

Reappraisal of Morphologic Differences Between Renal Medullary Carcinoma, Collecting Duct Carcinoma, and Fumarate Hydratase-deficient Renal Cell Carcinoma

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2016 WHO新分类

透明细胞肾细胞癌

多房性囊性肾癌

乳头状肾细胞癌

嫌色肾细胞癌

肾髓质癌

集合管癌

黏液样小管状和梭形细胞癌

Xp11易位性肾癌

未分类的肾细胞癌

肾脏乳头状腺瘤

嗜酸细胞瘤

遗传性平滑肌瘤病肾癌综合征

MIT家族易位性肾癌

(包括Xp11和t(6;11)易位性肾癌)

SDH缺陷相关性肾癌

管状囊性癌

获得性囊性肾疾病相关性肾癌

透明细胞乳头状癌

肾髓质癌

(Renal Medullary Carcinoma, RMC)

- 肾高度侵袭性恶性肿瘤，主要发生于青少年，生长迅速，预后差，患者的生存时间以月计算（1天-26月）
- 肉眼血尿、季肋部或腹部疼痛、体重下降和腹部包块是最常见症状
- 绝大多数患者都伴有镰状细胞病或镰状红细胞特征
- 文献报道多发生于黑人人种

肾髓质癌

(Renal Medullary Carcinoma, RMC)

- 病变主要位于肾髓质，常浸润肾盂、肾被膜及肾周软组织，有时肾皮质内可见卫星结节。肿块切面灰褐色，质地较韧或偏硬，常伴有出血坏死囊性变或灶性黏液变
- 瘤细胞呈网状、卵黄囊样、片状、微乳头状排列，并可有微囊形成，还可呈实性排列，偶见腺管状和小梁状结构
- 间质明显纤维化及大量中性粒细胞浸润形成微脓肿是特征性改变

肾集合管癌

(collecting duct carcinoma, CDC)

- 是一种少见的肾细胞癌，占有所有肾细胞癌的1% ~ 2%
- 血尿、腰腹痛为常见症状；病程短，进展快
- 病理特征：

肿瘤发生于髓质，呈灰白色或淡黄色，质地较肾透明细胞癌韧，无包膜，向肾盂和肾皮质侵袭

以腺管状或腺管乳头状结构为主，被覆单层或复层上皮，分化差的呈腺样囊性、巢状、条索状或肉瘤样，细胞界限不清，核异型性明显，肿瘤有明显的间质反应

延胡索酸水合酶缺陷型肾细胞癌 (FH-deficient RCC)

- 新近出现的一组高级别肾细胞癌，特别是遗传性平滑肌瘤病和肾癌综合征相关性肾细胞癌 (HLRCC)
- 侵袭性生长，具有管状乳头状结构
- 显示延胡索酸水合酶(FH)基因突变和功能缺失

遗传性平滑肌瘤病和肾癌综合征 相关性肾细胞癌（HLRCC）

- 由延胡索酸水合酶（fumarate hydratase, FH）基因胚系突变导致的一种遗传性综合征，表现为皮肤多发性平滑肌瘤，女性患者还可表现为多发子宫平滑肌瘤。肾脏受累的患者则表现为早发性的肾细胞癌
- 倾向于发生早期转移，预后较差

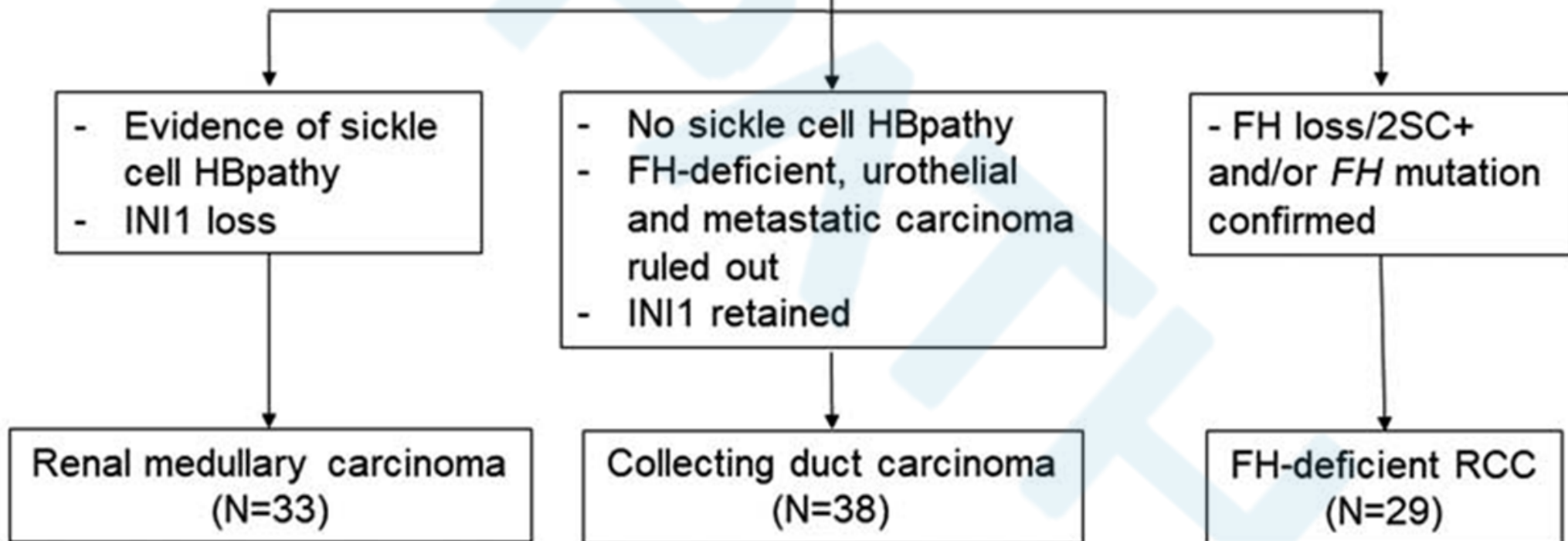
遗传性平滑肌瘤病和肾细胞癌综合征相关性肾细胞癌（HLRCC）

- 单侧单发肿块，大体上肿瘤较易囊性变，亦可呈实性，或囊实性混合，多位于肾皮质
- 瘤细胞排列成乳头状，胞浆丰富，核仁显著，大而红染，类似核内病毒包涵体样，核仁周围可见一圈淡染空晕，可呈实性、管状、囊状生长结构

材料与amp;方法

Case Selection

High grade renal carcinoma with any of the following features;
infiltrating glands, multinodular infiltrating papillary, tubular-papillary, solid sheets/cords/nests,
intracystic papillary, sieve-like/cribriform, tubulocystic carcinoma-like, reticular/yolk sac tumor-like



组织形态分类

- 纤维间质内中、小腺体浸润性生长
- 结节性浸润性乳头状
- 管状/管状乳头状/乳头状
- 实性片状、条索状、巢团状和/或具有横纹肌样特征
- 囊内乳头状
- 筛状
- 肾管状囊性癌样
- 网状/卵黄囊瘤样

免疫组化

- PAX8
- S100A1
- SMARCB1/INI1
- OCT3/4
- FH
- 2SC（是一种改组的半胱氨酸，是因延胡索酸水合酶失活致延胡索酸异常富集而形成的产物）

结果

TABLE 1. Clinical Features

	n/N (%)			<i>P</i>
	RMC (n = 33)	CDC (n = 38)	FH-deficient RCC (n = 29)	
Median age (range) (y)	27.0 (10-63)	65.5 (16-83)	45.0 (18-71)	< 0.001
Male:female	2.6:1	3.2:1	3.1:1	0.958
Race				
White	3/32 (9)	28/31 (90)	17/24 (71)	NA
African American	25/32 (78)	2/31 (7)	3/24 (12)	
Other	4/32 (13)	1/31 (3)	4/24 (17)	
Sickle cell disorder (%)	100*	0	0	NA
Family history of HLRCC or RCC (H)/HLRCC stigmata (S) (%)	0	0	H: 7/18 (39) S: 5/17 (29)	NA
Laterality†	24/32 (75)	14/32 (44)	12/28 (43)	< 0.0167
Tumor size (range) (cm)	6.4 (4-12)	6.3 (2-15.8)	8.5 (3-18)	< 0.05
pT stage category				
pT1-2	5/33 (15)	3/34 (9)	7/28 (25)	0.225
pT3-4	27/33 (85)	31/34 (91)	21/28 (75)	
Local recurrence	4/29 (14)	5/22 (23)	3/20 (15)	0.723
Lymph node metastasis	25/26 (96)	13/27 (48)	15/26 (58)	< 0.0167
Systemic metastasis	30/32 (94)	16/22 (73)	17/26 (65)	0.0169
Dead of disease mean time to death (range) (mo)	24/29 (83) 10.3; 7 d-25	14/23 (61) 11.6; 2.5-37	14/23 (61) 18.6; 2-64	0.145

*The history of sickle cell trait sickle cell hemoglobinopathy was unavailable in 18% (6/33); however, histologic sickled erythrocytes were seen.

†Predilection for right kidney.

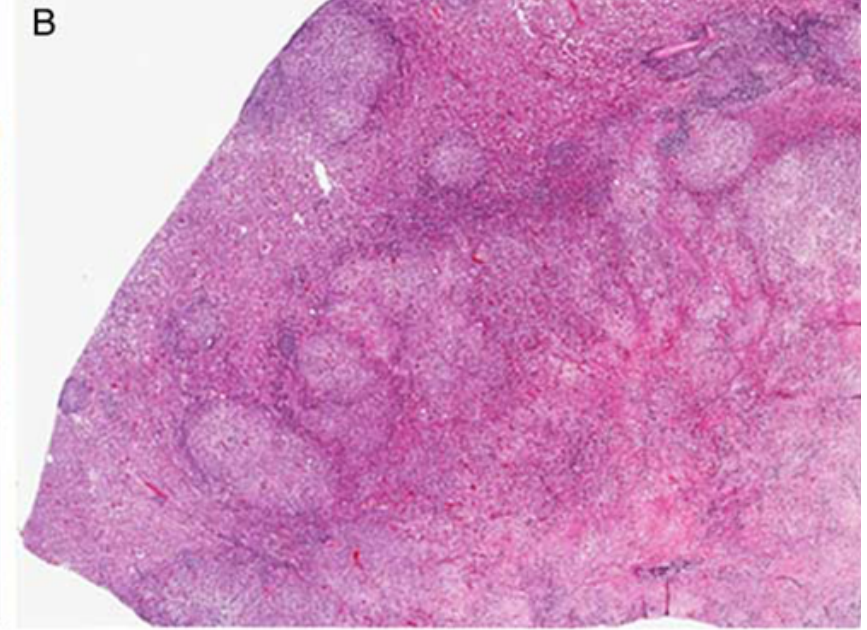
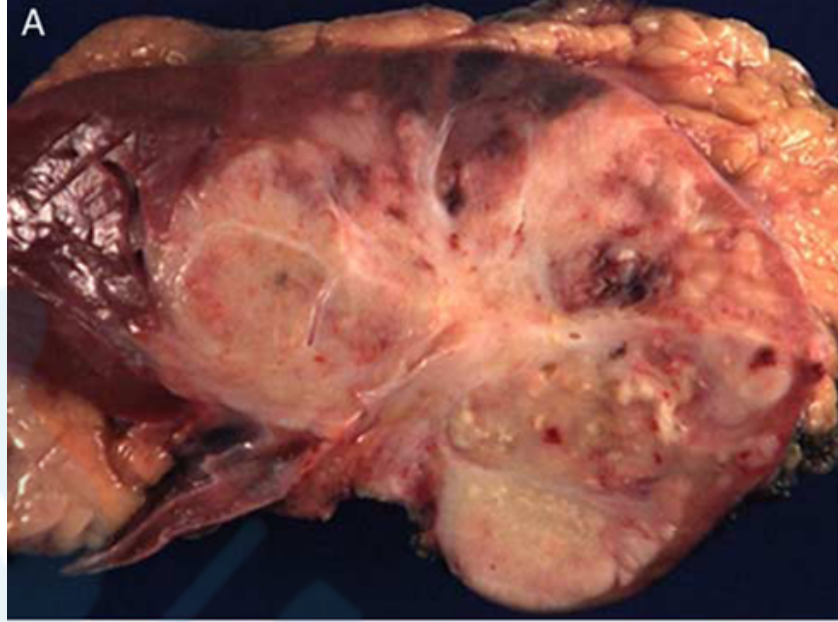
NA indicates not analyzed.

TABLE 2. Macroscopic and Microscopic Features

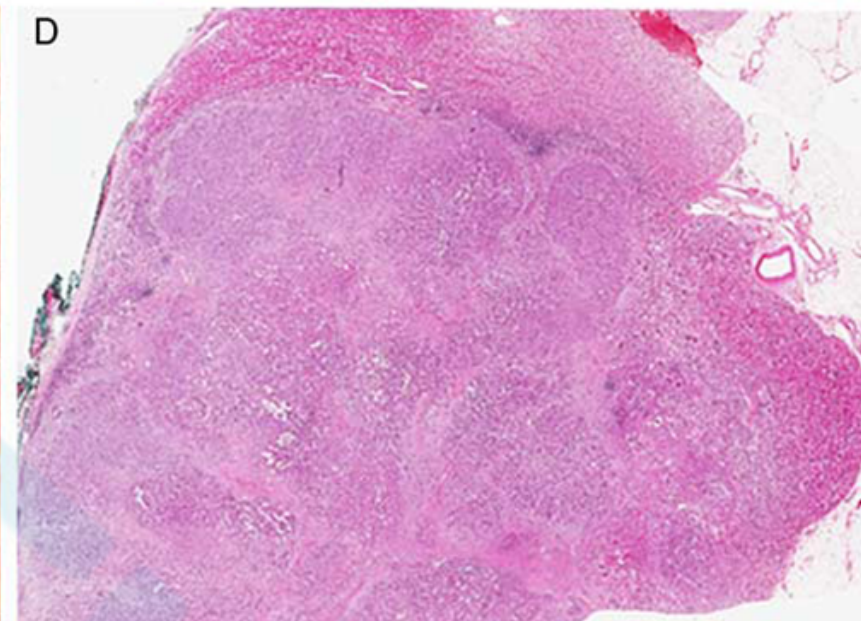
	n/N (%)			<i>P</i>
	RMC	CDC	FH-deficient RCC	
Macroscopic features				
Location; medulla cortex and medulla	18/32 (18/32) 14/32 (44)	14/34 (41) 15/34 (44)	3/24 (13) 16/24 (67)	NA
Infiltrating border	22/32 (69)	25/32 (78)	11/22 (50)	0.110
Renal vein invasion	13/32 (41)	14/32 (44)	7/23 (30)	0.669
Microscopic features				
#1 (infiltrating gland)	18/33 (55)	28/38 (74)	14/29 (48)	0.0775
#2 (MIP)	0/33 (0)	10/38 (26)	3/29 (10)	<0.0167
#3 (tubular, papillary)	12/33 (36)	32/38 (84)	25/29 (86)	<0.0167
#4 (solid sheet, cord, nest)	32/33 (97)	36/38 (95)	23/29 (79)	0.436
#5 (intracystic papillary)	5/33 (15)	6/38 (16)	16/29 (55)	<0.0167
#6 (sieve-like/cribriform)	29/33 (88)	15/38 (39)	18/29 (62)	<0.0167
#7 (tubulocystic)	0/33 (0)	0/38 (0)	19/29 (66)	<0.0167
#8 (reticular/YST-like)	28/33 (85)	3/38 (8)	1/29 (3)	<0.0167
HLRCC-like nucleoli (1 ⁺ ; 2 ⁺)	13/33 (39) (30%; 9%)	15/38 (40) (29%; 11%)	29/29 (100) (21%; 79%)	<0.0167
Coagulative necrosis	21/33 (64)	26/38 (68)	5/29 (17)	<0.0167
Dysplastic in situ change	2/33 (6)	16/38 (42)	3/28 (11)	<0.0167
Stromal myxoid change	31/33 (94)	10/38 (26)	11/28 (39)	<0.0167
Sarcomatoid change	5/33 (15)	11/38 (29)	8/19 (28)	0.388
ISUP/WHO grades 3, 4	19/33 (58), 14/33 (42)	24/38 (63), 14/38 (37)	21/29 (72), 8/29 (28)	0.475

MIP indicates multinodular infiltrating papillary.

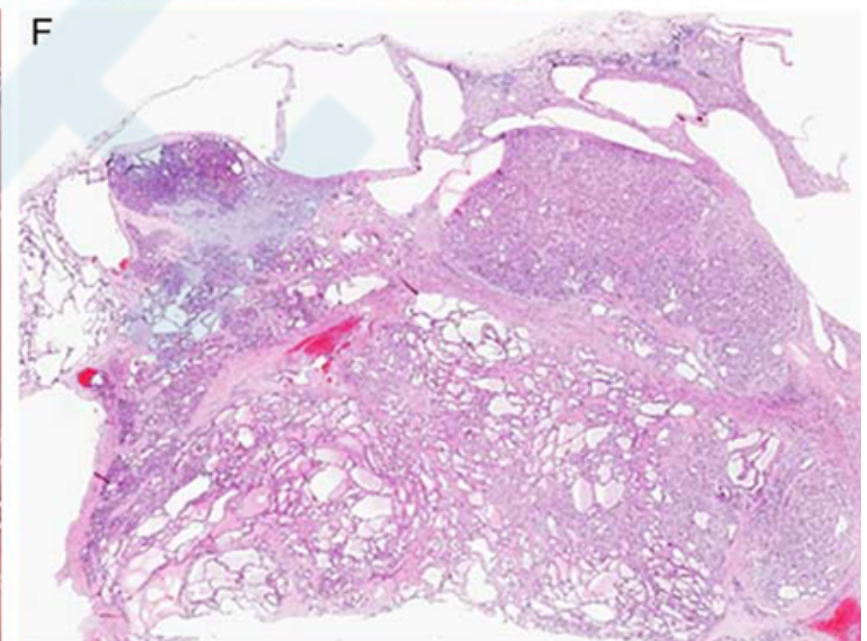
- RMC



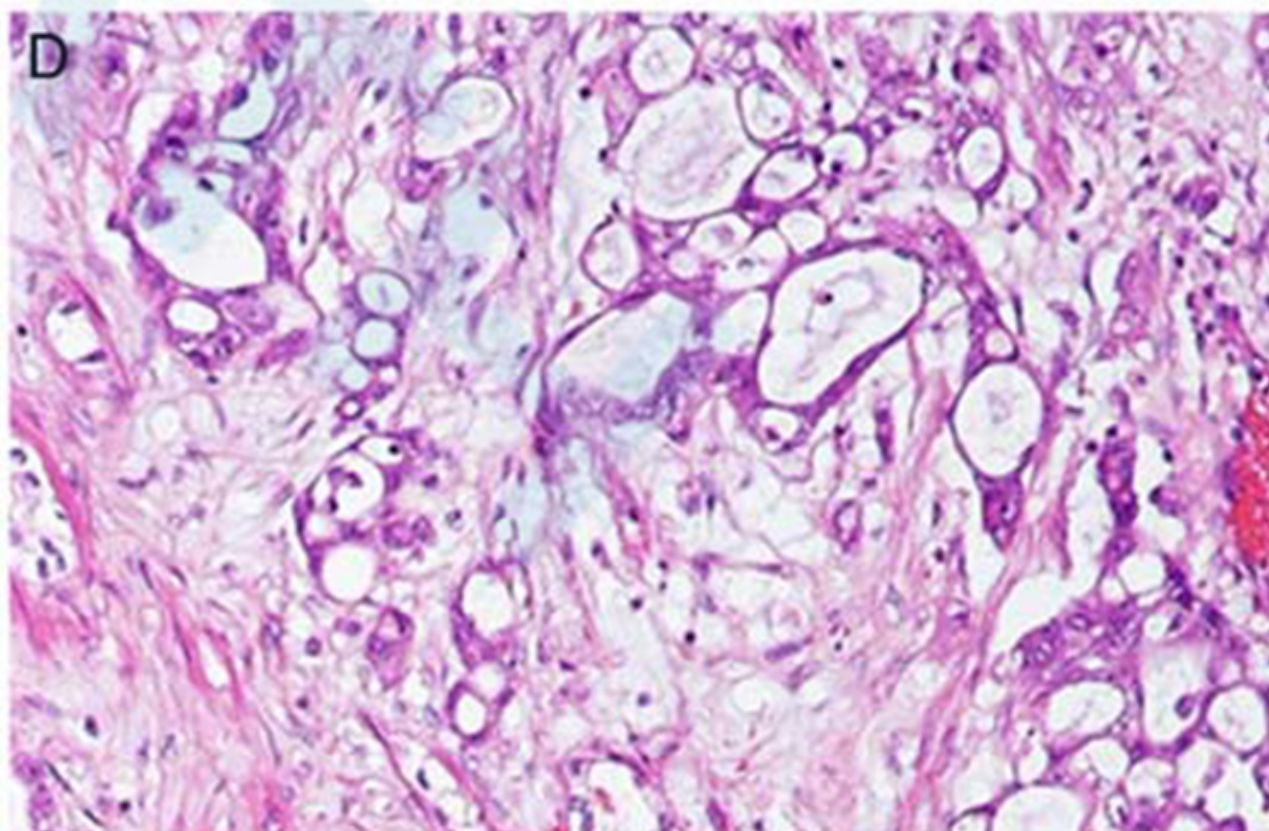
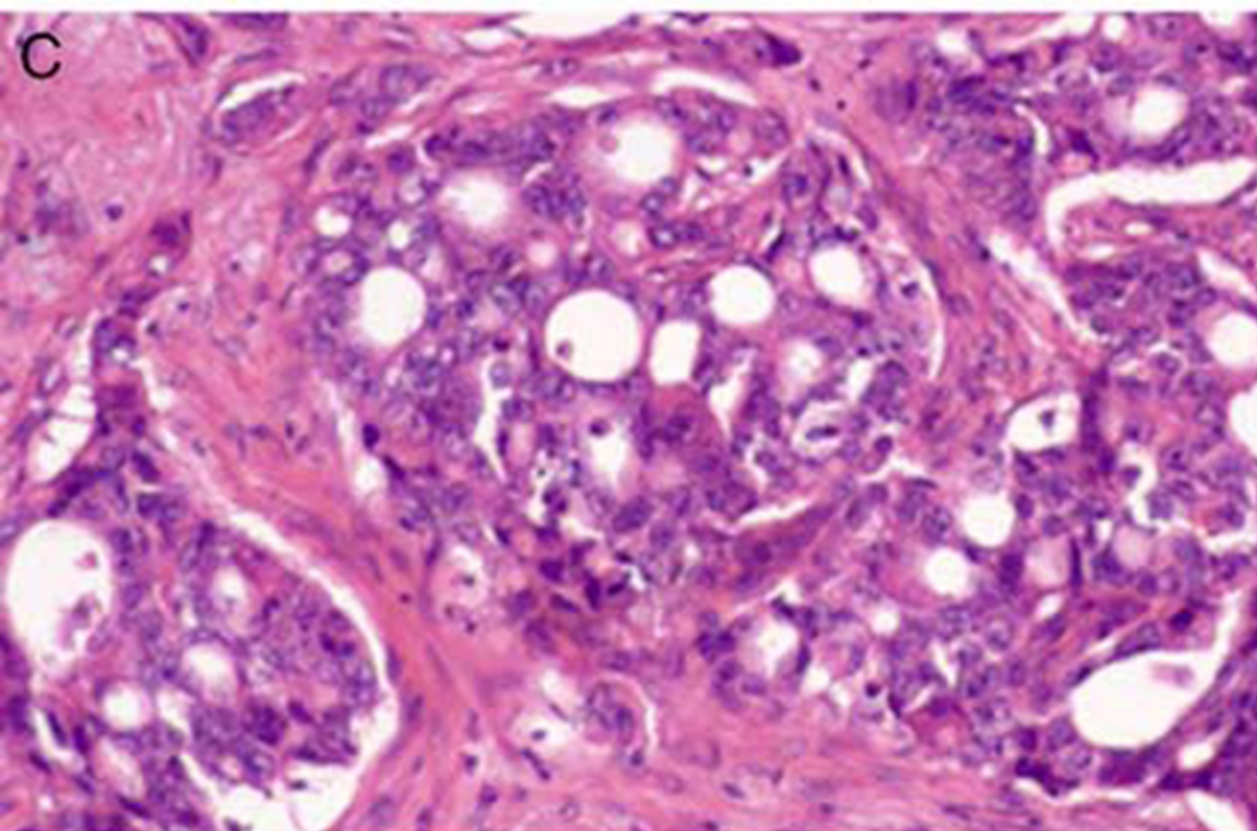
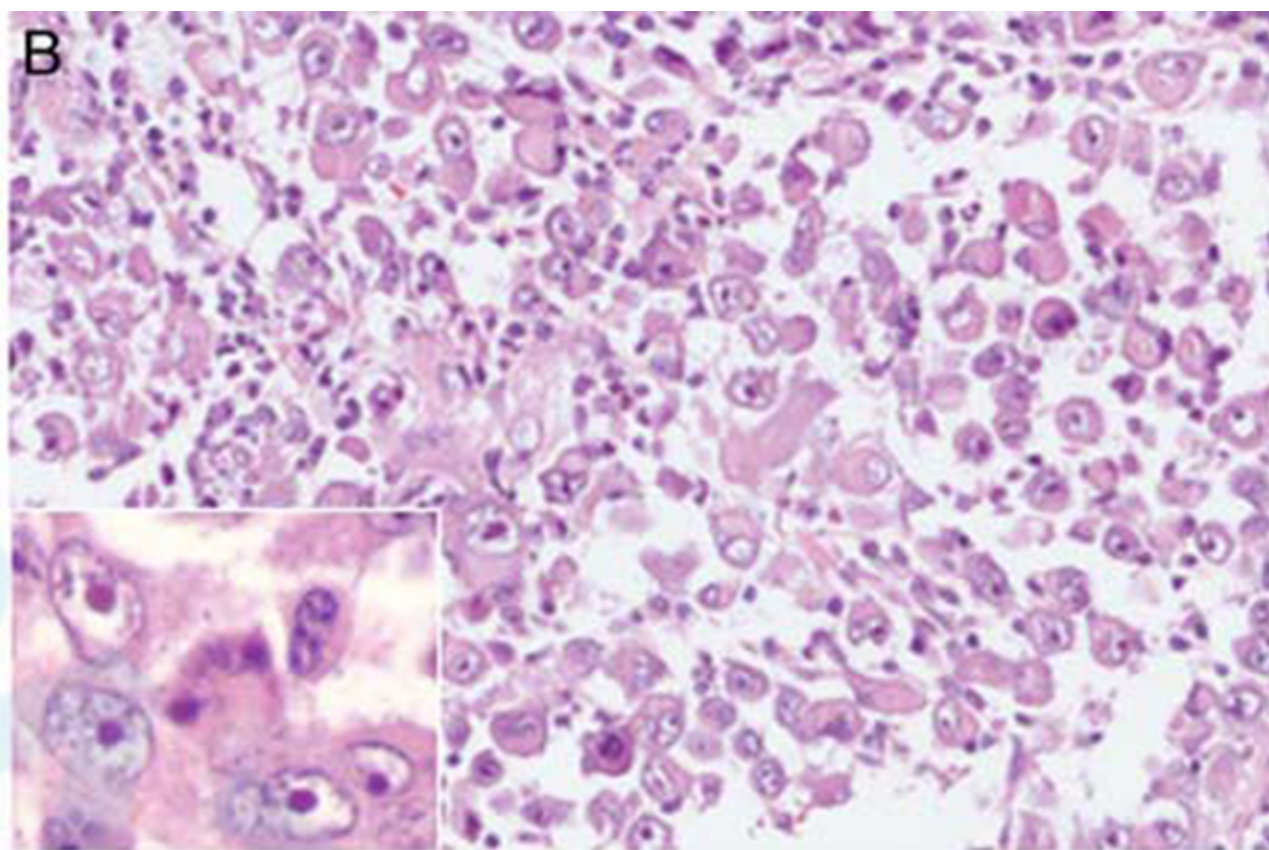
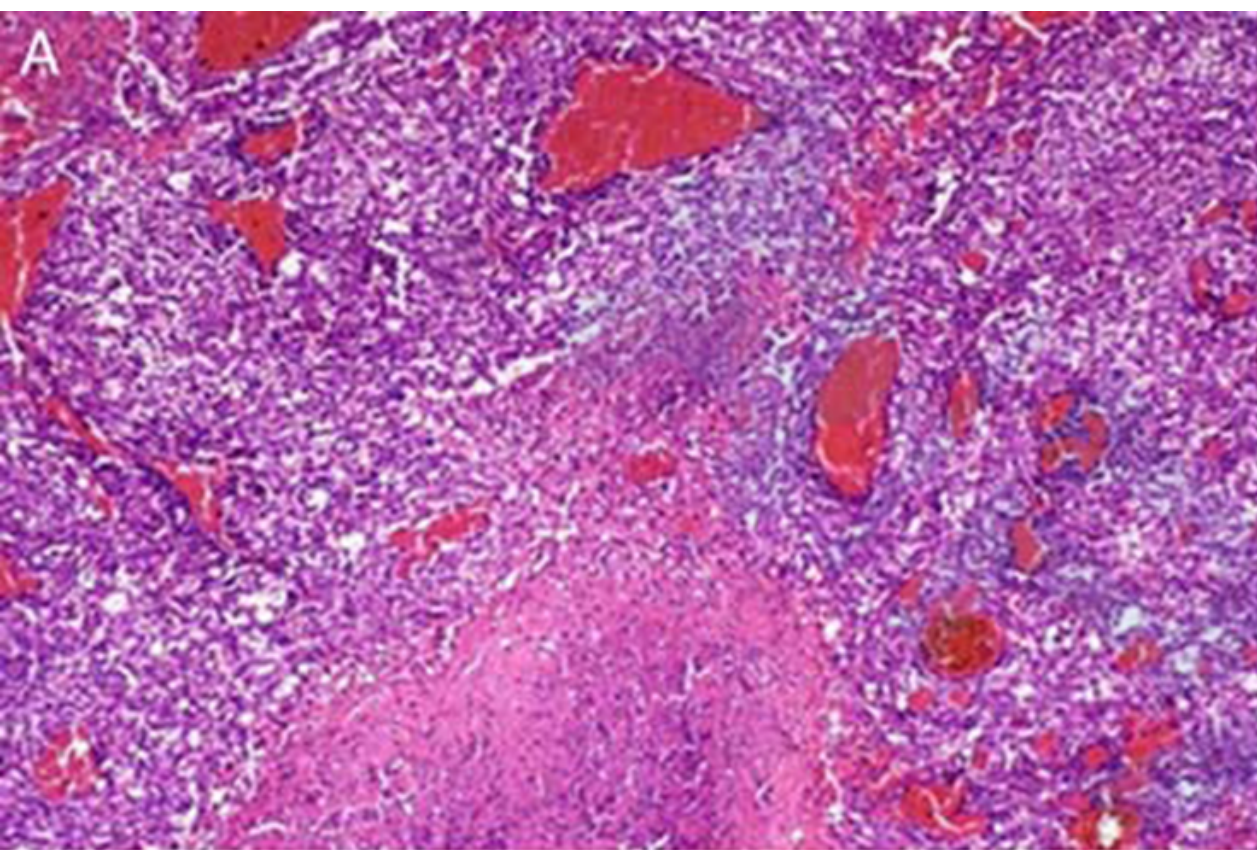
- CDC



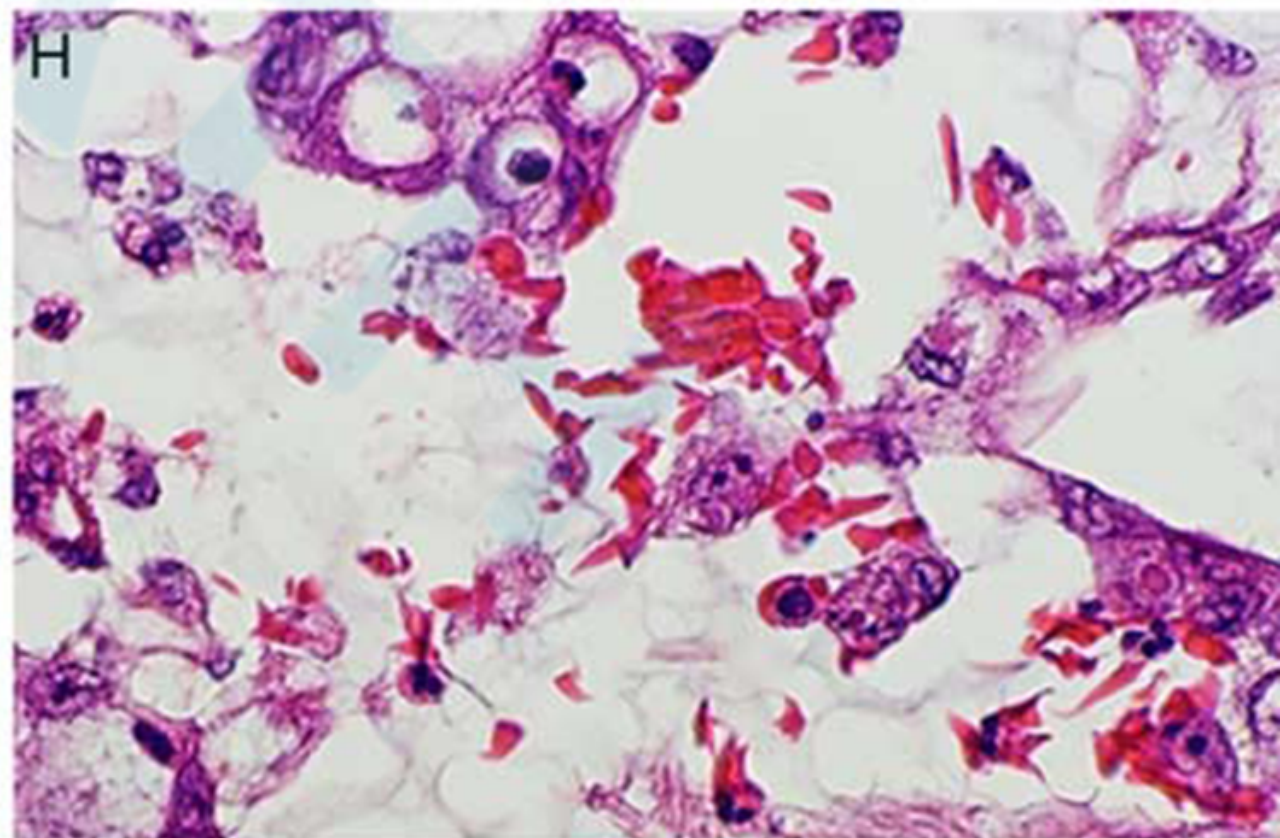
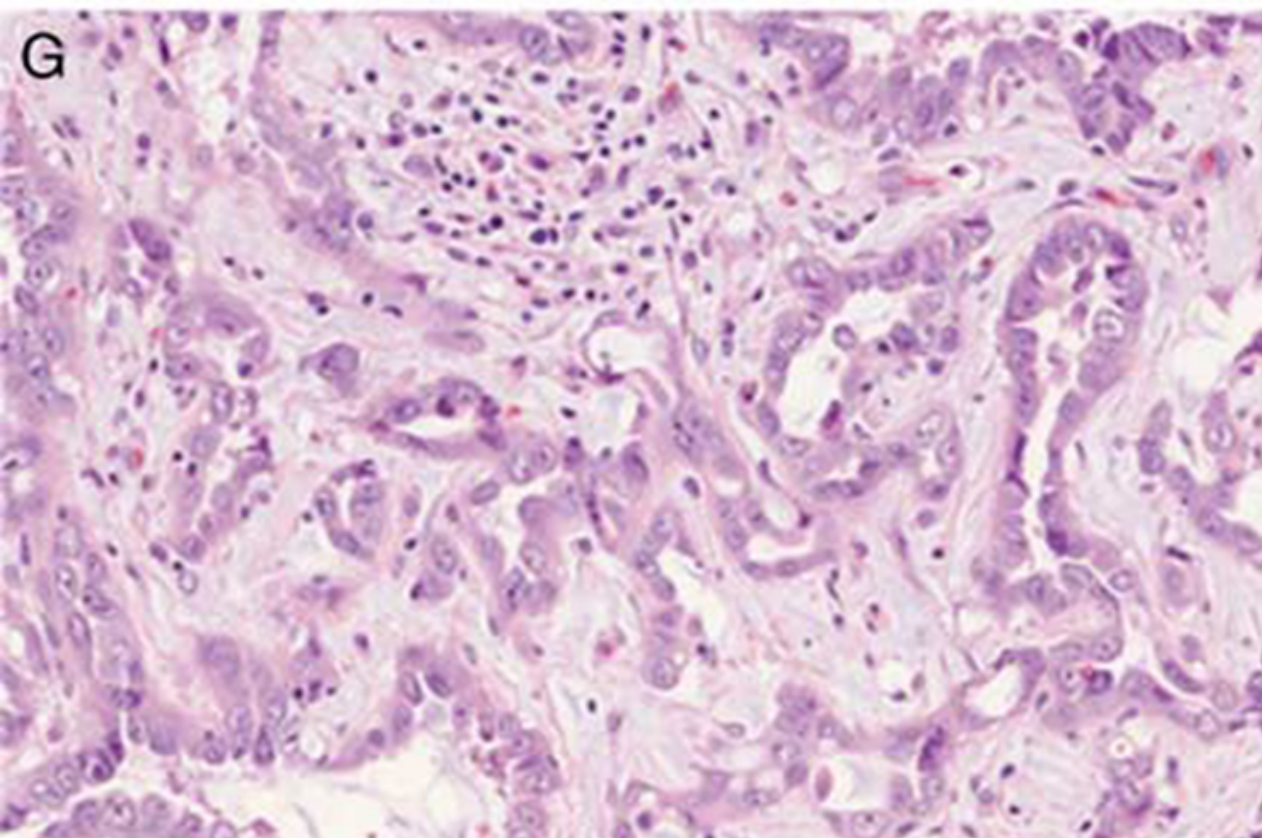
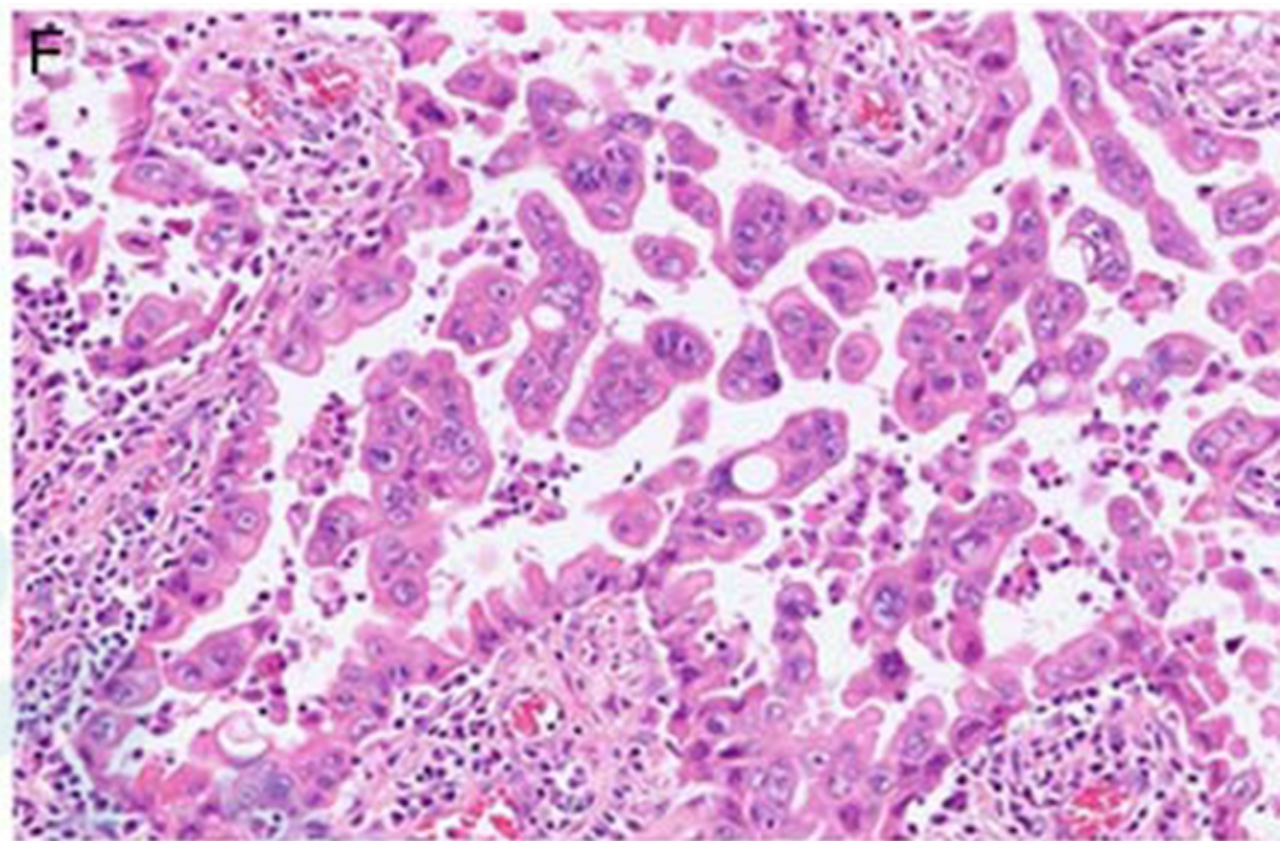
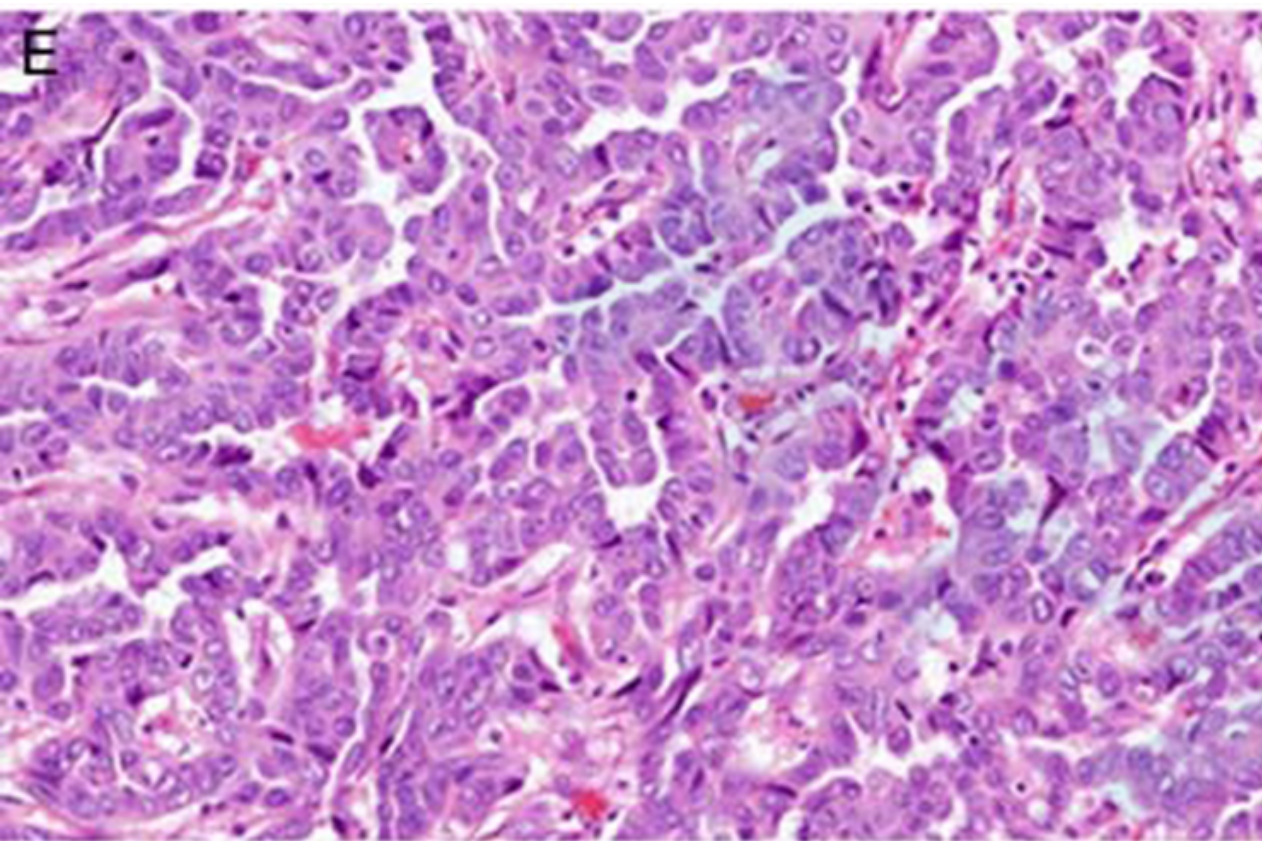
- FH-deficient
RCC



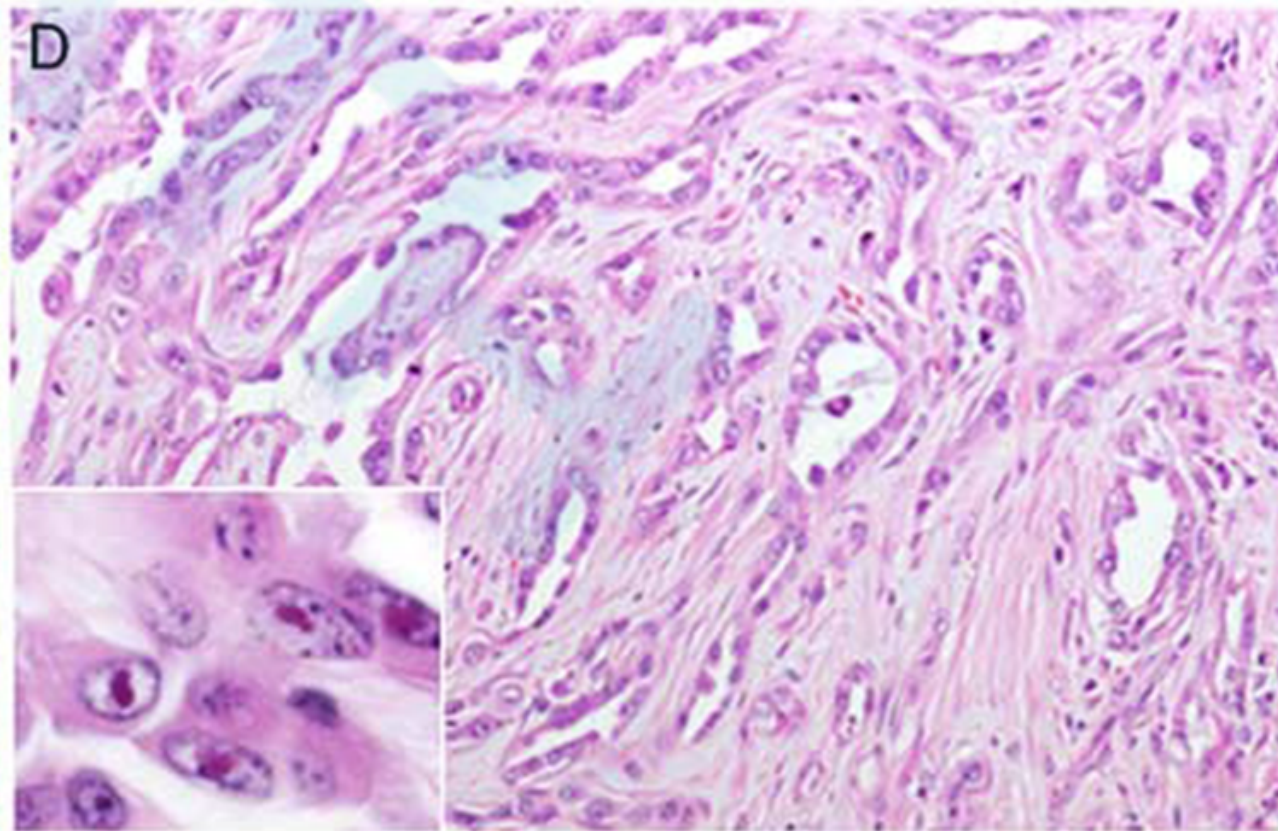
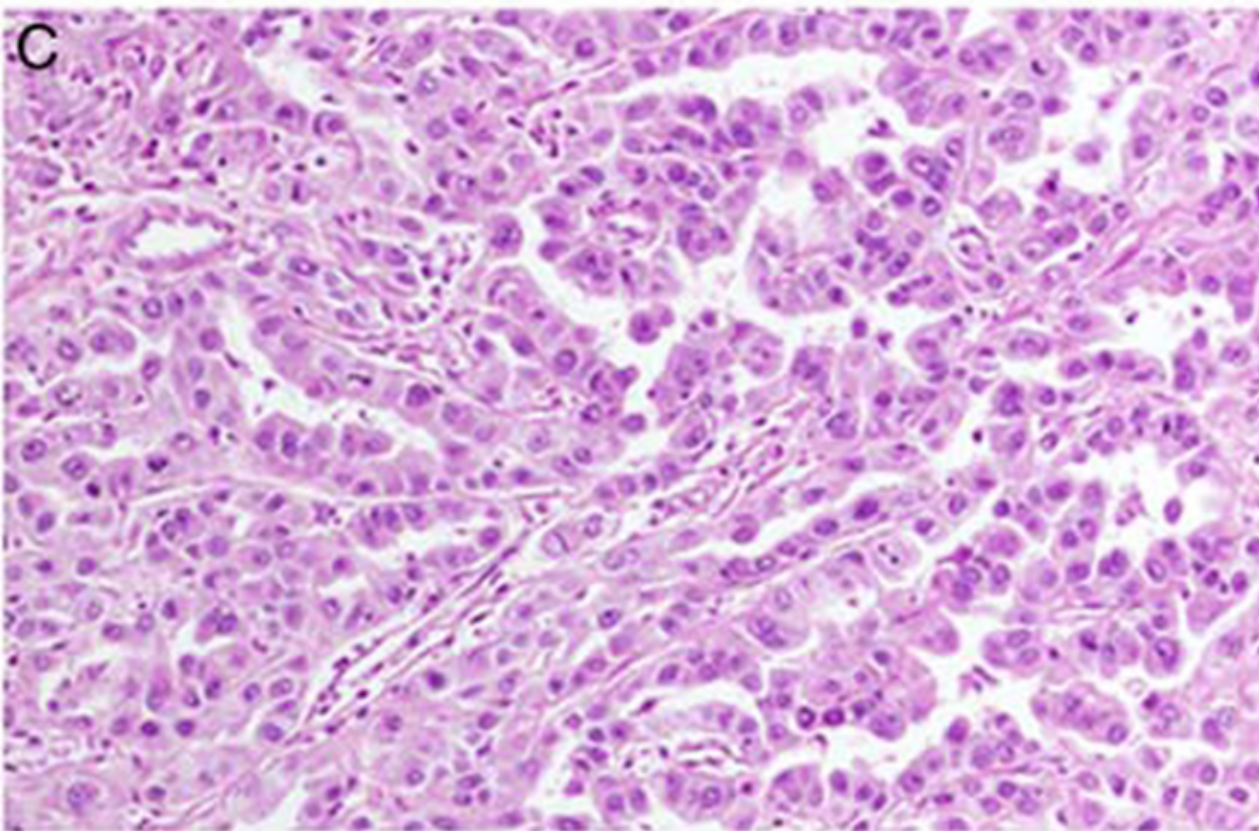
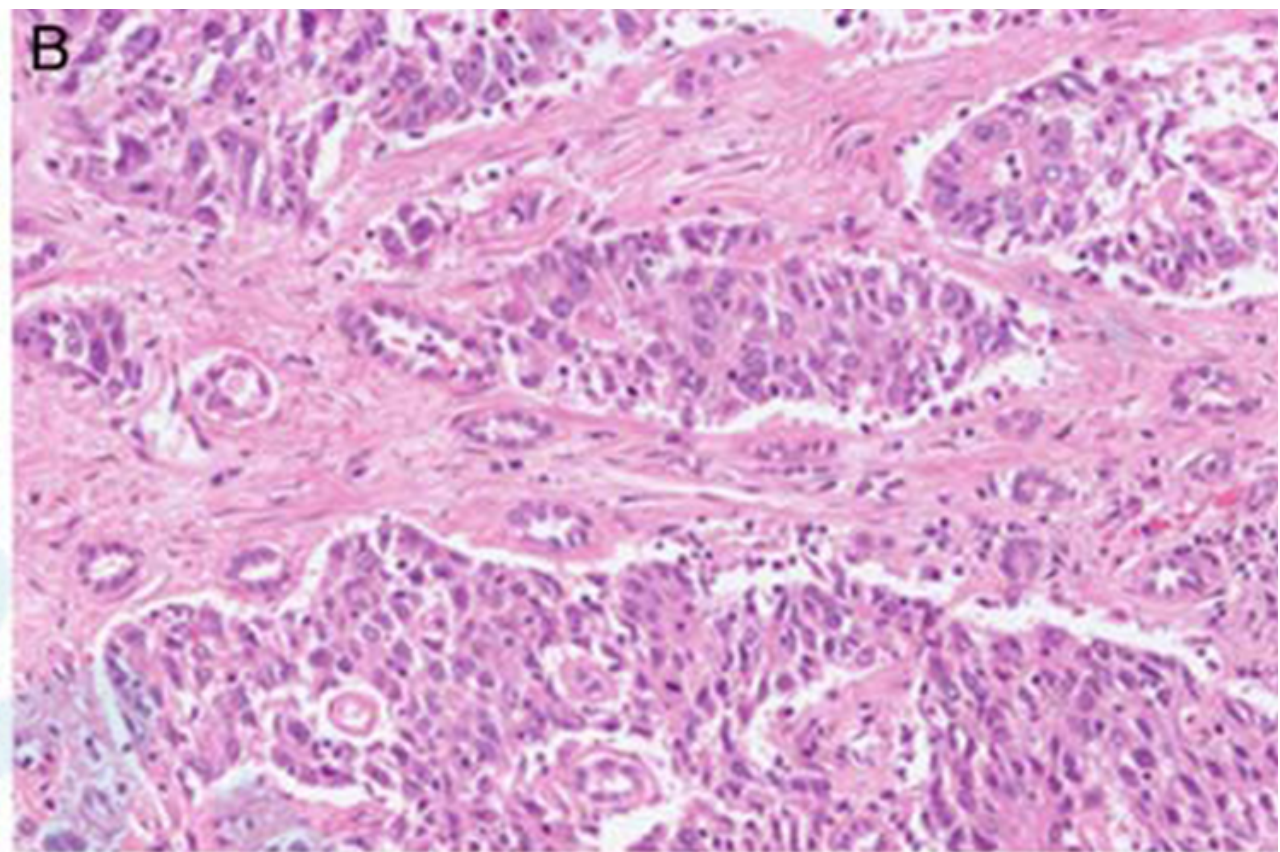
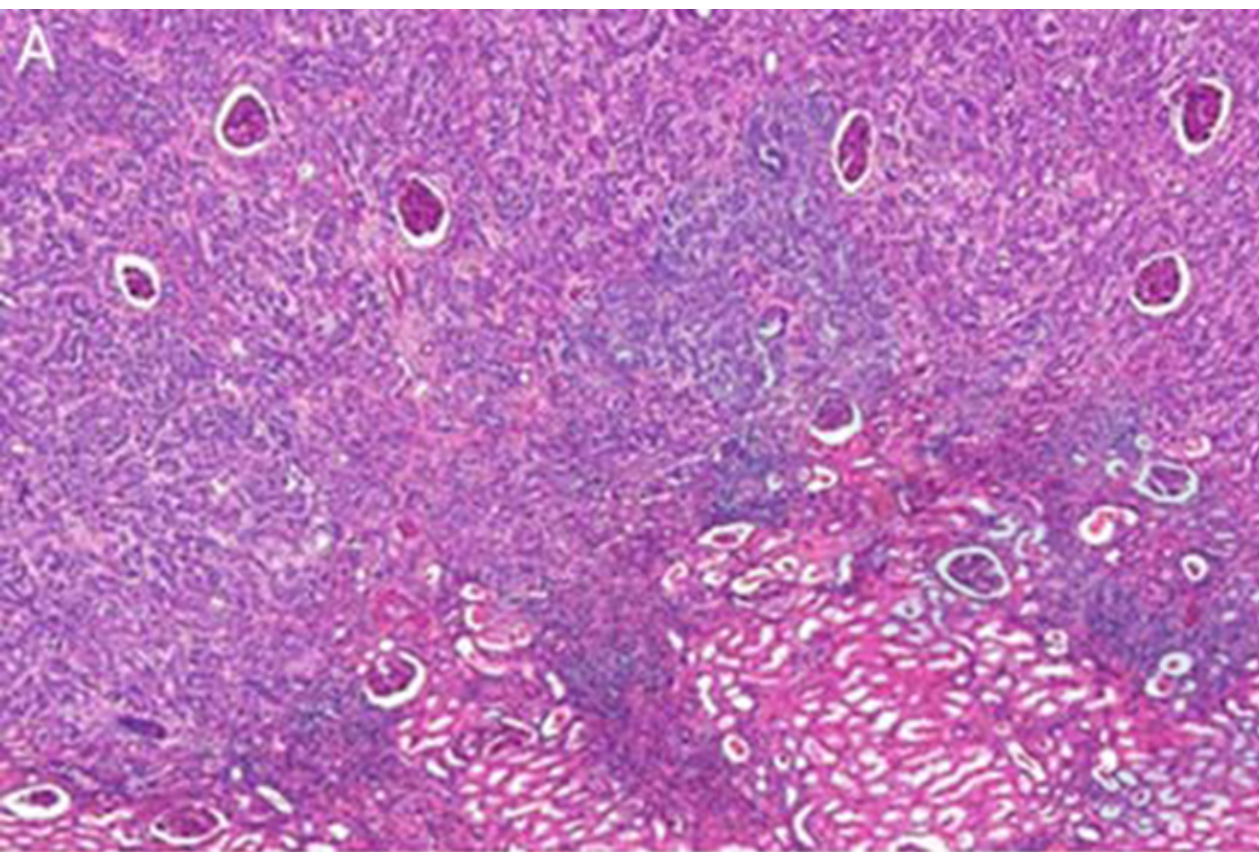
RMC



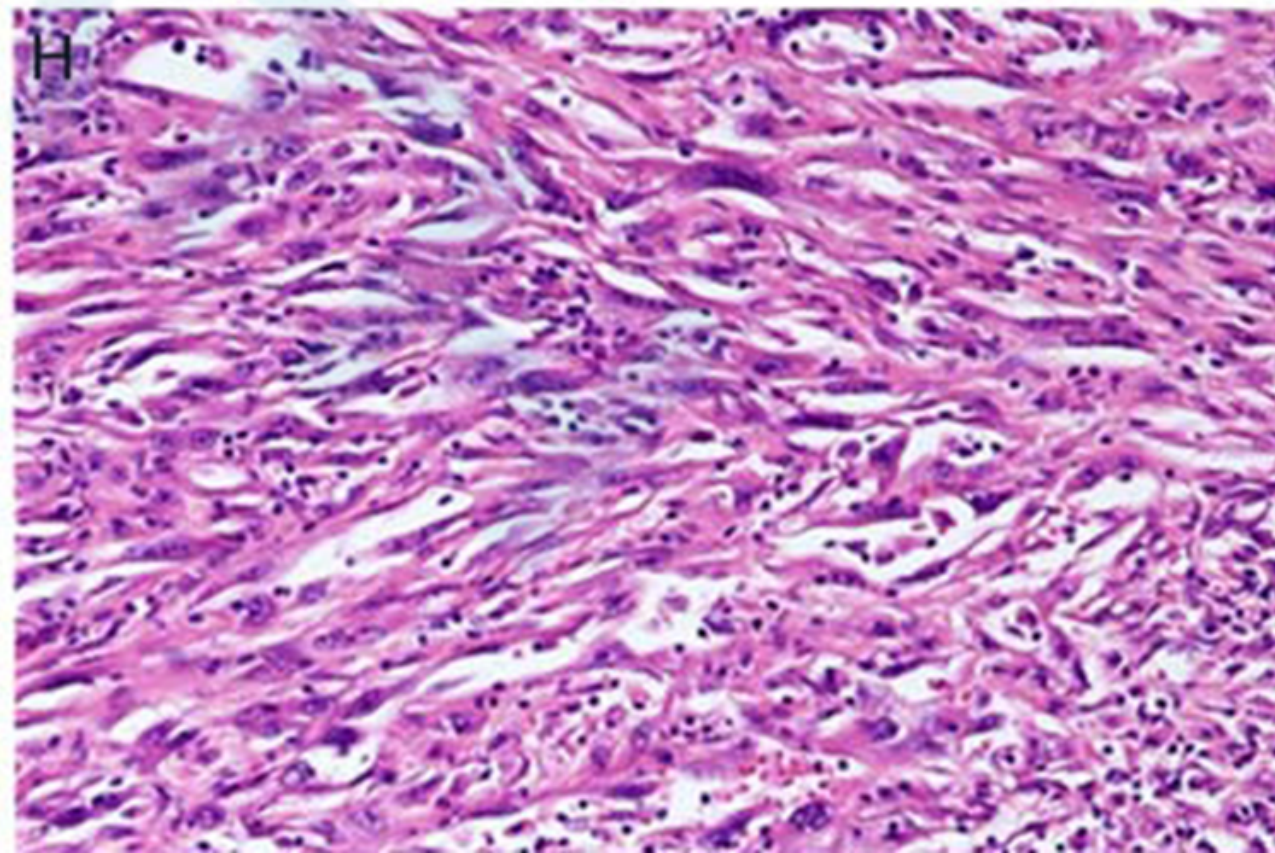
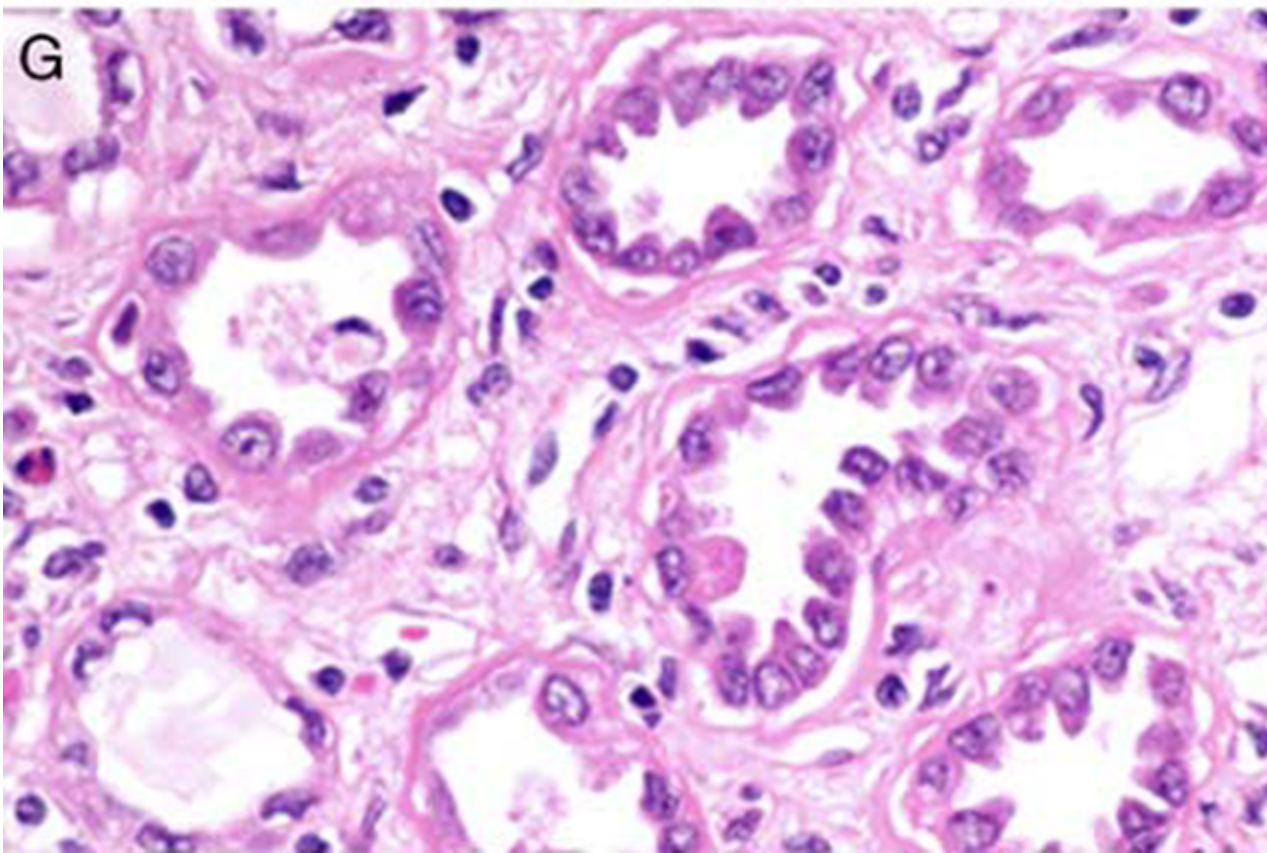
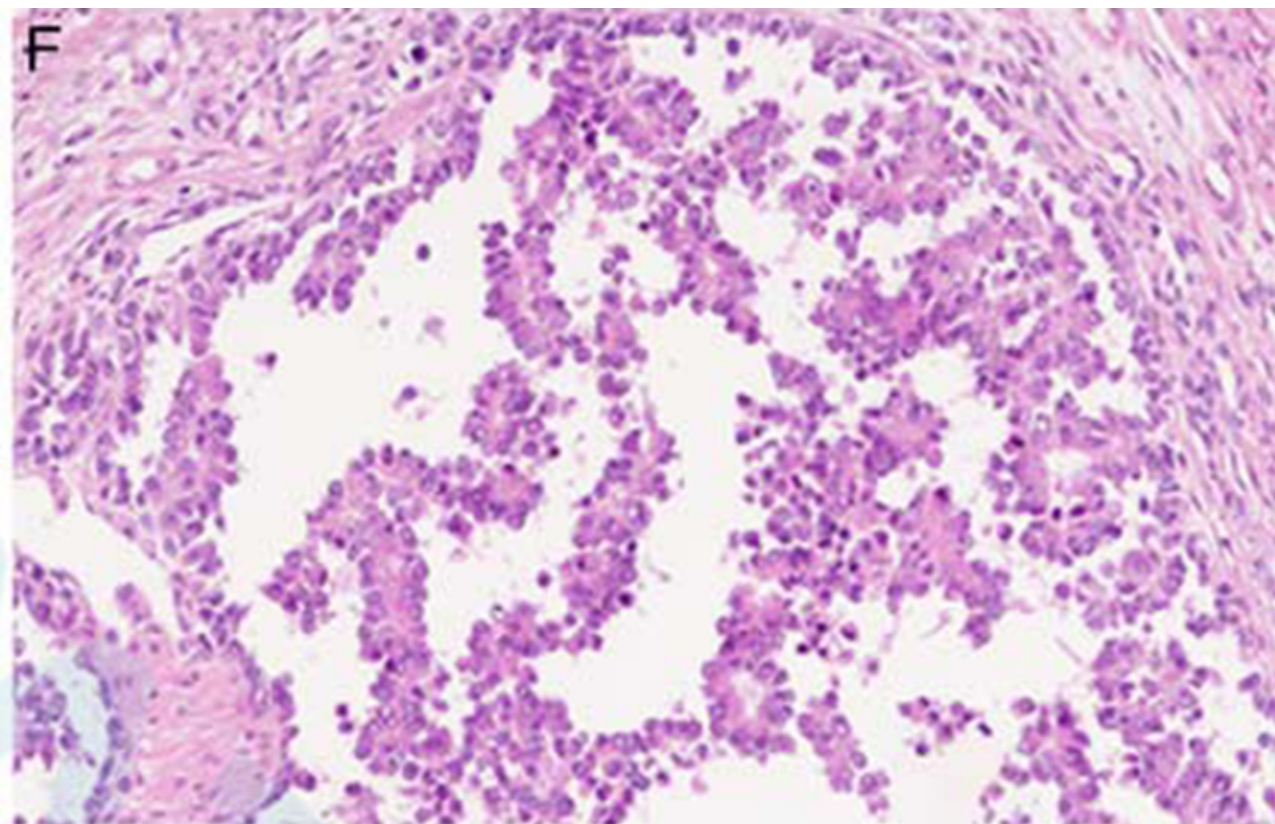
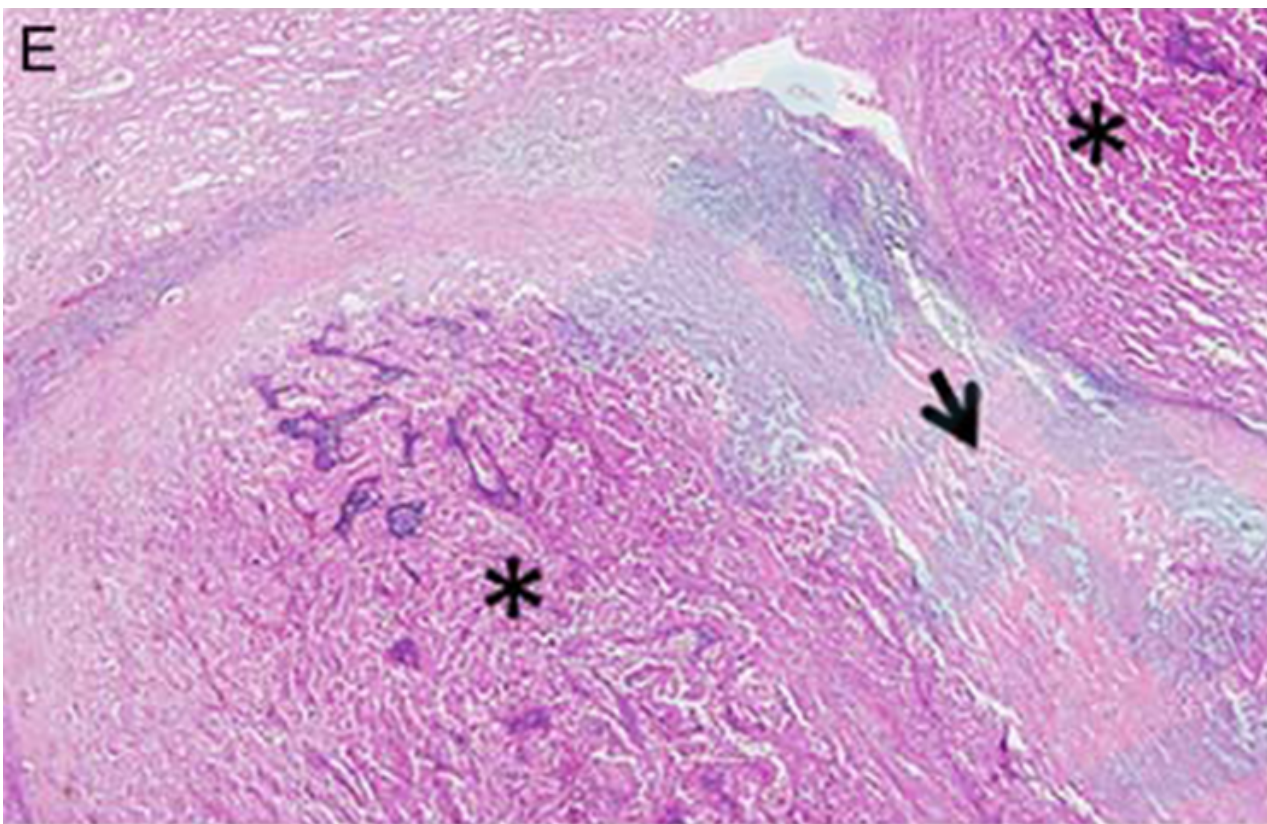
RMC



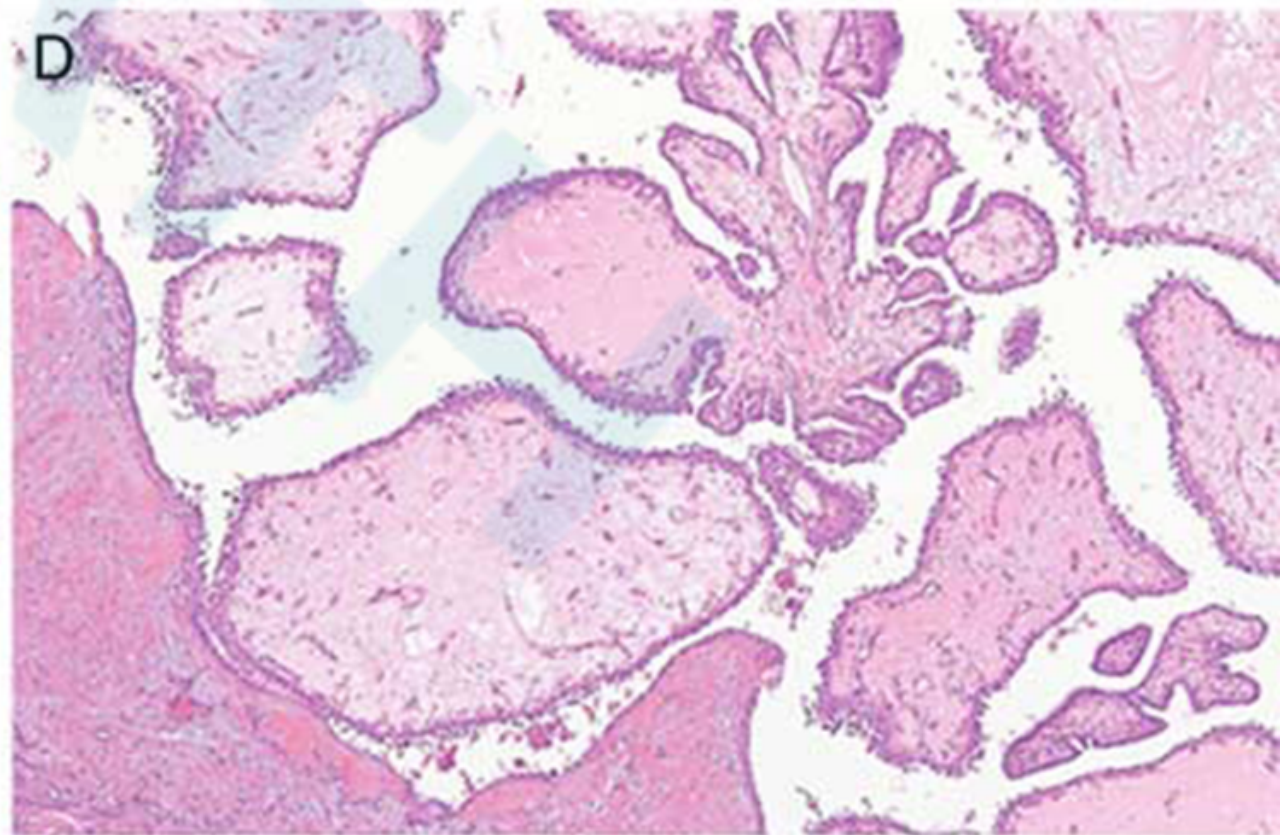
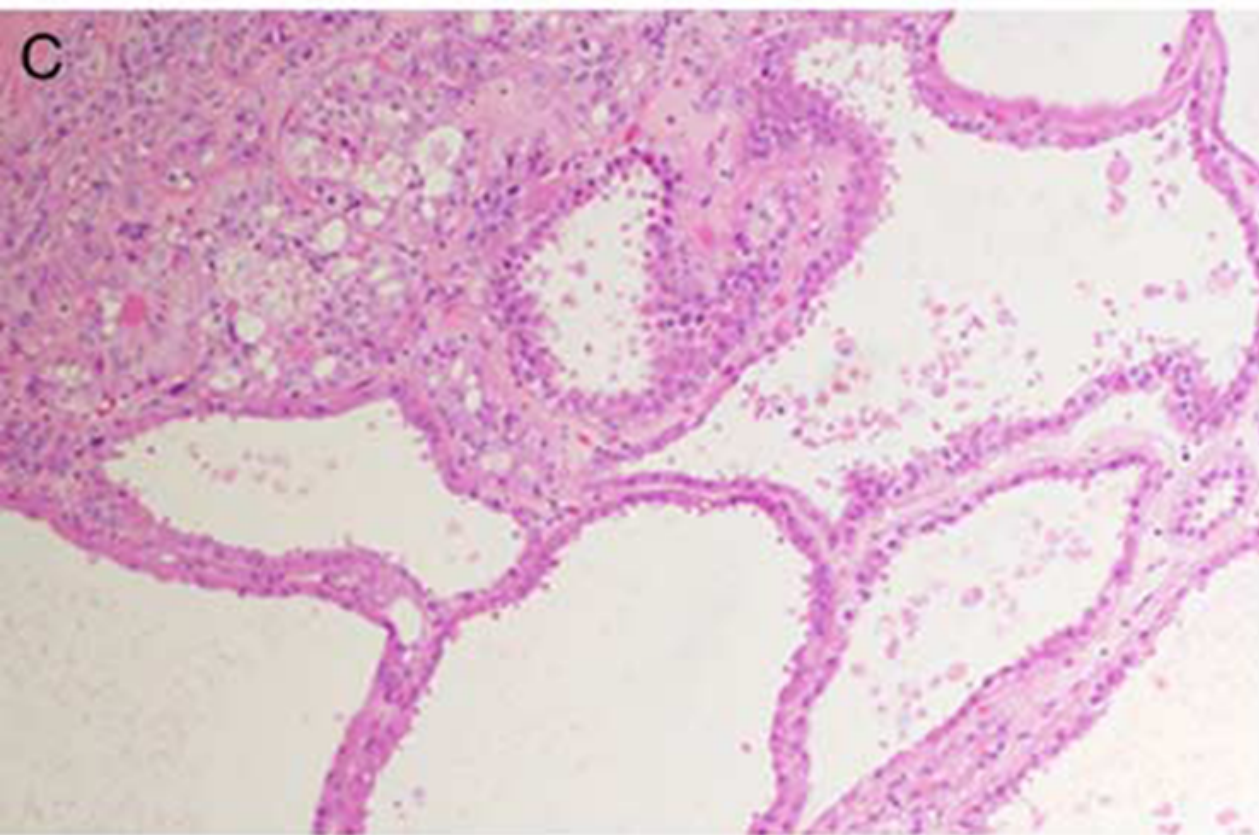
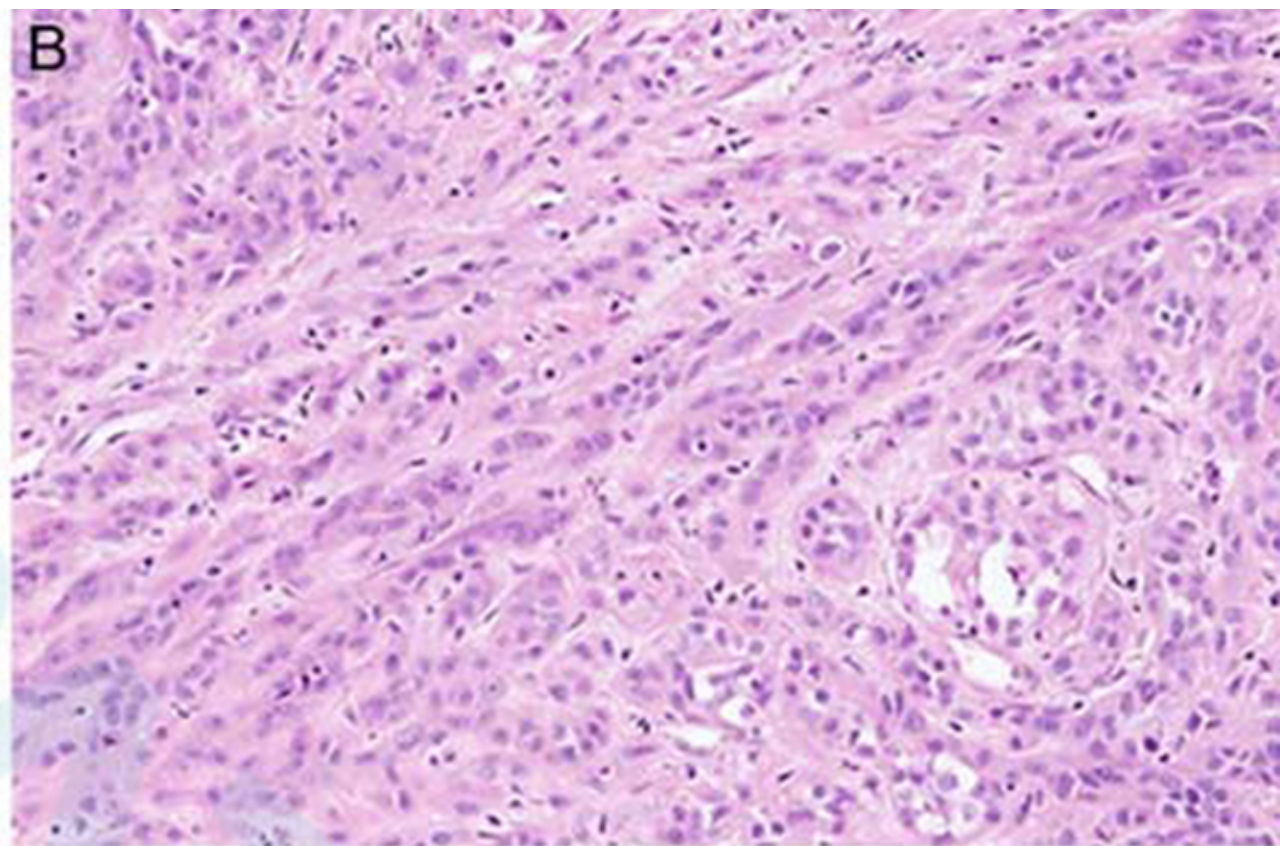
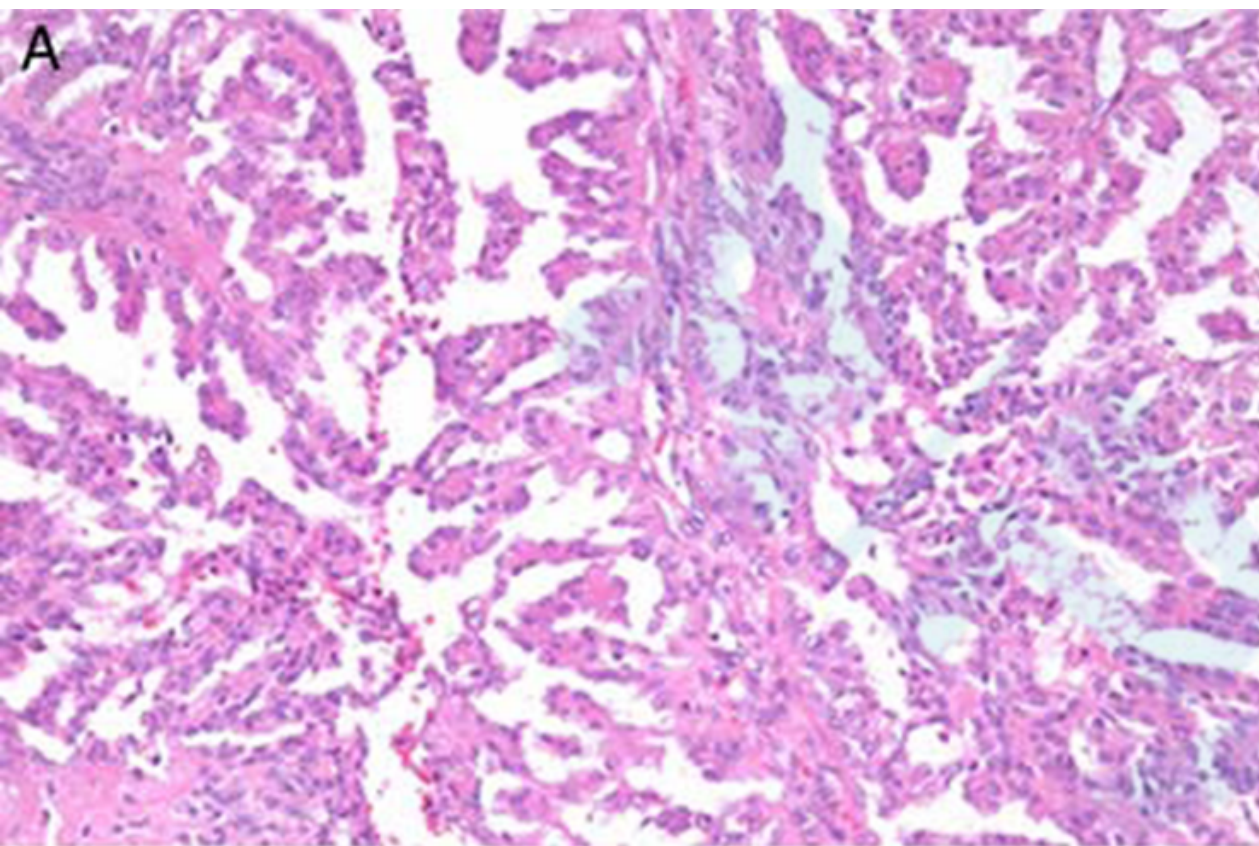
CDC



CDC



FH-deficient RCC



FH-deficient RCC

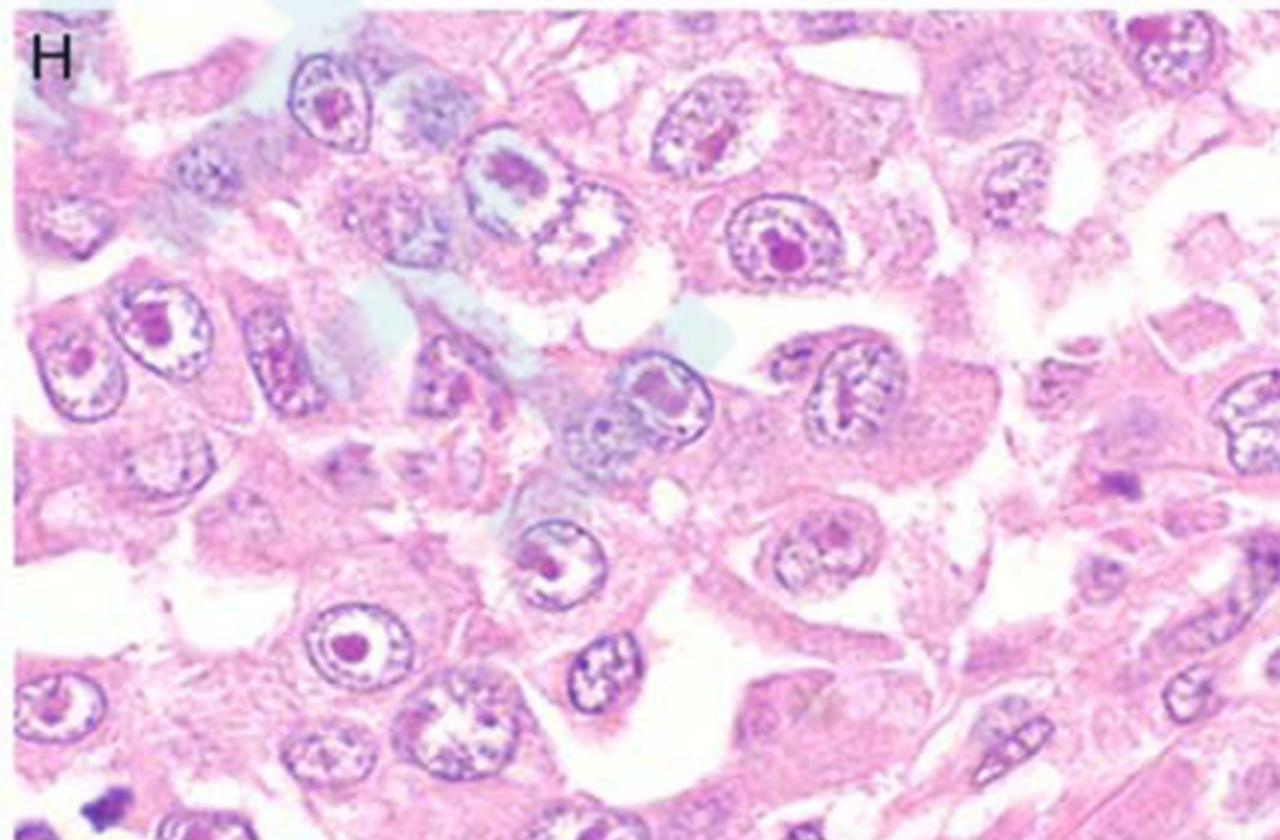
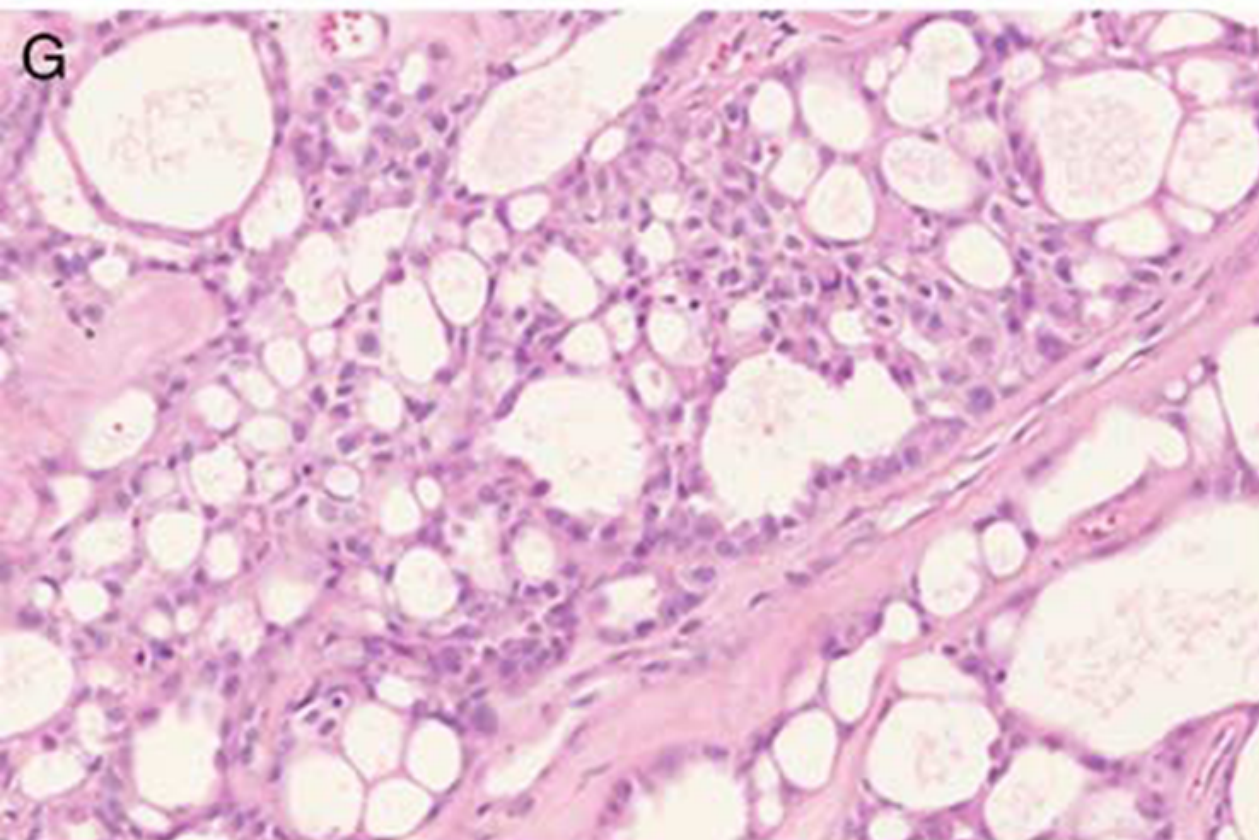
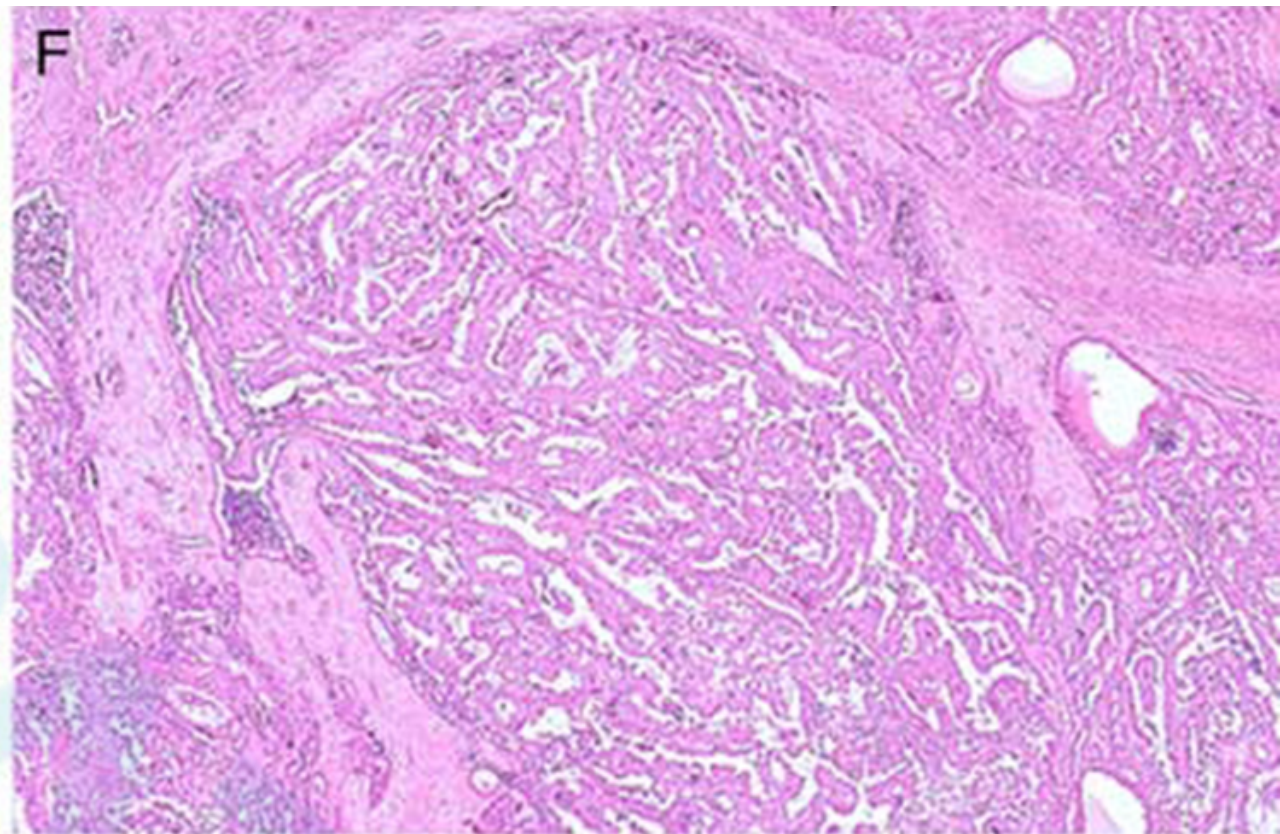
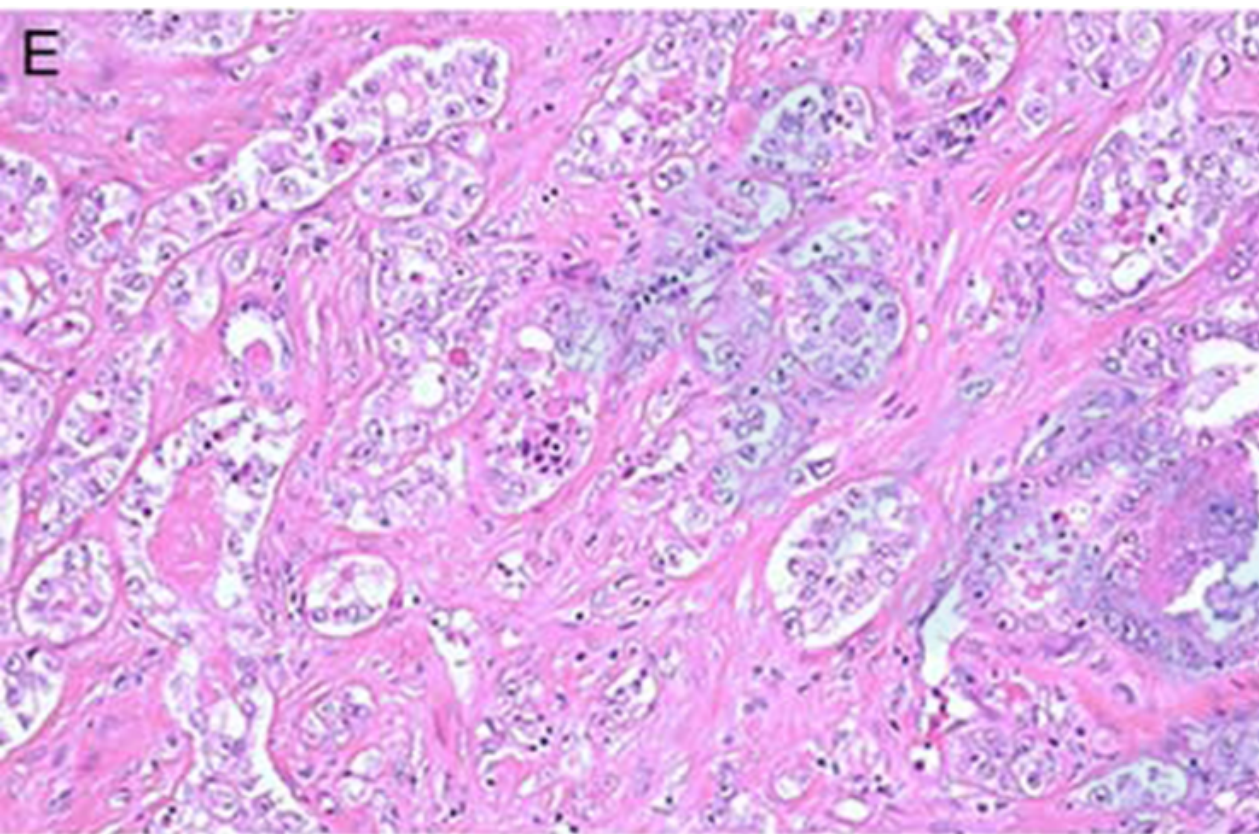
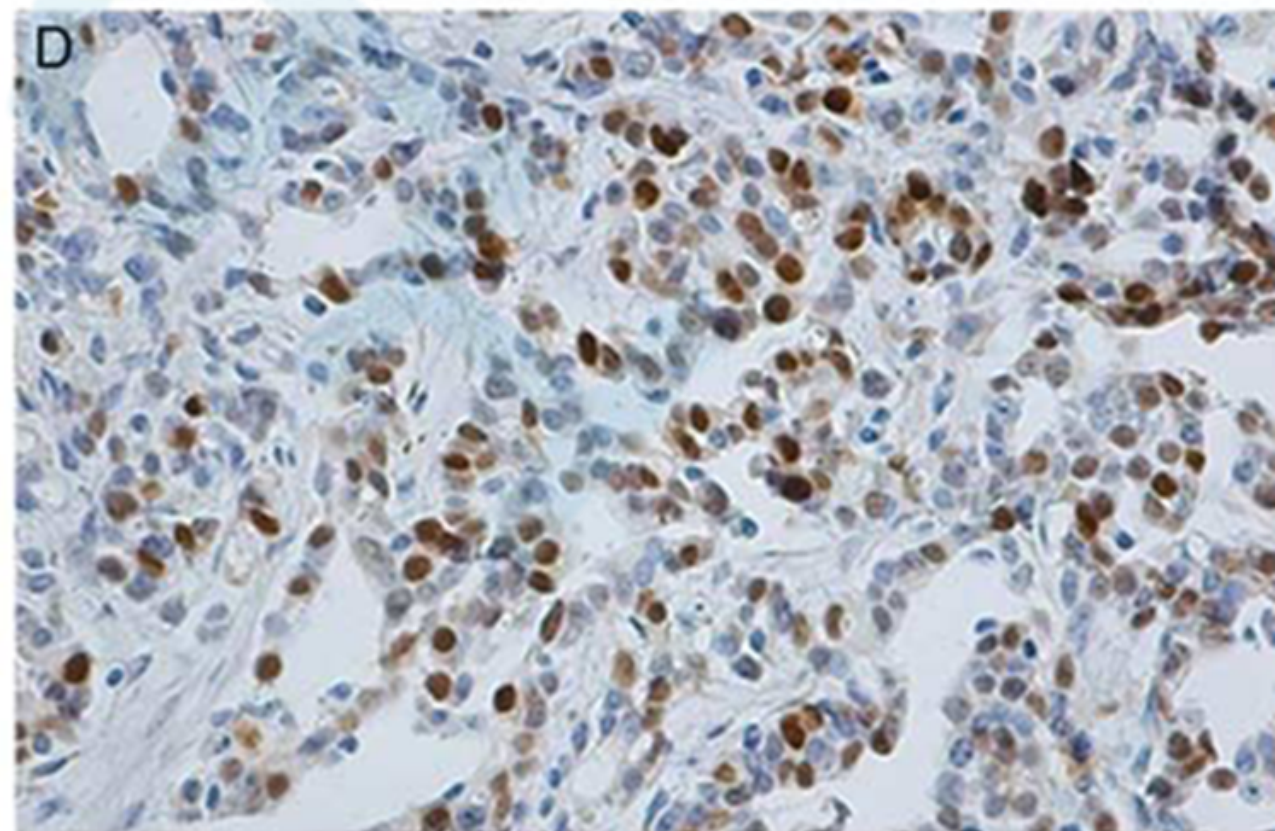
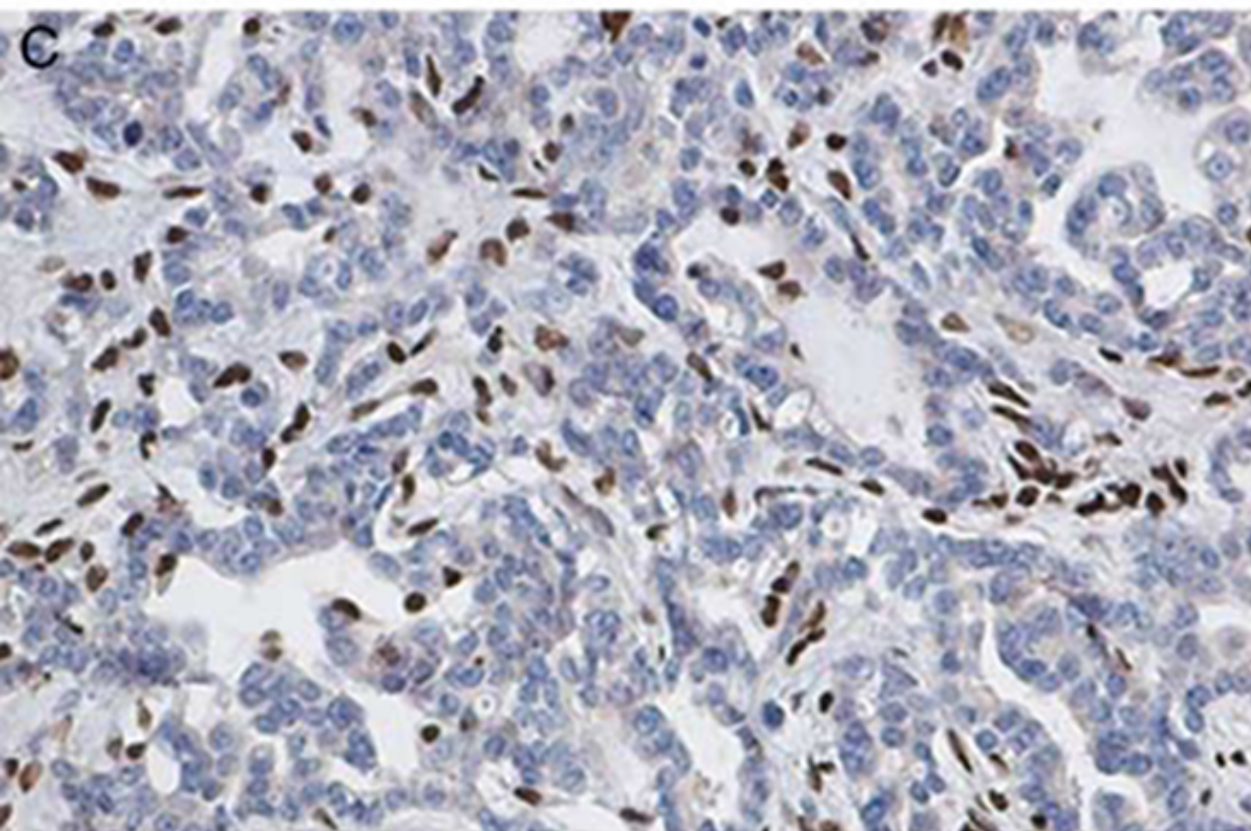
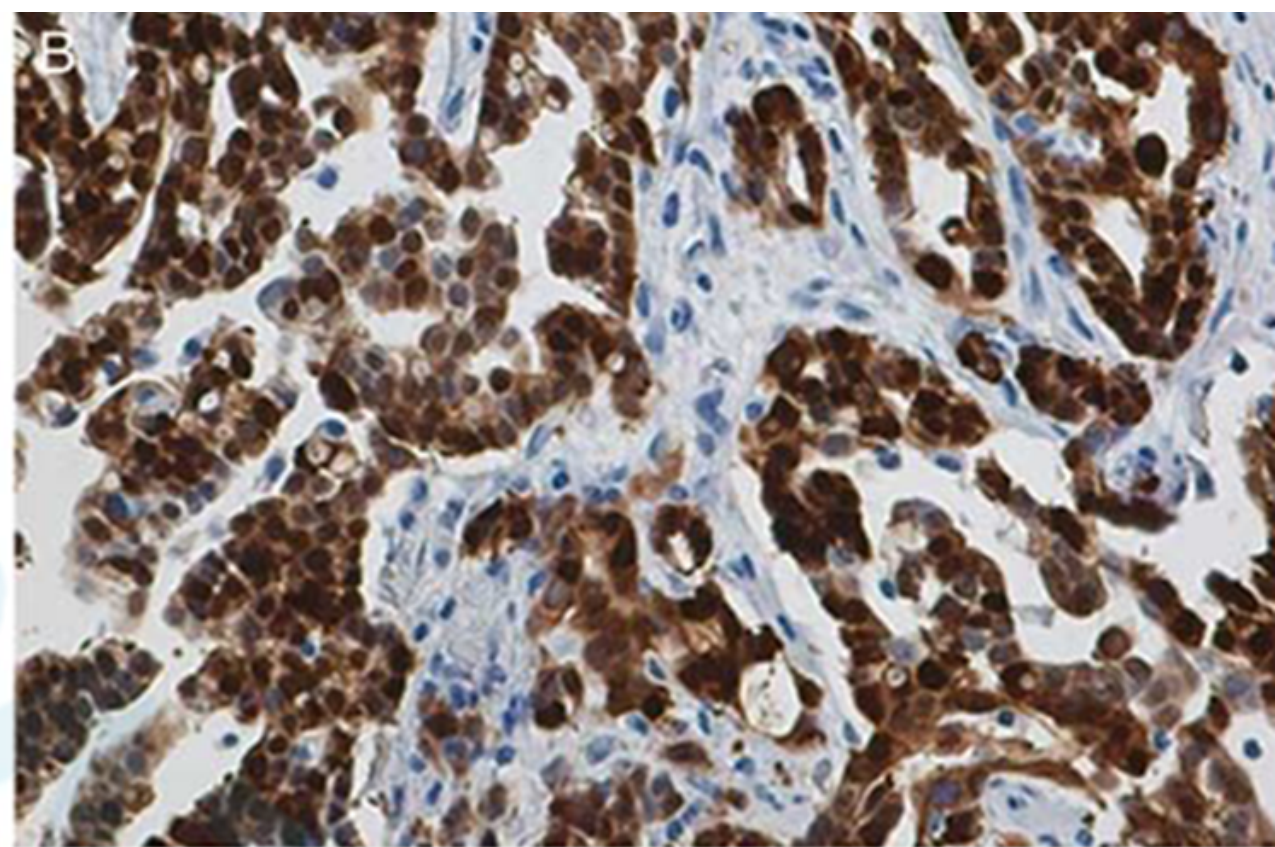
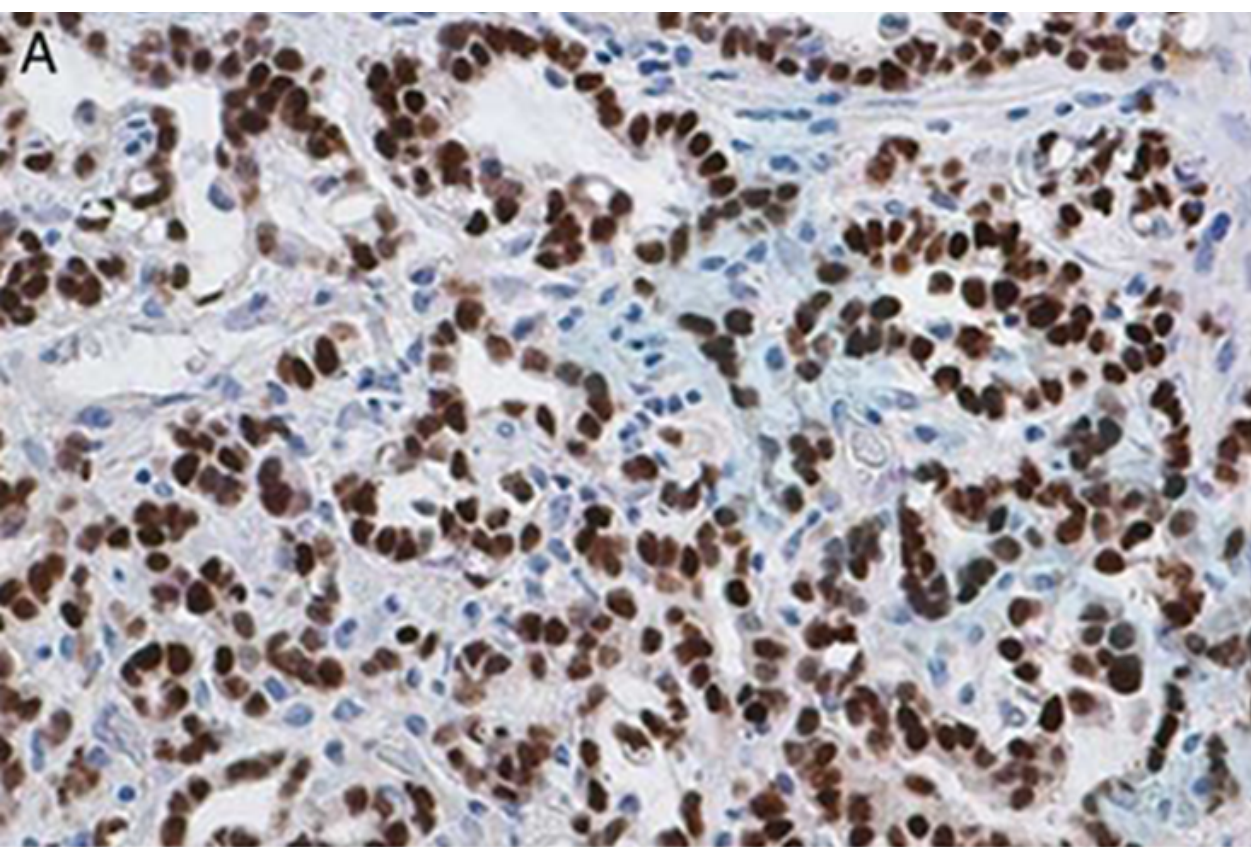


TABLE 3. Immunohistochemistry

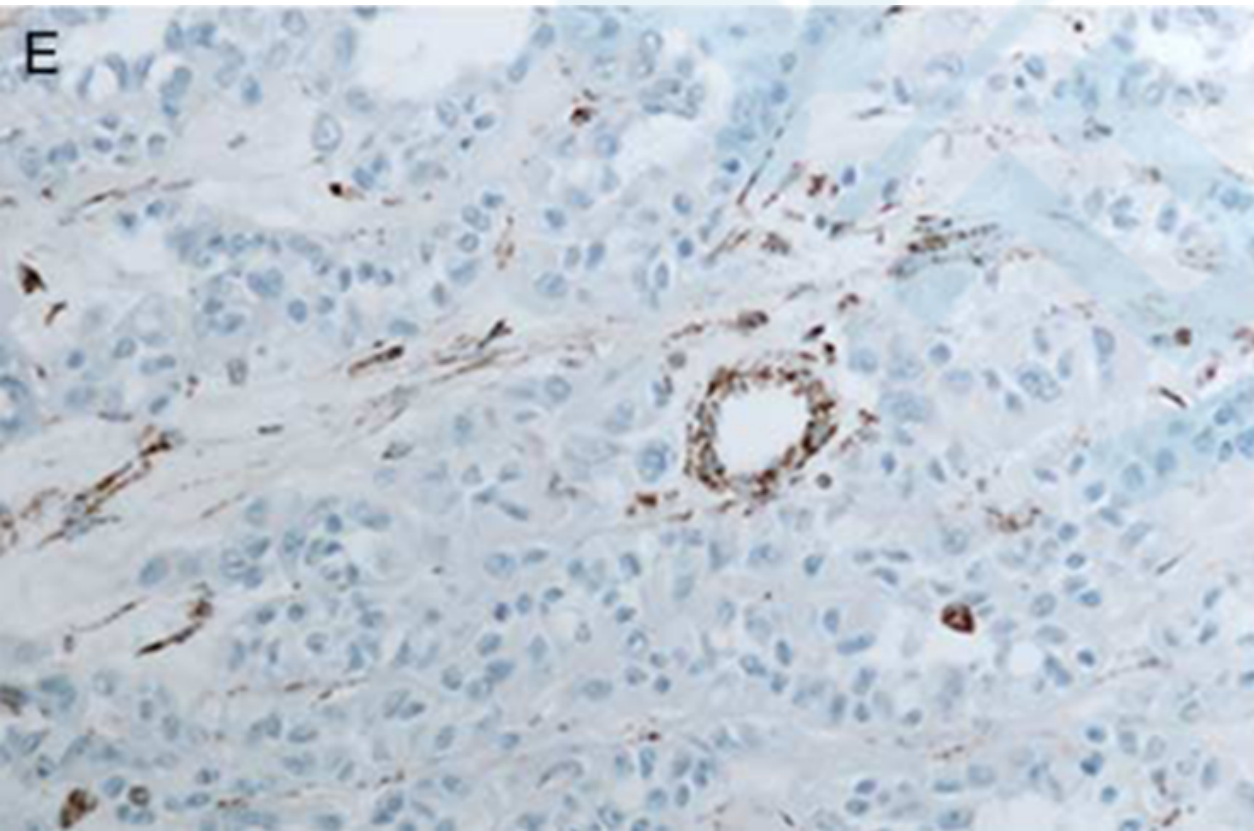
	n/N (%)		
	RMC	CDC	FH-deficient RCC
PAX8 ⁺	32/33 (97)	34/36 (94)	26/27 (97)
S100A1 ⁺	32/33 (97)	34/36 (94)	23/28 (82)
SMARCB1/INI1 (loss)	33/33 (100)	0/37 (0)	0/25 (0)
OCT3/4 ⁺	13/33 (39)*	0/37 (0)	0/26 (0)
FH			
+	32/33 (97)	32/38 (84)	0/29 (0)
+/-	1/33 (3)	6/38 (16)	2/29 (7)
-	0/33 (0)	0/38 (0)	27/29 (93)
2SC			
+	0/1 (0)	0/13 (0)	25/25 (100)
-	1/1 (100)	13/13 (100)	0/25 (0)

*1⁺,15%; 2⁺,18%; 3⁺,6%.

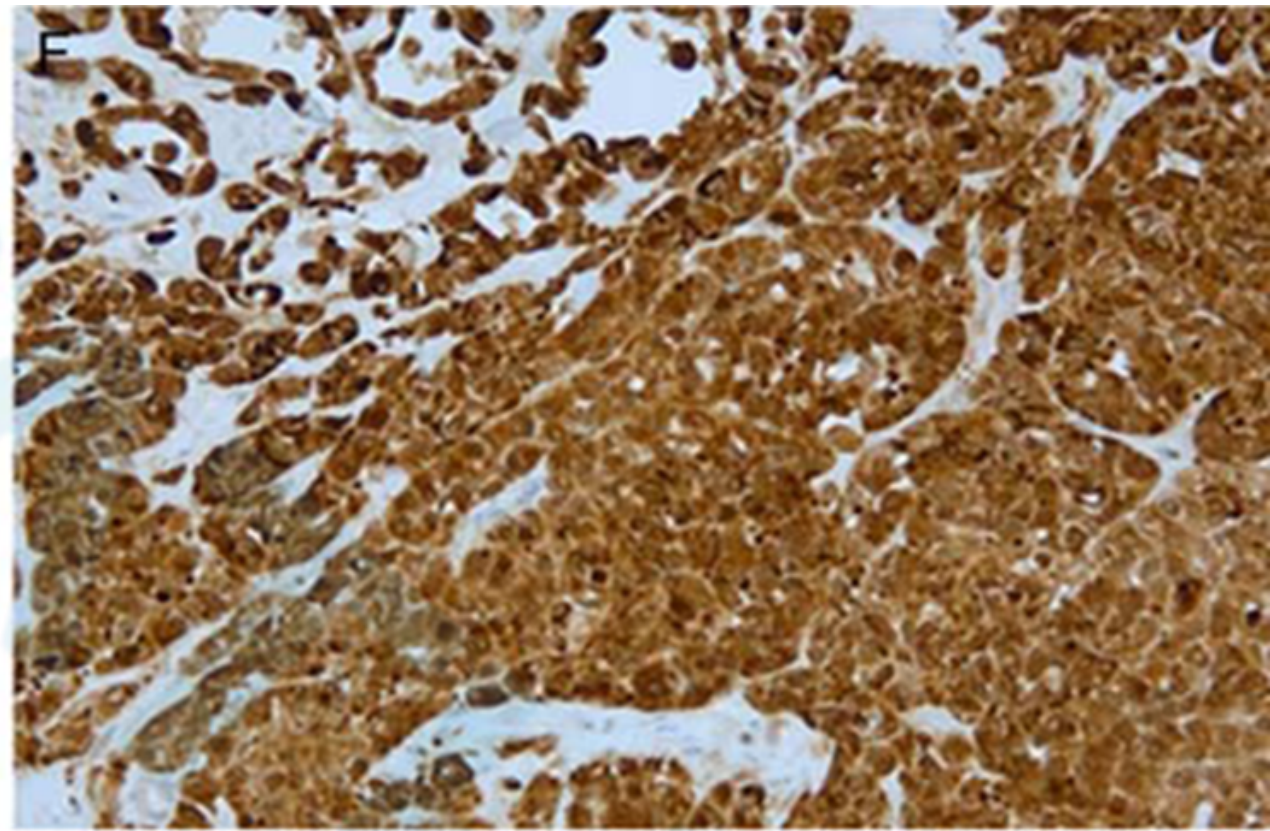
RMC



FH-deficient RCC

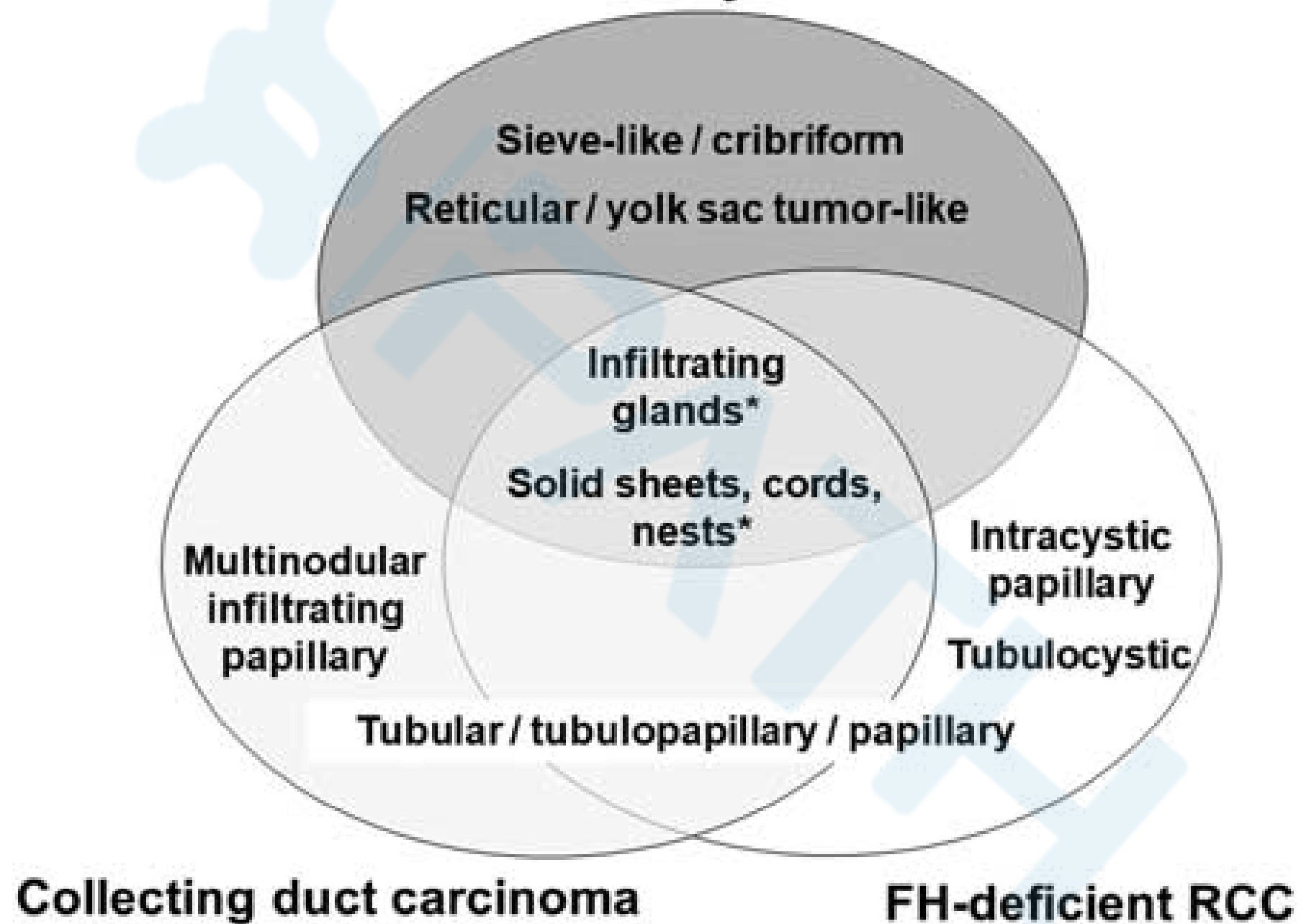


FH



2SC

Renal medullary carcinoma



DISCUSSION

- All subtypes of high-grade distal nephron-related adenocarcinomas may show some nonspecific morphologic features such as infiltrating glandular and solid sheets/cords/nested patterns; therefore, the possibility of urothelial carcinoma of upper urinary tract and metastatic carcinoma should be excluded. To help confirm renal origin , IHC for PAX8 and S100A1 can be useful

- RMC should be diagnosed on the basis of the clinical information (age, race, hemoglobinopathy) and immunohistochemistry (SMARCB1/INI1, OCT3/4), in addition to the sieve like/cribriform and/or reticular/YST-like morphology

- The morphologic patterns of tubulopapillary, intracystic papillary, and tubulocystic carcinoma-like area with viral inclusion–like macronucleoli with perinucleolar halos suggest the possibility of FH-deficient RCC including HLRCC-RCCs. As these features overlap with CDC, IHC combination of FH and 2SC may help in the diagnosis of FH-deficient RCC

- A definitive diagnosis of CDC should only be made if RMC and FH-deficient RCC are excluded

SUMMARY

- Despite the substantial overlap of morphology of tumors within the spectrum of high-grade, infiltrative renal adenocarcinoma, after rigorous histologic evaluation, use of IHC markers, and correlation with clinical findings, reproducible differences in morphology emerge between RMC, CDC, and FH-deficient RCC

谢谢！