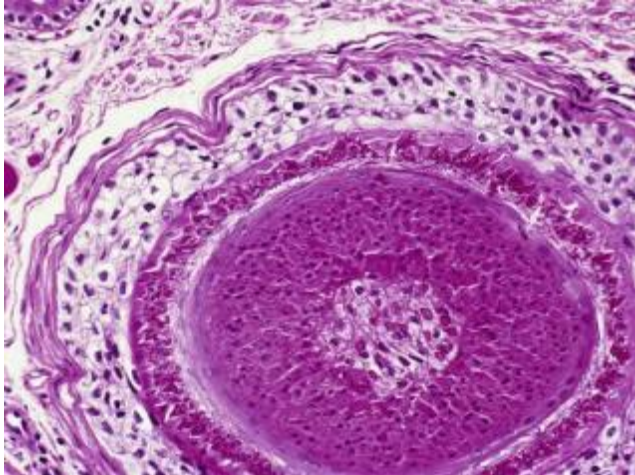


27 Y O women with lesion on face

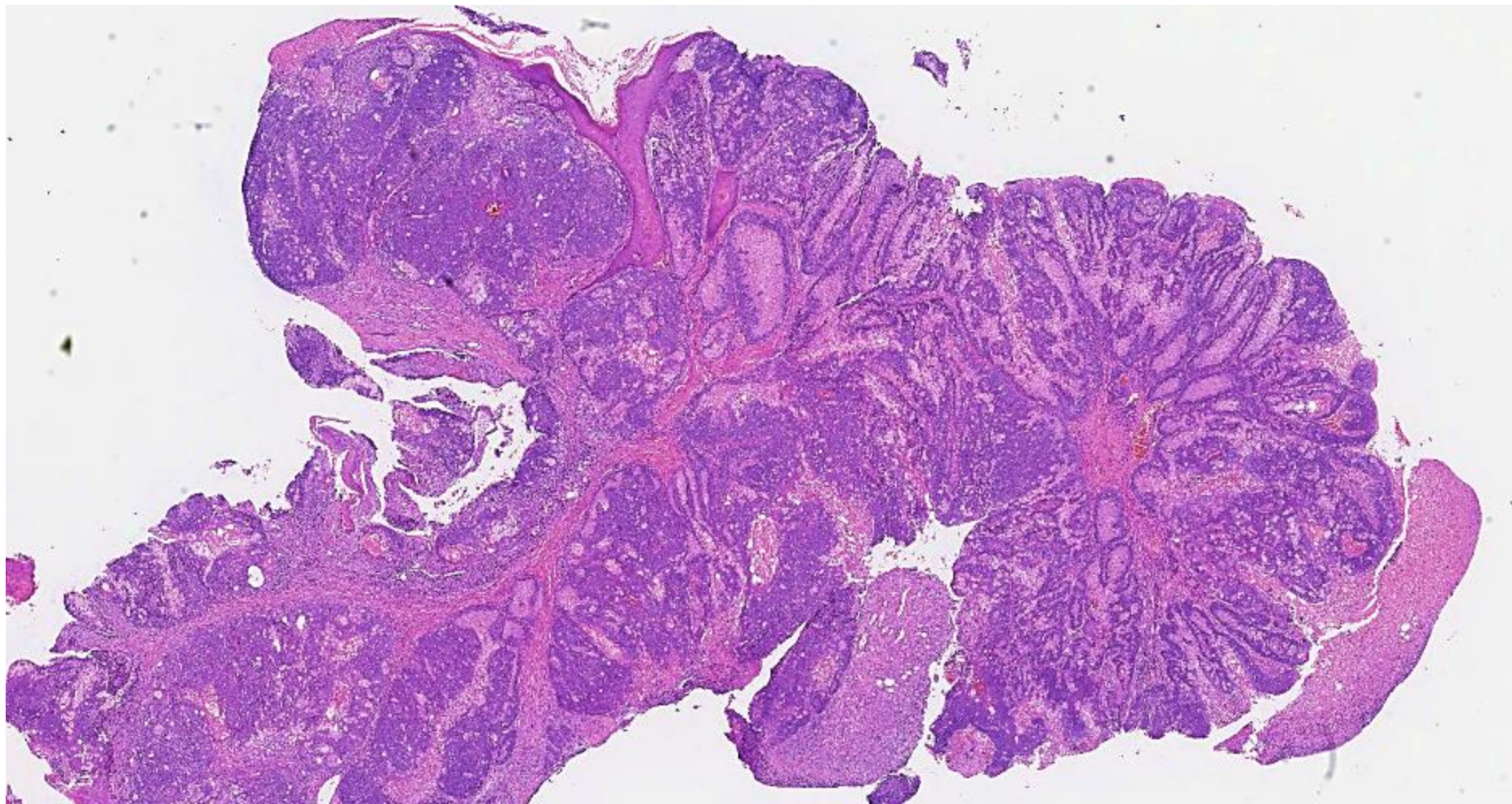




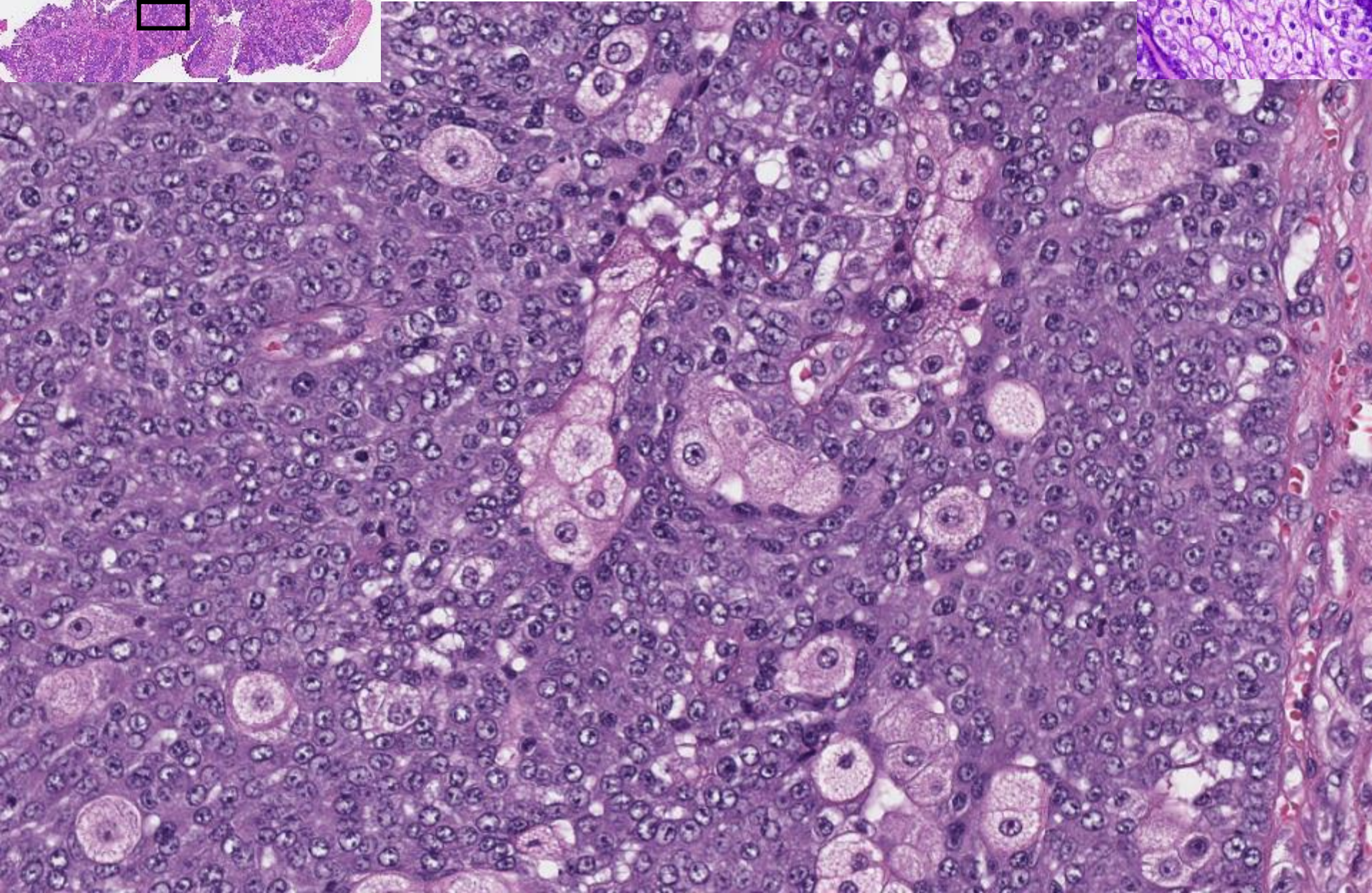
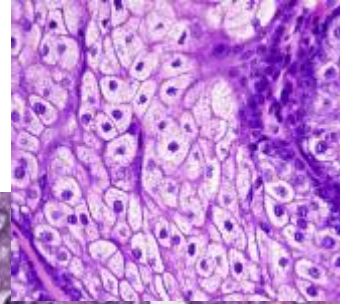
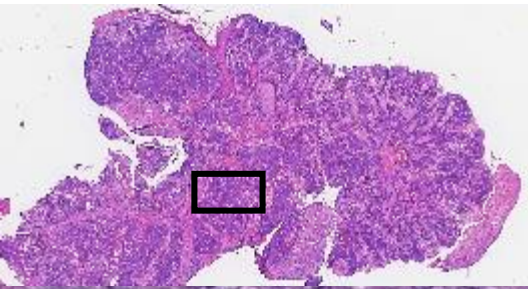
Tricholemmoma



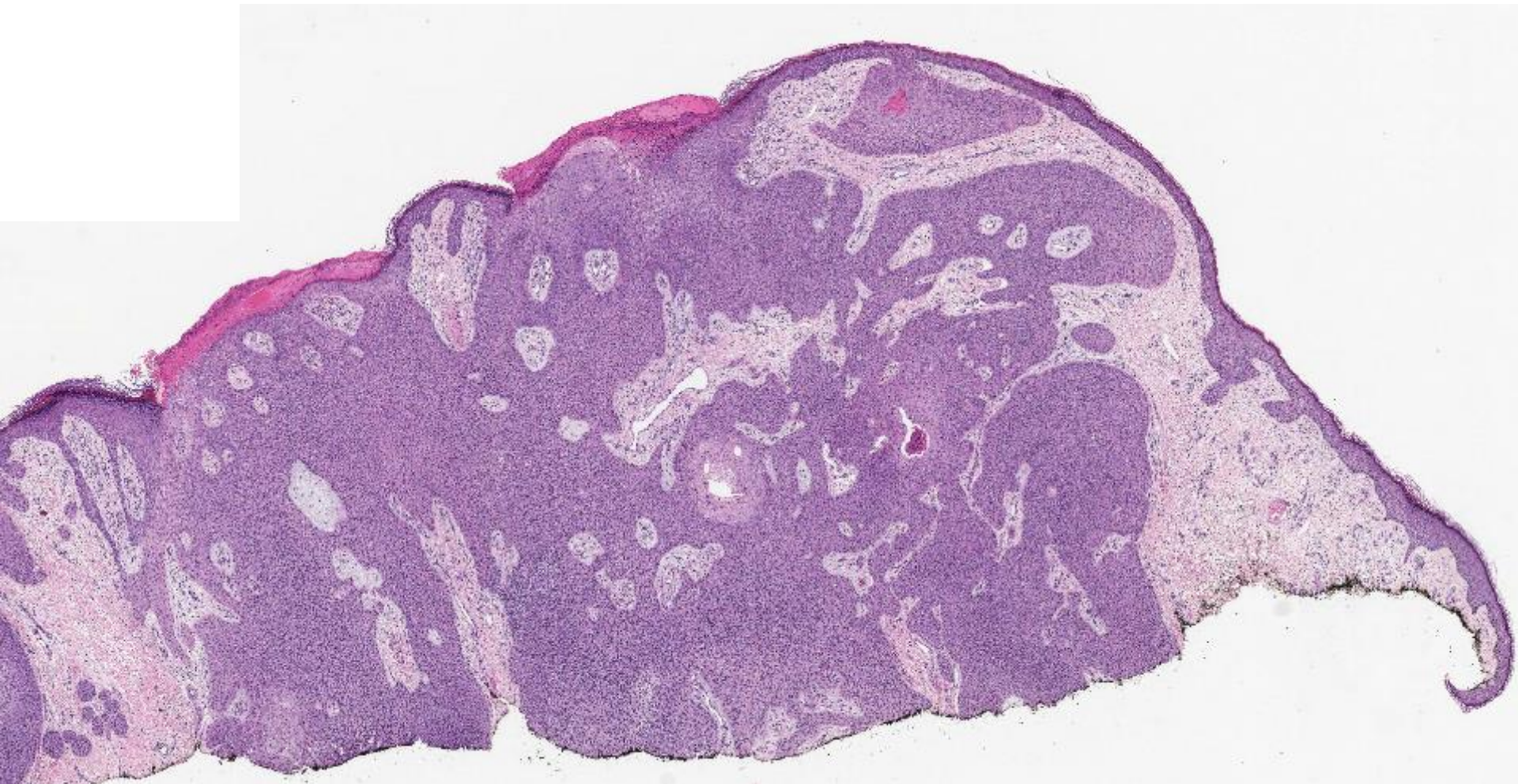
47 yo man with orbital mass



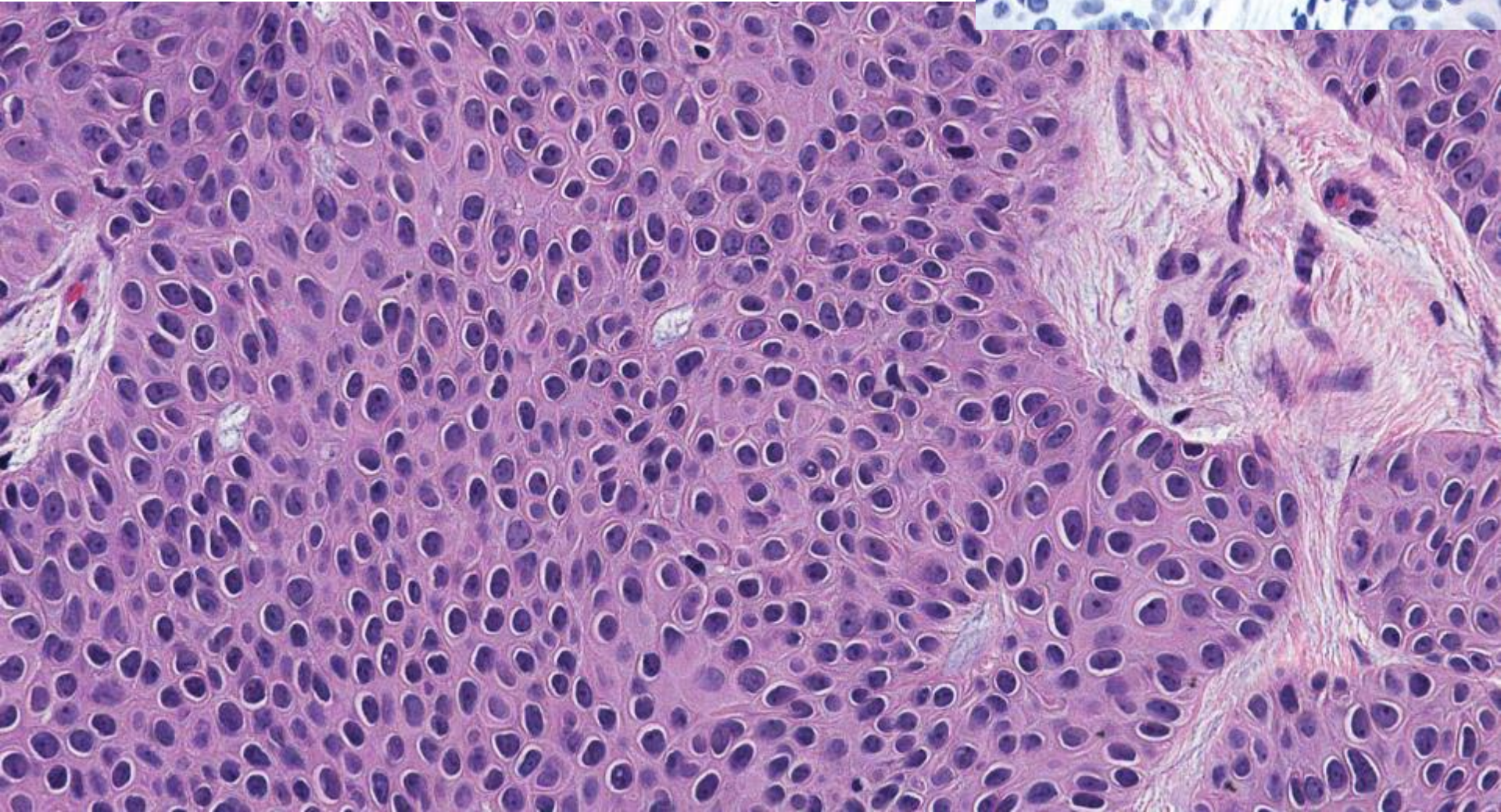
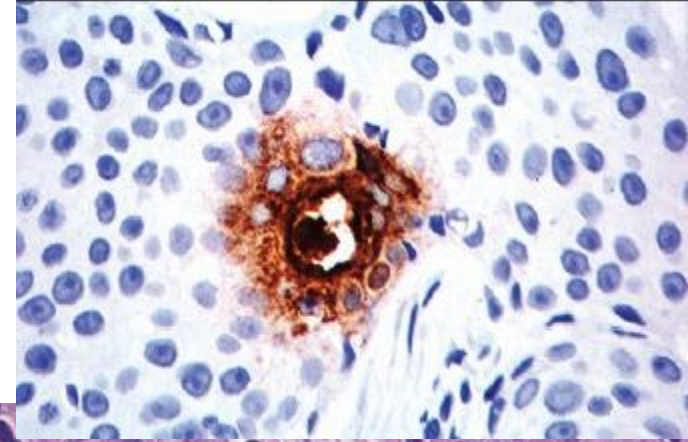
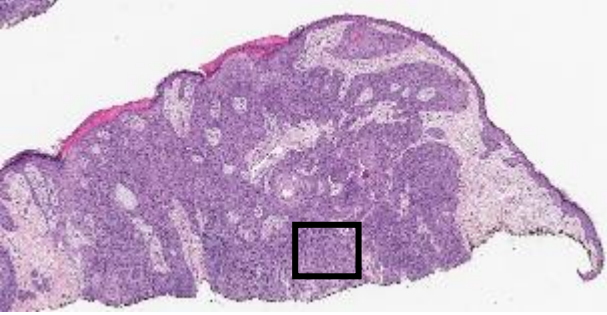
Sebaceous Carcinoma



51 year old women with forehead lesion



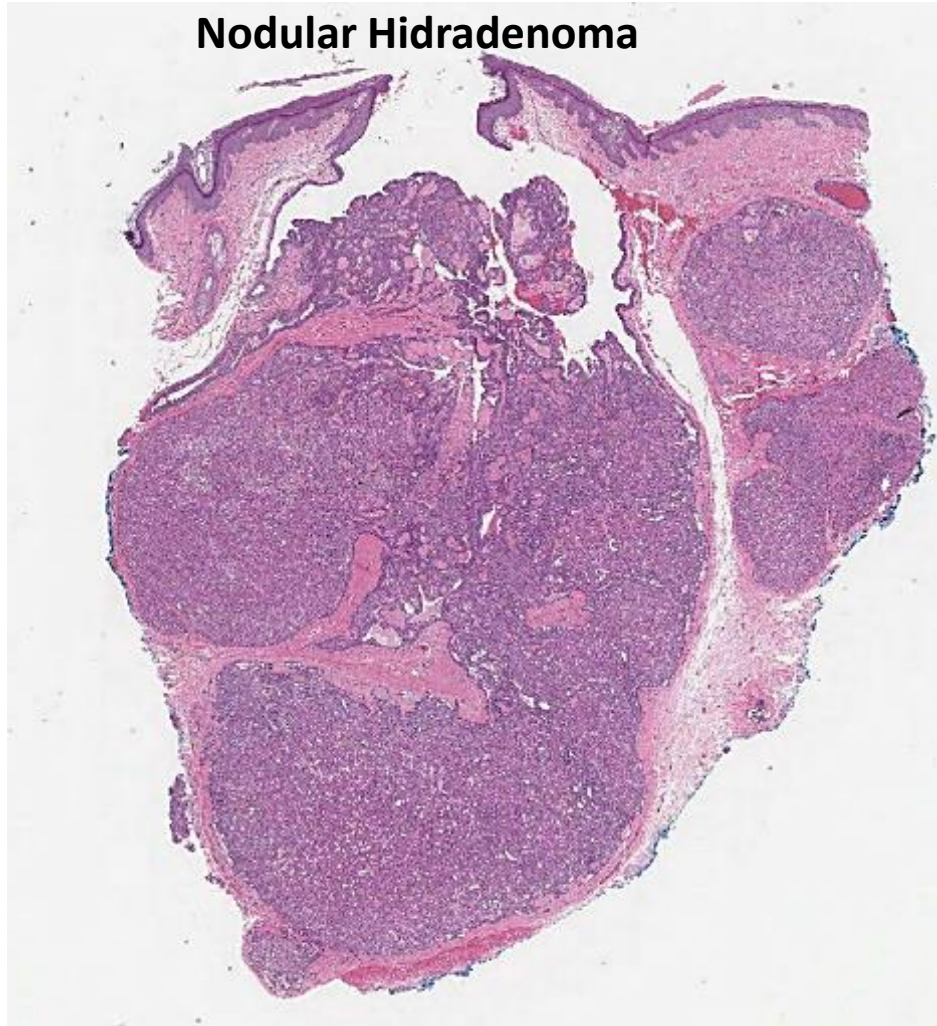
Eccrine Poroma



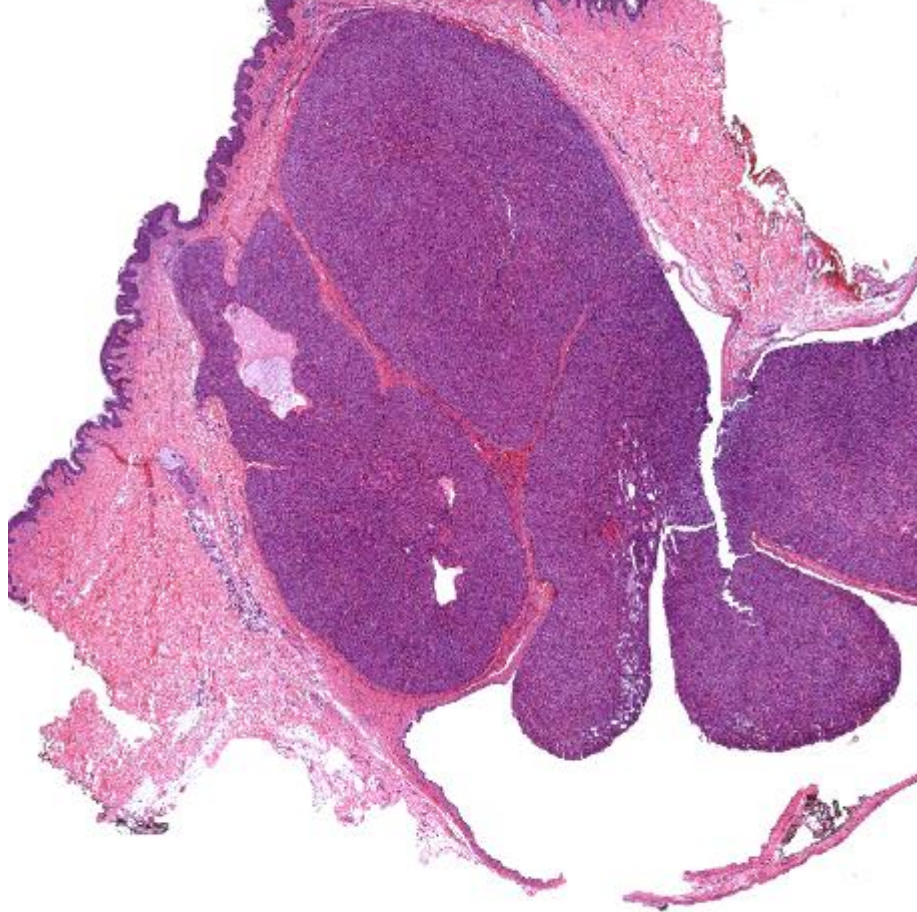
Malignant or Benign ?

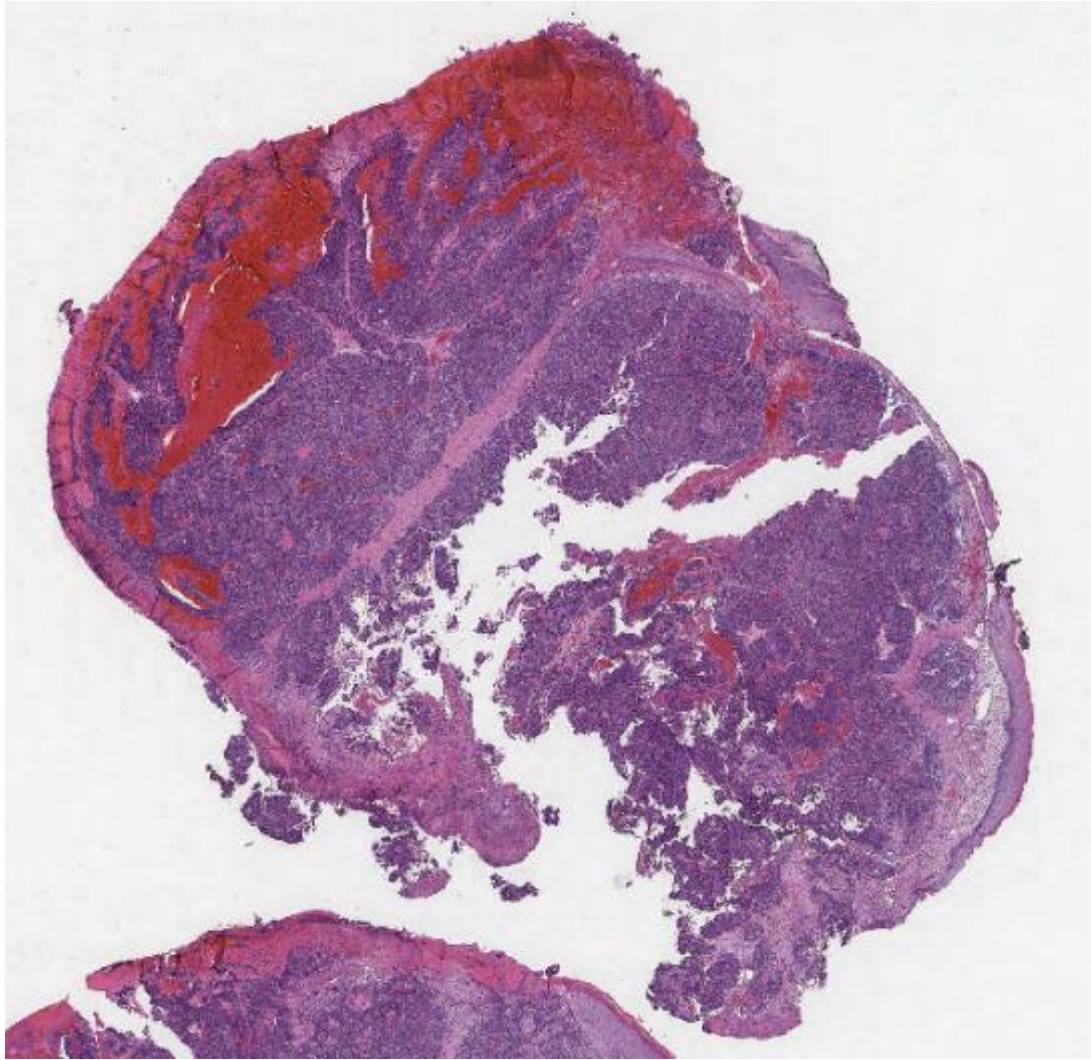
Infiltrative Borders

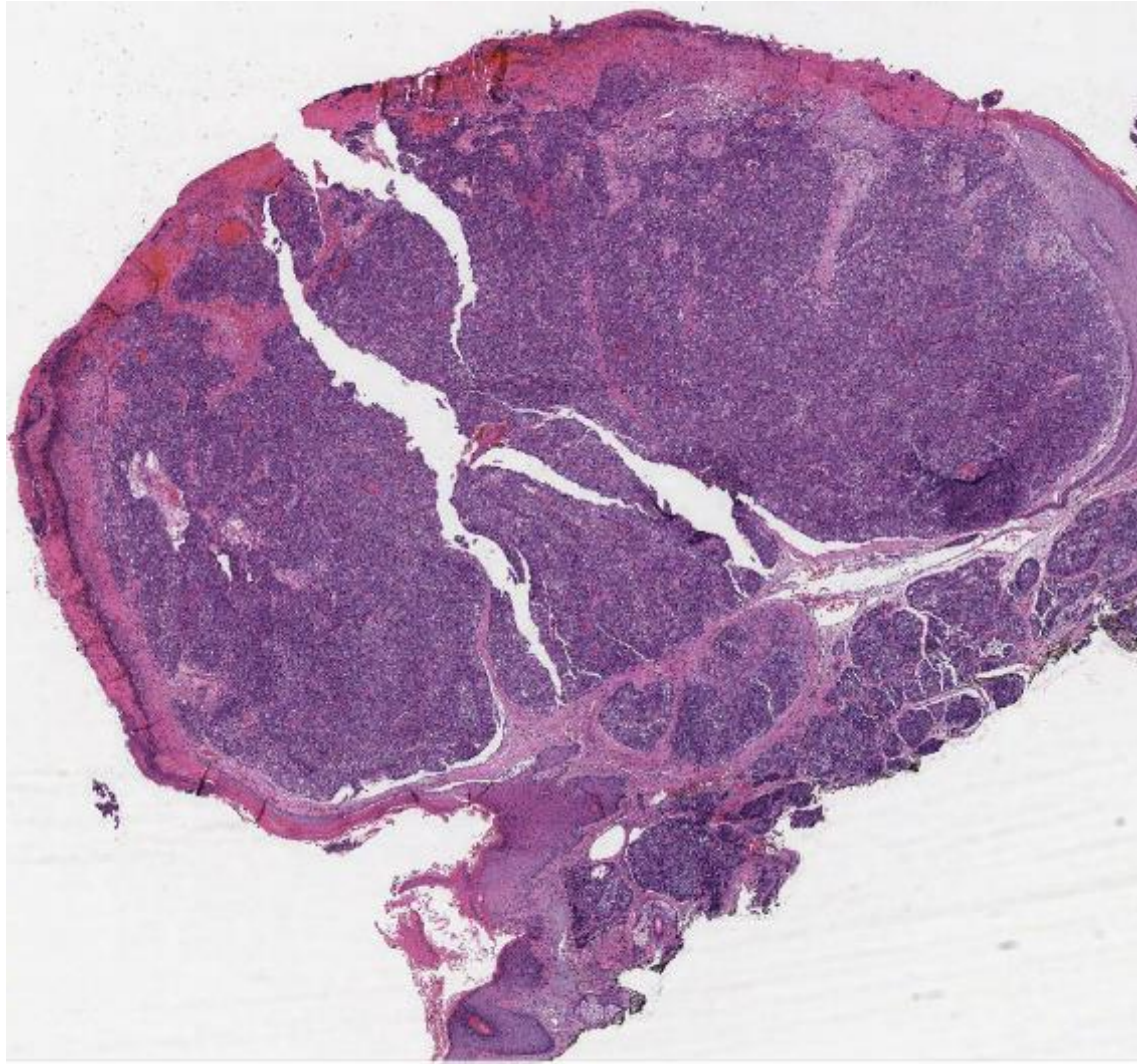
Nodular Hidradenoma

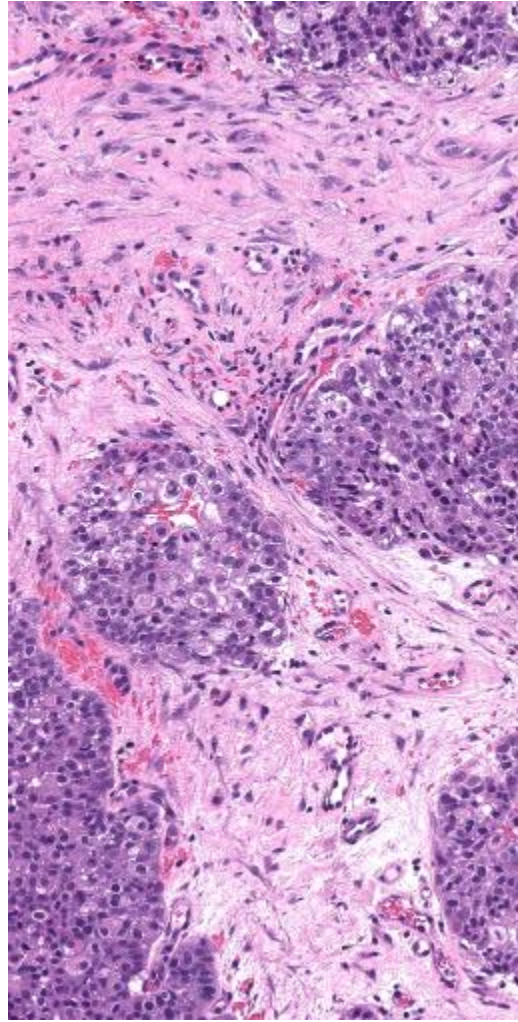
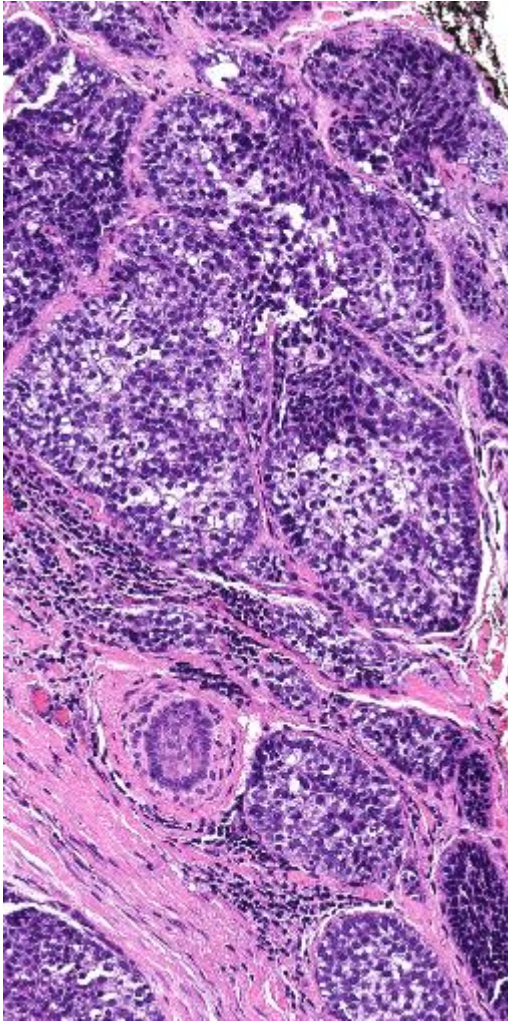


Eccrine Spiradenoma/Cylindroma









Sebaceous carcinoma

Malignant Vs. Benign

Benign

- Symmetric and **smooth bordered** at scanning magnification
- Vertically oriented with respect to the surface of the skin
- Aggregates of epithelial cells uniform
- No necrosis en masse
- Densely fibrotic stroma, rich in fibrocytes in the case of trichogenic
- Mitoses variable, but typical
- Neoplasms forming a blunt, rounded interface with the native dermis.
- Nuclei monomorphous.

Malignant

- **Irregular borders**, asymmetry at scanning magnification
- Horizontal orientation
- Markedly irregular aggregates of epithelial cells
- Necrosis en masse
- Infiltration of the dermis or subcutis without the interposition of densely fibrotic stroma
- Mitoses frequent, can be atypical
- Stroma irregular, often scant, sometimes myxoid
- Nuclei pleomorphic.

Epidemiology (SEER Database)

1988 to 2006 (18 years)

- **4032** malignant cutaneous adnexal tumors.
- Median age at diagnosis was **70 y**
- Most on the **head & neck**
- The 10-year disease-specific survival was **97 percent**.

Estimated for 2017

- **Melanoma** annual newly diagnosed cases : **87,110**
- Estimated annual **death** out of melanoma: **9710**
- More than **4 million** cases of BCC are diagnosed in the U.S. each year.
- More than **1 million** cases of SCC are diagnosed each year in the U.S.A
- Estimated annual death out SCC & BCC: **9800**

Table 3. Cutaneous Appendageal Carcinomas Diagnosed During 2001 Through 2005 in the SEER 16 Program Registries¹⁸ by Histologic Type: Cases and Percentage Distribution by Anatomic Location^a

Histologic Type	Cases, No. (%)						
	Face	Scalp and Neck	Trunk	Extremities ^b	Upper Limb	Lower Limb	Multisite/NOS
Total	875 (48.6)	252 (14.0)	313 (17.4)	342 (19.0)	199 (11.0)	143 (7.9)	19 (1.1)
Apocrine-ecrine tumors ^c	378 (40.8)	131 (14.1)	165 (17.8)	239 (25.8)	129 (13.9)	110 (11.9)	13 (1.4)
Adenoid cystic carcinoma	33 (43.4)	17 (22.4)	16 (21.1)	10 (13.2)	5 (6.6)	5 (6.6)	0
Hidradenocarcinoma	33 (15.7)	25 (11.9)	38 (18.1)	56 (26.7)	27 (12.9)	29 (13.8)	2 (1.0)
Microcystic adnexal carcinoma	155 (68.0)	24 (10.5)	19 (8.3)	28 (12.3)	18 (7.9)	10 (4.4)	2 (0.9)
Porocarcinoma	32 (25.4)	11 (8.7)	23 (18.3)	60 (47.6)	20 (15.9)	40 (31.7)	0
Eccrine carcinoma	41 (29.5)	27 (19.4)	30 (21.6)	37 (26.6)	24 (17.3)	13 (9.4)	4 (2.9)
Mucinous carcinoma	55 (68.8)	14 (17.5)	7 (8.8)	4 (5.0)	3 (3.8)	1 (1.3)	0
Other apocrine-ecrine tumors	29 (23.6)	13 (10.6)	32 (26.0)	44 (35.8)	32 (26.0)	12 (9.8)	5 (4.1)
Apocrine carcinoma	18 (32.1)	9 (16.1)	23 (41.1)	4 (7.1)	3 (5.4)	1 (1.8)	2 (3.6)
Spiradenocarcinoma	6 (23.1)	3 (11.5)	8 (30.8)	8 (30.8)	5 (19.2)	3 (11.5)	1 (3.8)
Digital papillary carcinoma	1 (4.2)	0	0	22 (91.7)	19 (79.2)	3 (12.5)	1 (4.2)
Malignant mixed tumor	4 (23.5)	1 (5.9)	1 (5.9)	10 (58.8)	5 (29.4)	5 (29.4)	1 (5.9)
Sebaceous carcinoma	395 (62.8)	76 (12.1)	107 (17.0)	48 (7.6)	32 (5.1)	16 (2.5)	3 (0.5)
Skin appendage carcinoma, NOS	102 (41.5)	45 (18.3)	41 (16.7)	55 (22.4)	38 (15.4)	17 (6.9)	3 (1.2)

Table 4. Five-Year Relative Survival Rates (RSRs)^a Among Patients Diagnosed as Having Cutaneous Appendageal Carcinomas During 1992 Through 2004 in the SEER Program Registries¹⁸ by Histologic Type, Sex, and Race^b

Histologic Type	Overall		Sex				Race				Stage ^d					
			M		F		White		Black		Localized		Regional		Distant	
	No.	RSR, %	No.	RSR, %	No.	RSR, %	No.	RSR, %	No.	RSR, %	No.	RSR, %	No.	RSR, %	No.	RSR, %
Total	1984	96.5	1024	95.9	960	97.0	1849	96.6	135	95.6	1445	99.2	288	92.8	32	43.4
Apocrine-ecrine tumors ^c	844	97.2	422	93.6	422	99.5	759	96.8	85	96.9	596	99.2	136	94.3	19	50.8
Adenoid cystic carcinoma	106	98.6	46	98.1	60	97.7	97	98.4	9	100	62	98.6	21	100	1	NR
Hidradenocarcinoma	351	92.8	209	92.1	142	92.4	320	92.0	31	96.9	250	96.4	52	83.8	7	NR
Microcystic adnexal carcinoma	155	99.5	62	96.7	93	99.0	151	99.5	4	NR	120	99.8	22	93.9	2	NR
Mucinous carcinoma	91	100	33	84.5	58	100	74	100	17	97.2	70	100	11	100	1	NR
Other apocrine-ecrine tumors	141	93.8	72	89.0	69	95.9	117	95.5	24	84.9	94	95.6	30	90.7	8	NR
Apocrine carcinoma	81	91.7	37	77.0	44	96.7	64	92.2	17	88.9	47	95.5	22	85.5	6	NR
Spiradenocarcinoma	21	96.7	12	98.2	9	NR	20	96.7	1	NR	18	93.9	1	NR	0	NR
Digital papillary carcinoma	18	100	15	100	3	NR	16	100	2	NR	13	100	3	NR	1	NR
Malignant mixed tumor	21	83.5	8	NR	13	79.4	17	88.9	4	NR	16	84.3	4	NR	1	NR
Sebaceous carcinoma	687	95.8	374	94.9	313	94.3	663	96.2	24	84.5	528	98.4	78	85.0	6	NR
Skin appendage carcinoma, NOS	453	94.8	228	96.4	225	91.9	427	94.5	26	95.3	321	96.8	74	95.4	7	NR

Benign/Malignant

- 2004-2010
- 80.36% were benign
- 19.64% were malignant.
- **Sweat gland tumors** constituted the largest group (42.86%), followed by the **hair follicle tumors** (35.71%) then **sebaceous gland tumors** (21.43%).
- Male/female 1.07 : 1.
- HN (64.28%) then trunk (14.28%).

Etiology

Disease	Inheritance	Tumor	Locus	Gene
Cowden disease	AD	Tricholemmoma/ Hamartomas	10q23	PTEN/ MMAC1
Muir-Torre syndrome	AD	Sebaceous neoplasms	2p22	hMSH2
Gardner syndrome	AD	Follicular cysts/PTX	5q21	APC
Bloom syndrome	AR	Skin tumors	15q26.1	BLM/RECQL3
Birt-Hogg Dubé Syndrome	AD	Follicular Hamartomas	17p11.2	BHD
Cylindromatosis familial	AD	Cylindromas	16q12-13	CYLD1
Brooke-Spiegler syndrome	AD	Cylindromas	9p21	CYLD
Nevoid basal cell carcinoma syndrome	AD	Trichoblastoma/BCC	9q22.3	PTCH1

Clinical signs and symptoms

- Benign adnexal neoplasms are smooth surfaced, symmetrical papules or nodules the same color as the patient's skin or darker.
- Most adnexal carcinomas are irregularly shaped plaques, sometimes ulcerated.

Site Specific Tumors

- Extremities:
 - Papillary digital adenocarcinoma
 - Papillary eccrine adenoma
- Axillae:
 - Apocrine Carcinoma
- Vulva and Perineum
 - Hidradenoma papilliferum
 - Extramammary Paget's disease
 - Ductopapillary apocrine carcinoma

Potential Multiplicity

- Cylindroma (Brooke-Spiegler syndrome)
- Syringoma
- Poromas
- Trichoepithelioma
- Trichilemmoma (Cowden's syndrome)
- Sebaceous tumors (Muir-Torre syndrome)



TNM classification of skin appendageal carcinomas

TNM classification^{1,2}

T – Primary tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but no more than 5 cm in greatest dimension
T3	Tumour more than 5 cm in greatest dimension
T4	Tumour invades deep extradermal structures, i.e., cartilage, skeletal muscle, or bone

Note: In the case of multiple simultaneous tumours, the tumour with the highest T category is classified and the number of separate tumours is indicated in parentheses, e.g., T2(5).

N – Regional lymph nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

M – Distant metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

¹ {894,2219}.

² A help desk for specific questions about the TNM classification is available at www.uicc.org/index.php?id=508.

Tumour spread and staging

- Low-grade carcinomas: seldom metastasize
- Lymphatic or hematogenous dissemination.

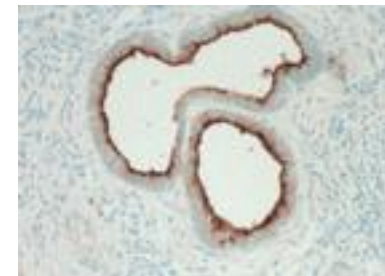
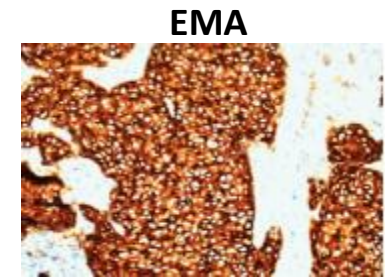
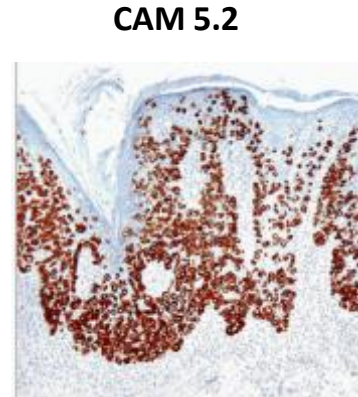
Sentinel node biopsy

- 5 patients with eccrine carcinomas (2 aggressive digital papillary adenocarcinoma, 2 hidradenocarcinoma & 1 eccrine carcinoma)
- No clinical evidence of metastatic disease
- 3 of the 5 patients (60%) were found to be positive for metastatic carcinoma.

Bogner, et. al., (2003).Cancer, 97(9), 2285-2289.

Immunoprofile

- Sebaceous glands:
 - LMWK & EMA positive
 - S100 & CEA negative
- Sweet gland (ductal differentiation):
 - Luminal staining by CEA & EMA
- Ber-Ep4, CD34, Ki-67 & D2-40: MAC, TE, SCC & BCC
- CAM 5.5: Extramammary Paget's disease.



Adnexal tumors

	Hair follicle	Sweat glands	Sebaceous glands	Complex
Benign	Follicular cyst inf type	Hidrocystoma	Sebaceous hyperplasia	Organoid nevus
	Follicular cyst ist-cat	- eccrine	Sebaceous adenoma	Combined adnexal tumor
	Trichofolliculoma	- apocrine	Sebaceoma	Sebocrine adenoma
	Trichoepithelioma	Syringoma		
	-Trichoadenoma	- clear cell variant		
	-Trichoblastoma	Mixed tumor		
	-Desmoplastic trichoep	Cylindroma		
	Tumor of the follicular inf	Spiradenoma		
	Dilated pore of Winer	Poroma group		
	Pilar sheath acanthoma	- Hydroacanthoma simplex		
	Inverted follicular keratosis	- Eccrine poroma		
	Tricholemmoma	- Dermal duct tumor		
	Pilomatrixoma	- Hidradenoma		
	Fibrofolliculoma	Papillary eccrine adenoma		
	Trichodiscoma	Tubular apocrine adenoma		
Neurofollicular hamartoma	Hidradenoma papilliferum			
	Syringocystadenoma papilliferum			
	Proliferating tricholemmal cyst			
Malignant		"Syringoid tumors"		
		- MAC		
		- Syringoid eccrine carcinoma		
		- Adenoid cystic carcinoma		
		Digital papillary adenocarcinoma		
	Malignant tricholemmal cyst	Malignant cylindroma		
	Tricholemmal carcinoma	Malignant spiradenoma		
	Pilomatrix carcinoma	Porocarcinoma		
	?BCC	Hidradenocarcinoma		
		Malignant mixed tumor		
		Eccrine ductal carcinoma		
		Mucinous (colloid) carcinoma		
		Apocrine carcinoma		
		Extramamary Paget's Disease		
			Sebaceous carcinoma	

