LA MORFOLOGIA DE LOS TUMORES RENALES HEREDITARIOS

Maria J Merino MD
National Cancer Institute

Porqué hablamos de tumores en los Sindromes Hereditarios Renales?

- Porque solo la Morphología puede reconocer y diagnosticar estos síndromes.
- Porqué el patólogo guía con su diagnóstico al cirujano y al oncólogo a establecer las terapias que màs benefician al paciente y su familia..
- Porqué el patólogo puede ayudar a salvar vidas cuando los tumores son encontrados en estadio temprano.
- 5%.....seguramente la incidencia sera mas alta.

Sindromes Hereditarios

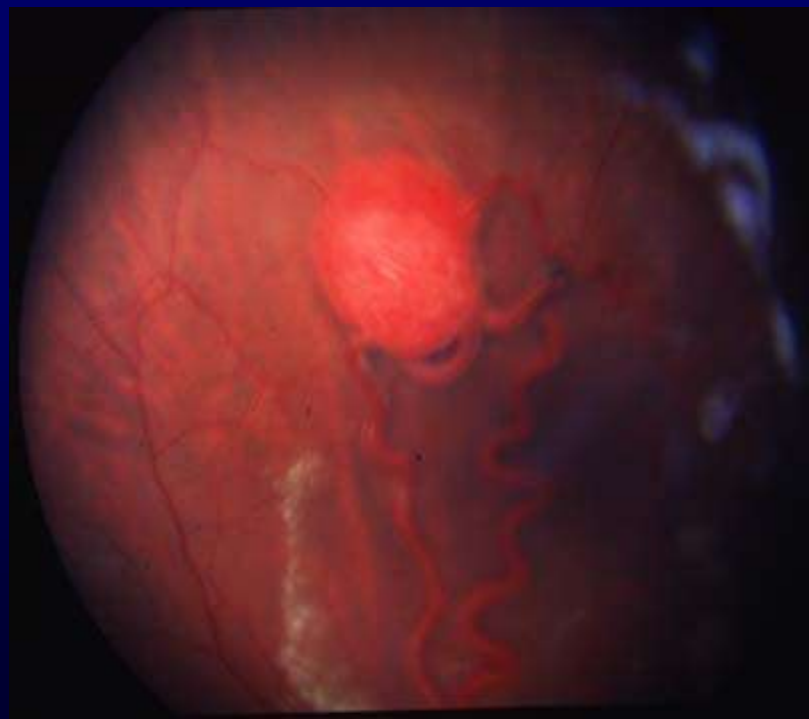
- Von Hippel-Lindau
- EsclerosisTuberosa
- Sindromes asociados a Wilm's

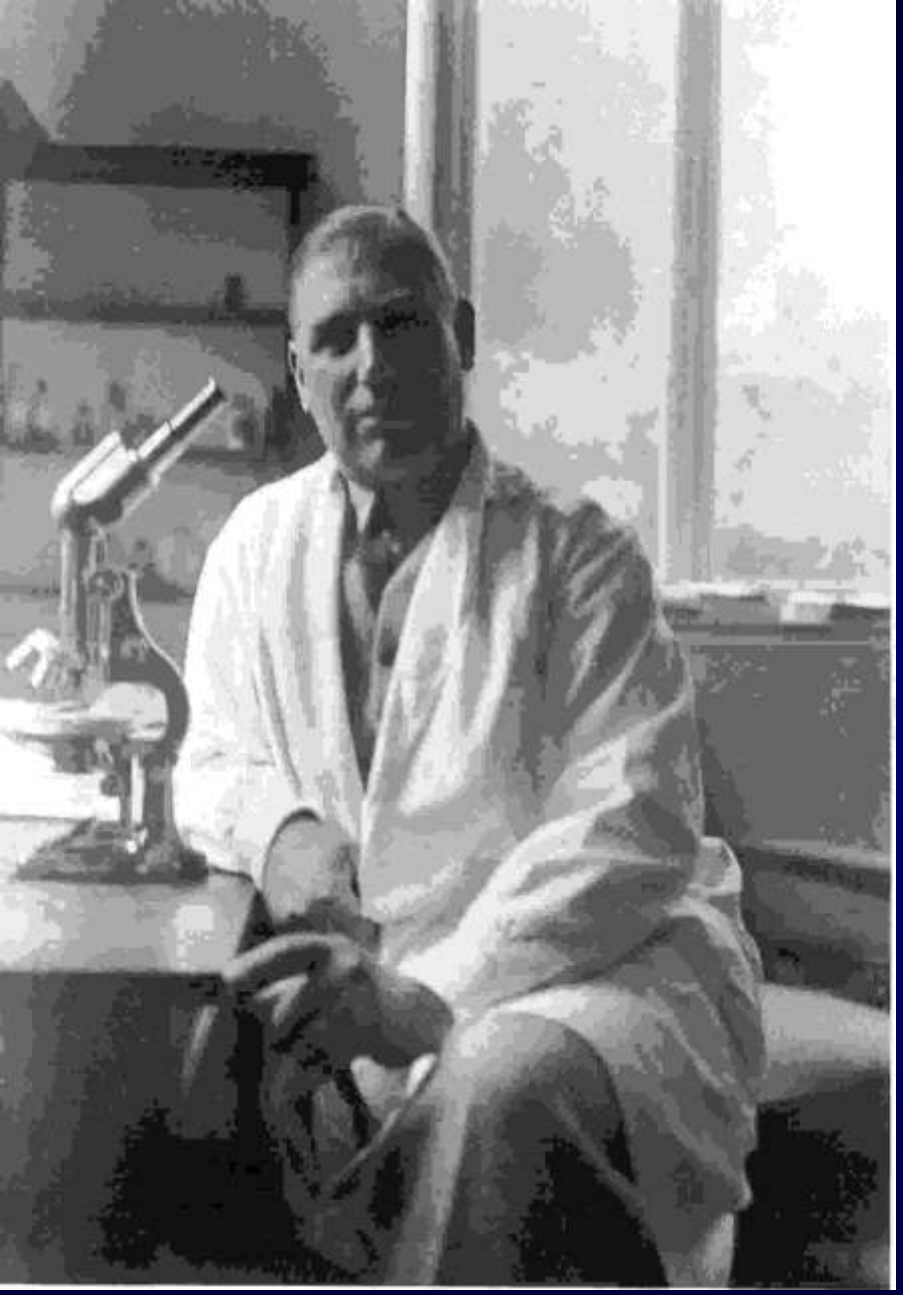
- Von Hippel-Lindau disease
- Papillary tipo I
- Birt-Hubb-Dube
- HLRCC
- Esclerosis Tuberosa
- SDH
- Sindromes asociados con Wilm's

Cancer de riñon es una enfermedad compleja

EUGENE VON HIPPEL

In 1904 VH wrote "about a very rare disease of the retina" and in 1911 added "the anatomical basis" of that disease, which he named angiomatosis retinae. He studied one extended family, with several generations exhibiting numerous lesions typical of those of von Hippel-Lindau Disease (VHL).





ARVID LINDAU

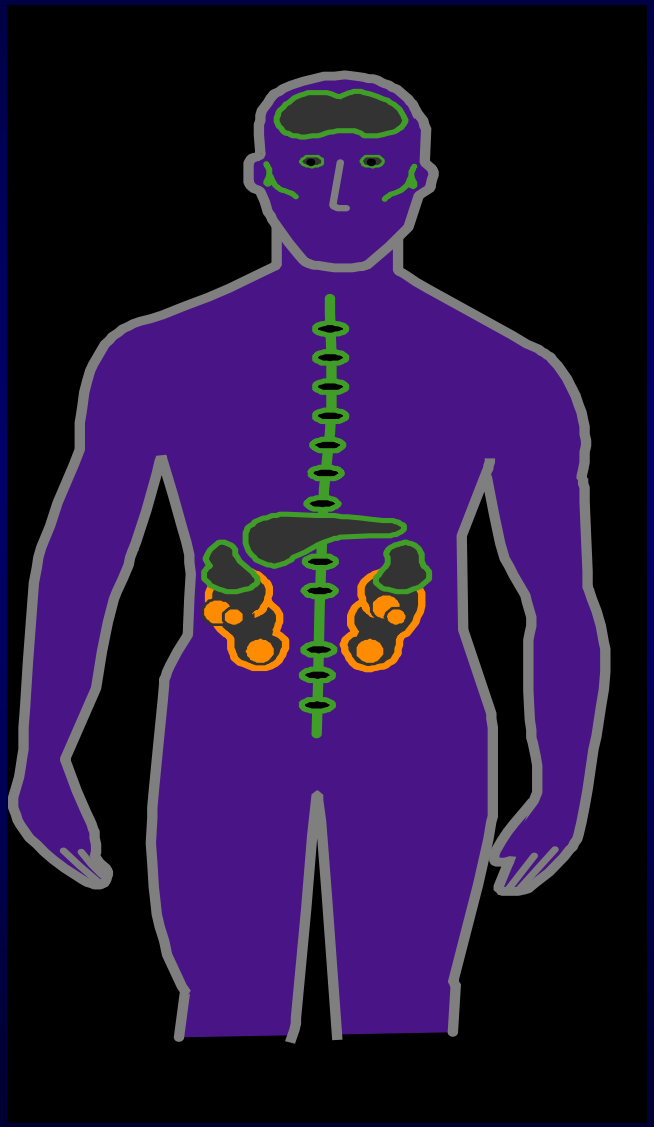
A swedish ophthalmologist credited with the critical observations in 1927 that hemangioblastomas of cerebellum and retina are part of a larger "angiomatous lesion of the central nervous system" and that the condition was inheritable. Although he observed the classic visceral manifestations of renal and pancreatic involvement, Lindau chose to downplay these findings since he thought they were asymptomatic. Subsequent scattered clinical reports of small families confirmed the association of CNS hemangioblastomas and renal and pancreatic cysts, renal cell ca, pheochromocytomas, and epididymal cystadenomas.

In 1964 Melmon and Rosen, described a large VHL family and codified the term "von Hippel-Lindau“.

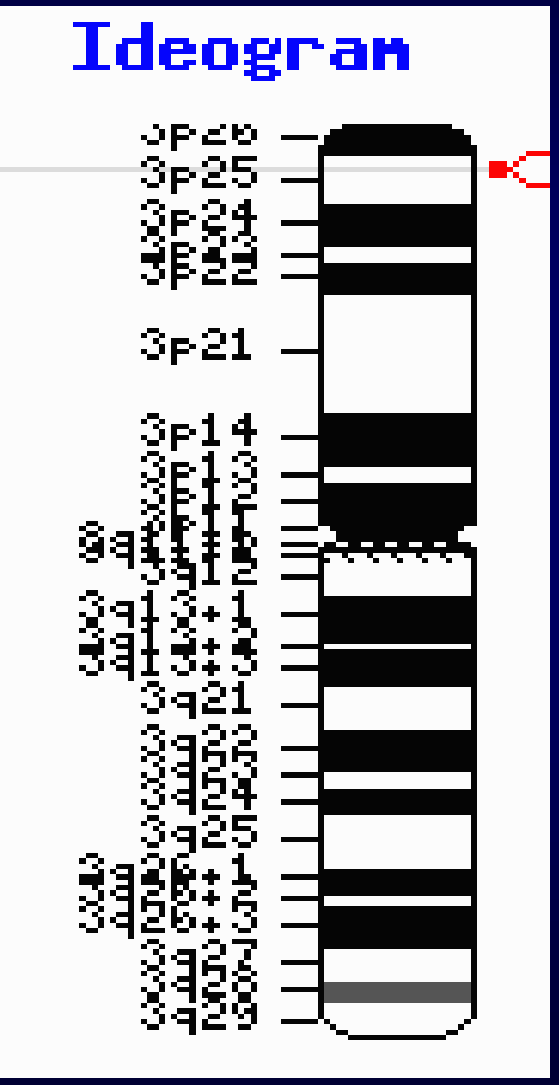
VHL Manifestaciones Clínicas

- **Autosómica dominante**
- **Tumores en:**
  - **-Ambos riñones (35-45%)**
  - -Adrenales
  - -Pancreas
  - -Hemangioblastomas
  - -Ojos
  - -Oido Interno

Diagnosis: Dos tumores separados y/o historia familir de VHL. 20% de los pacientes no dan historia.



Gen del VHL

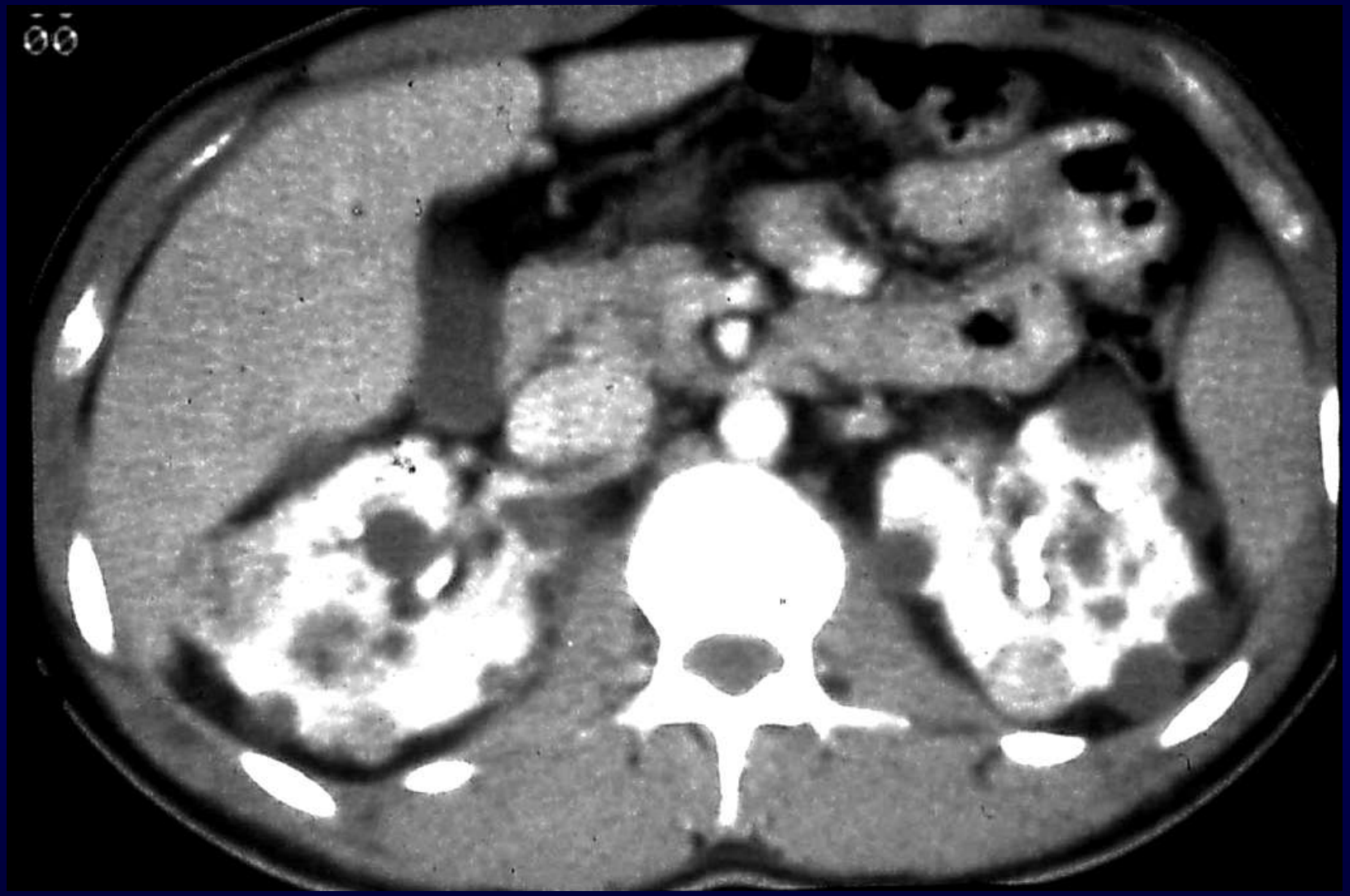


Dos tipos de tumores de células claras

Esporàdico: Tumores solitarios , de alto grado. Alteraciones del gen VHL ocurren entre 60% -80% de los casos.

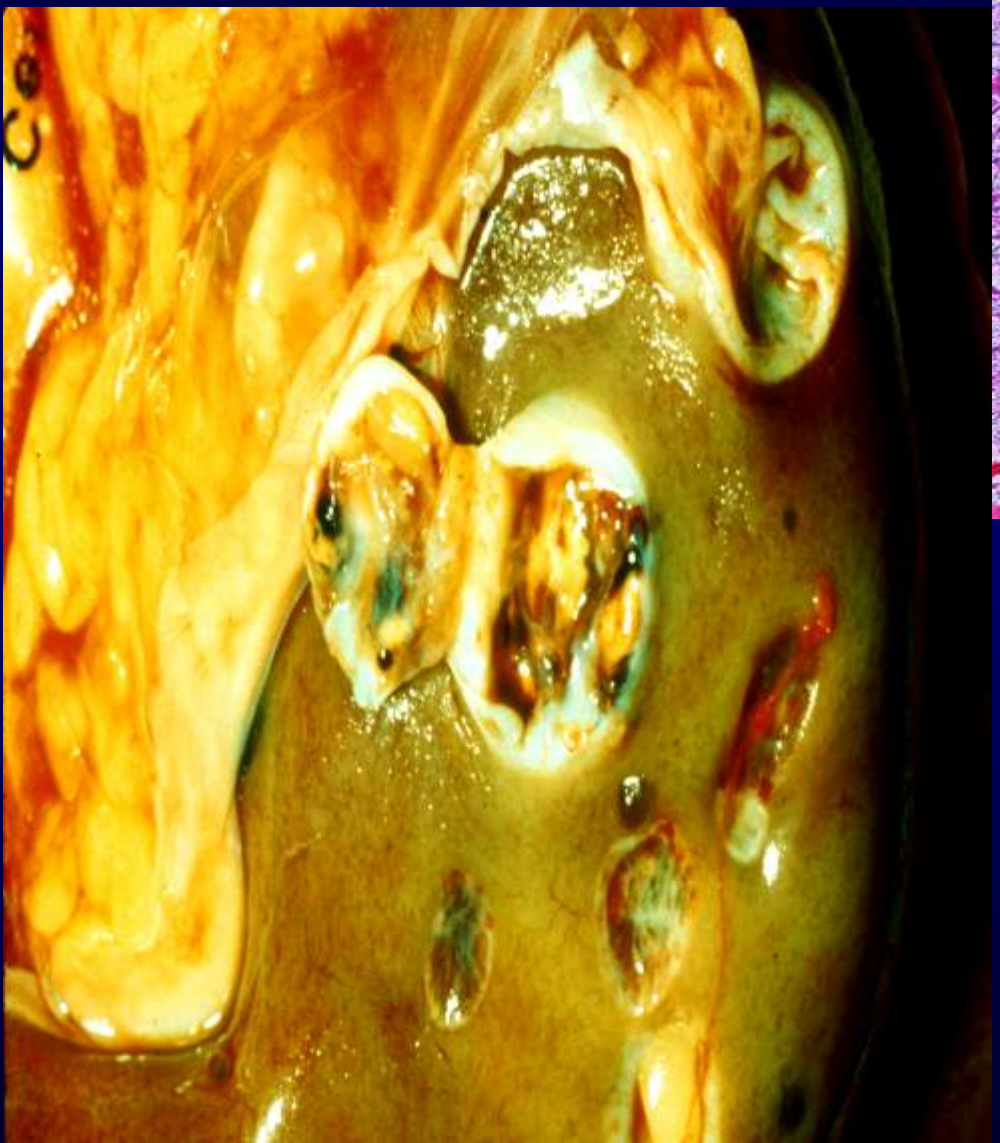
Hereditarios: Multiple y bilaterales, Quistes, bajo grado.
Alteraciones del gen en 100% de los casos.

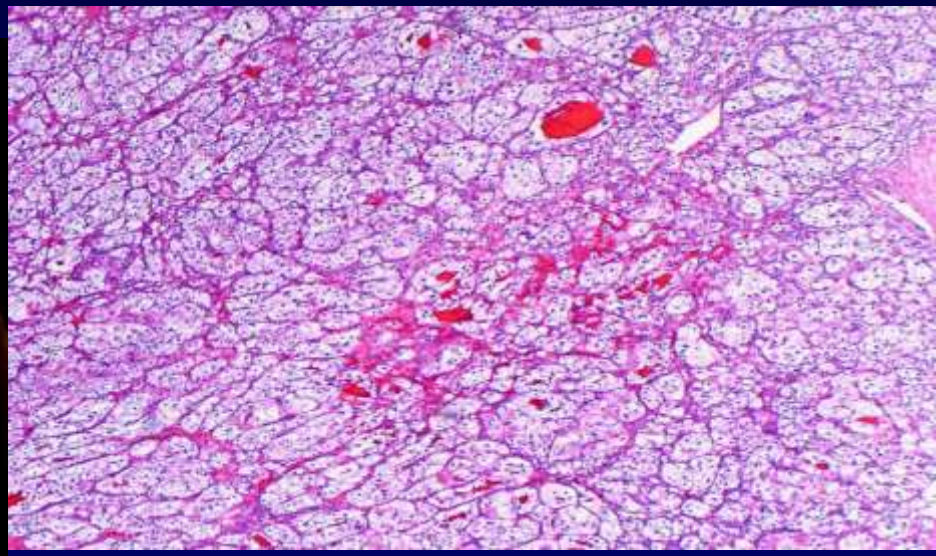
Renal Cell Carcinoma

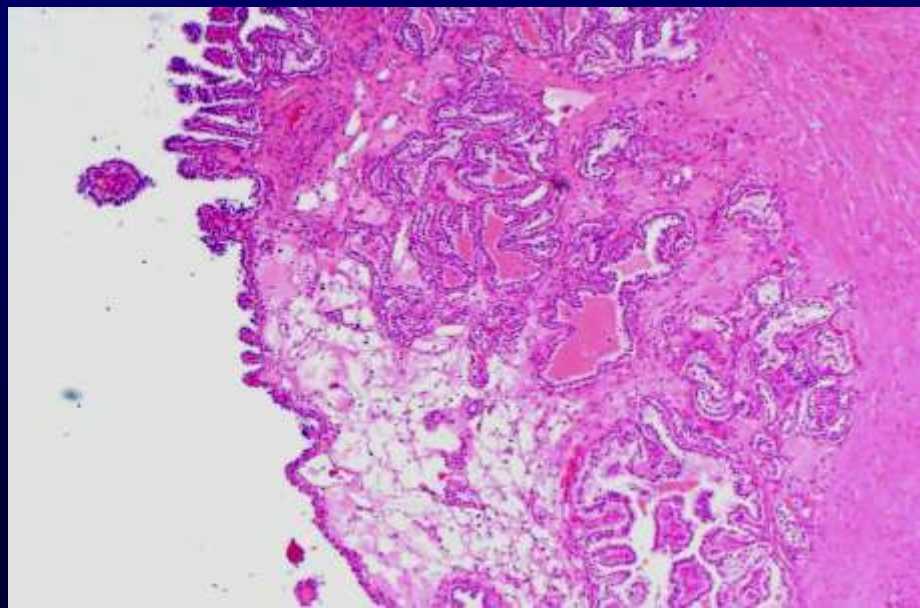


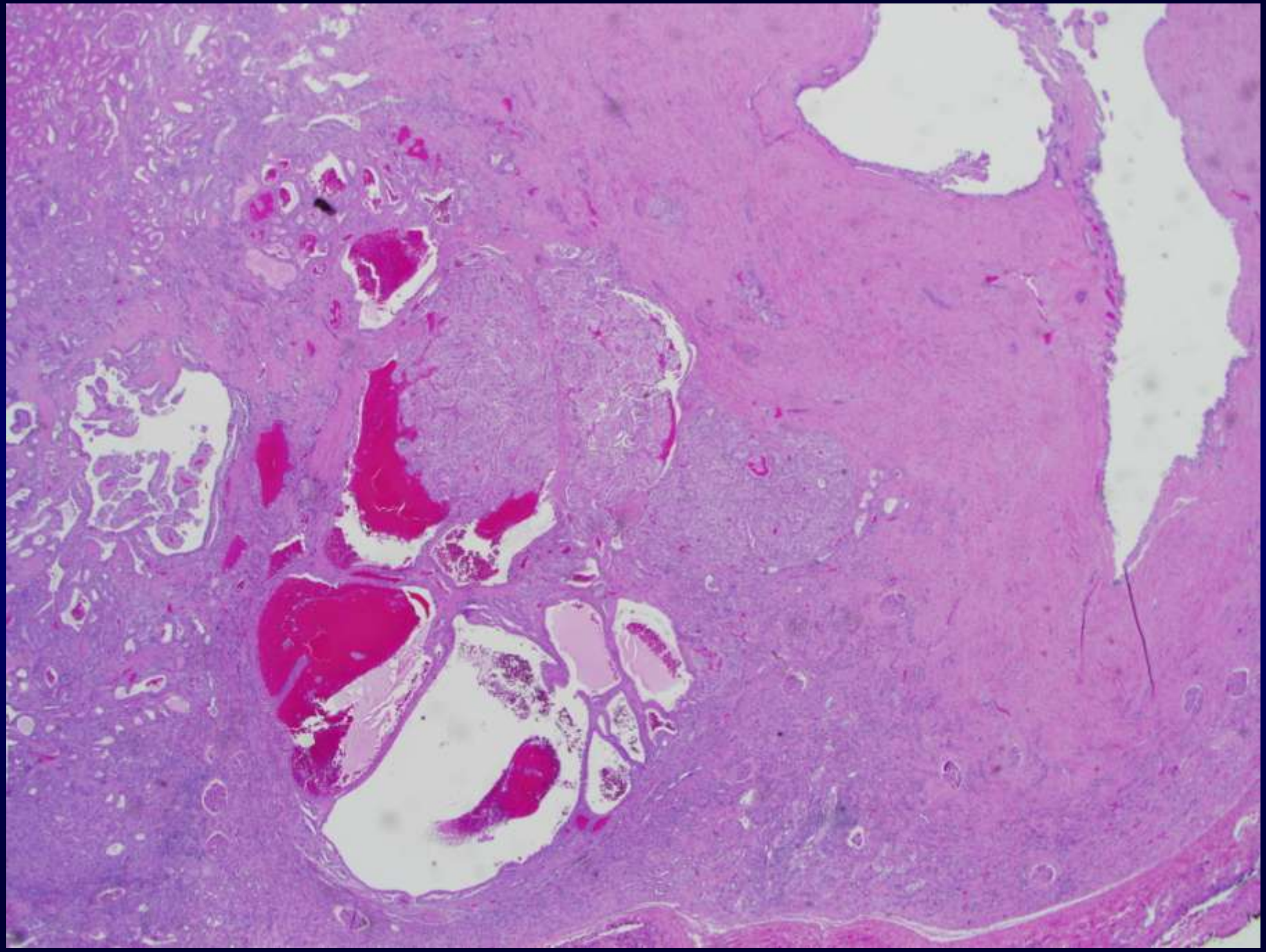
CT Scan: Bilateral, Multifocal lesions

von Hippel-Lindau (VHL)
Lesiones Multiples

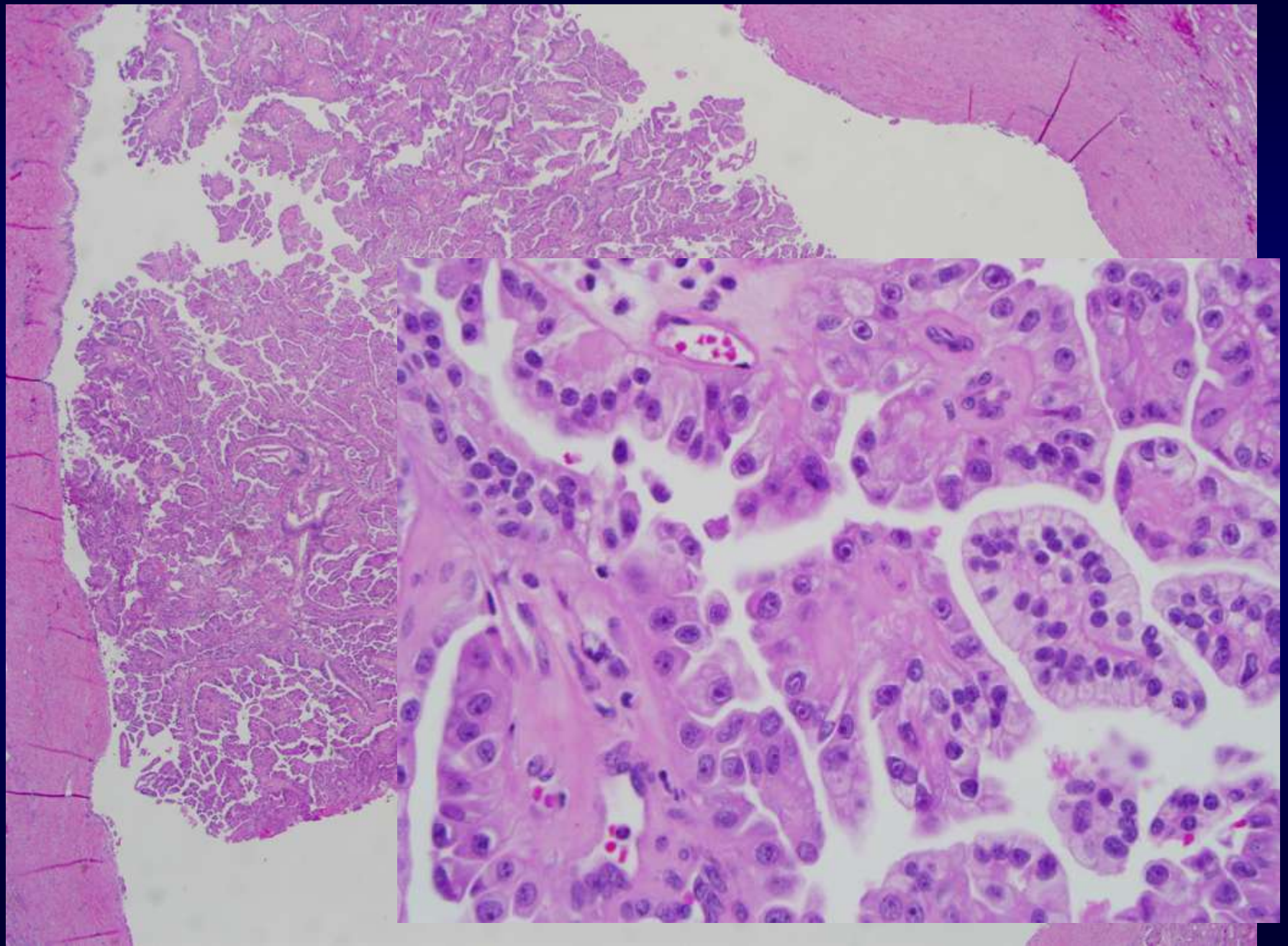








Joven de 17 años, asintomàtica, hija de paciente con HLRCC



Lesiones pulmonares y de pared costal son parte del syndrome de von Hippel Lindau Syndrome y simulan enfermedad metastatica.

- 10 pacientes
- 8 lesiones en pulmon

  Edad 15-67

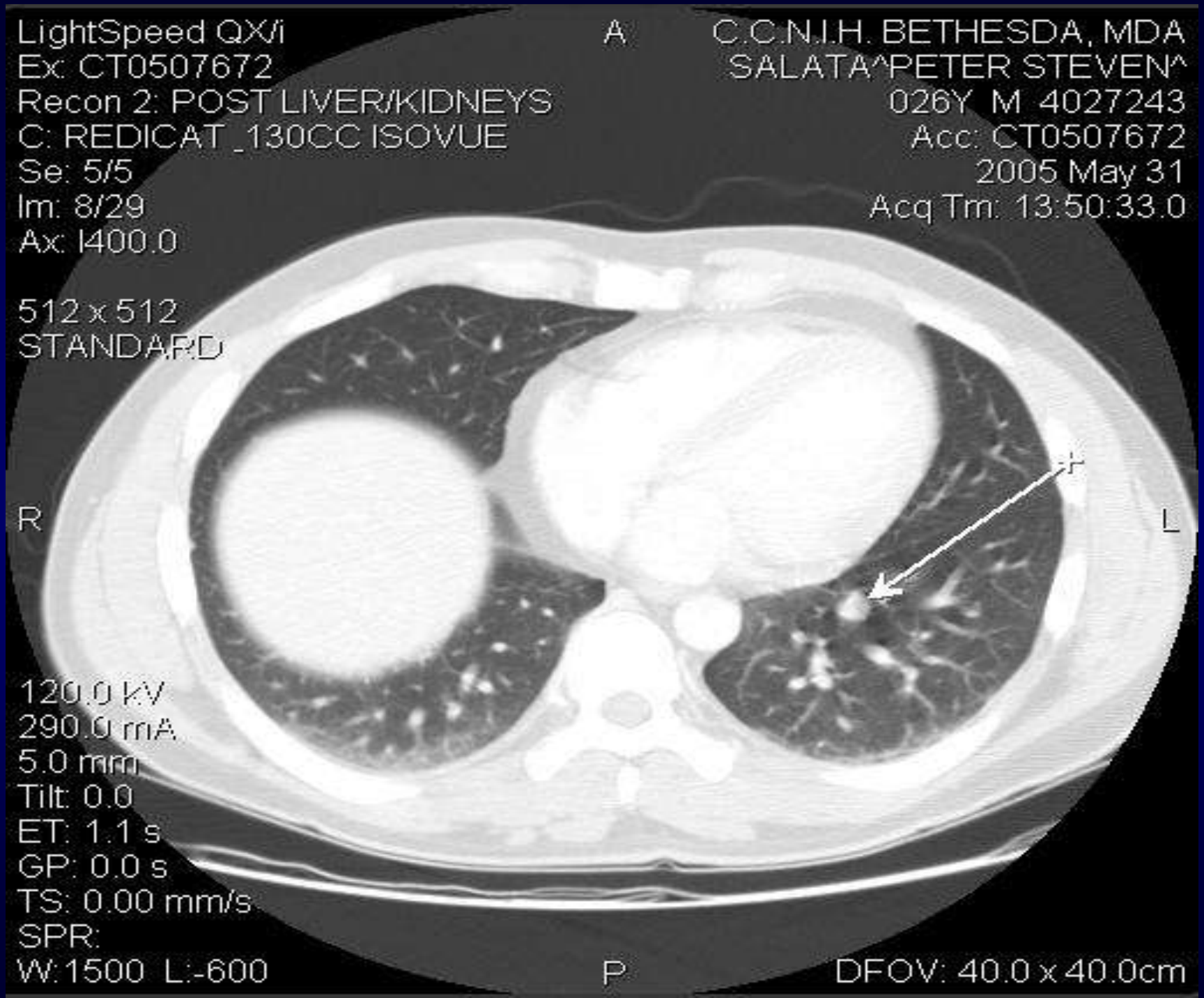
  4 Toracotomia por dx de RCC metastatico

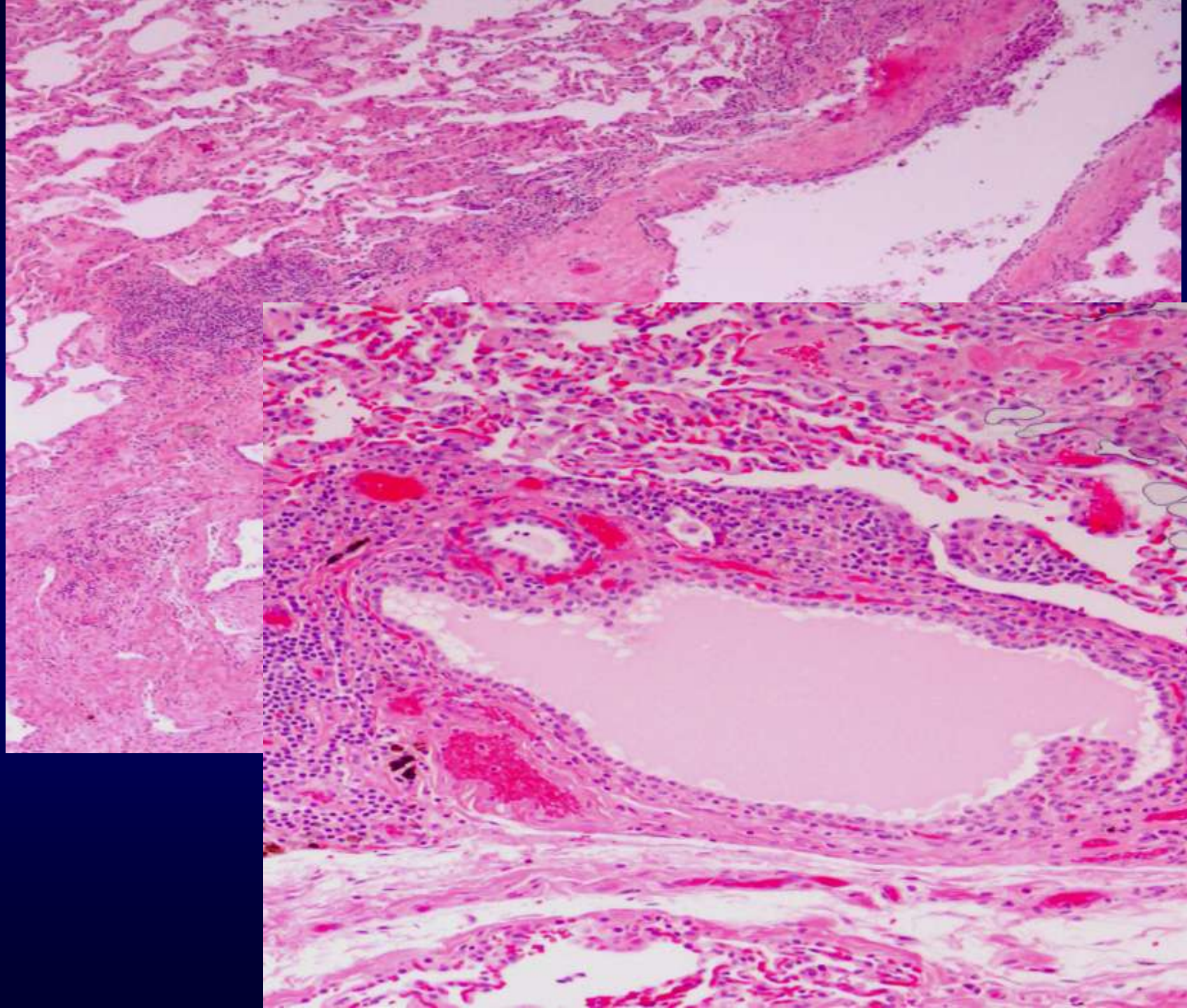
  4 quistes benignos
- 2 tumores en pared costal

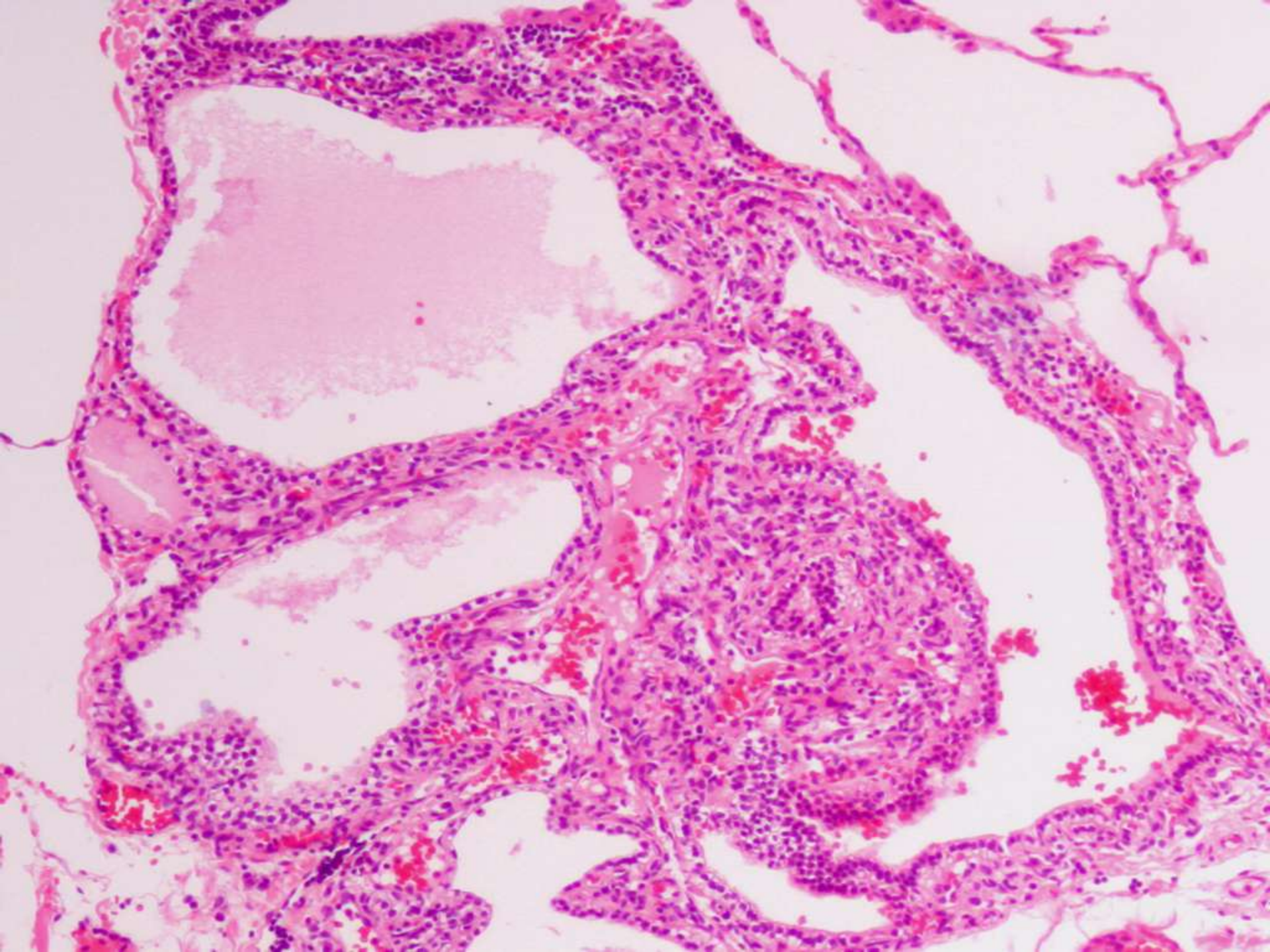
  Edad 56, 49

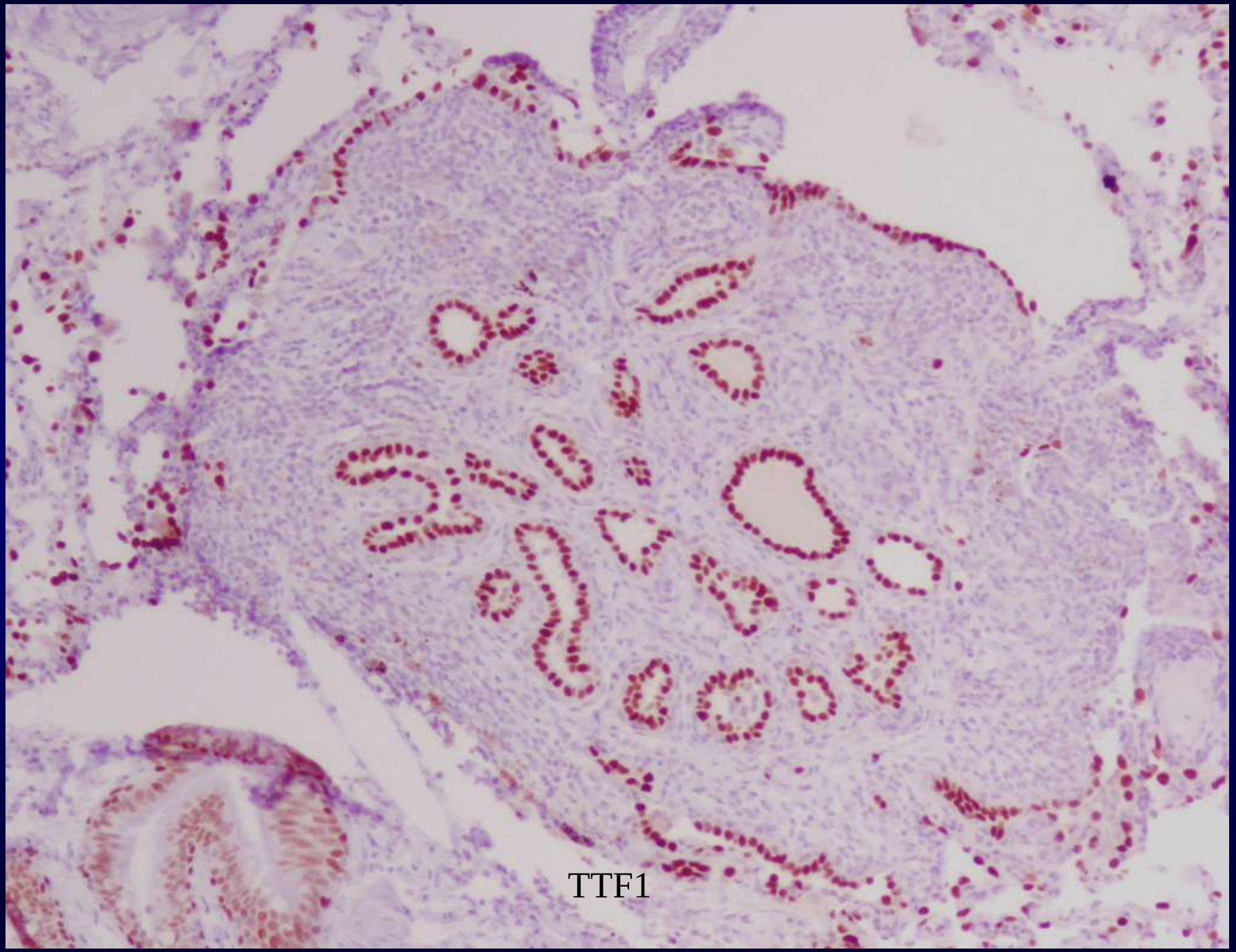
  Pneumonectomia (1) dx of mesotelioma maligno,

  Reseccion de masa (1) dx RCC metastatico

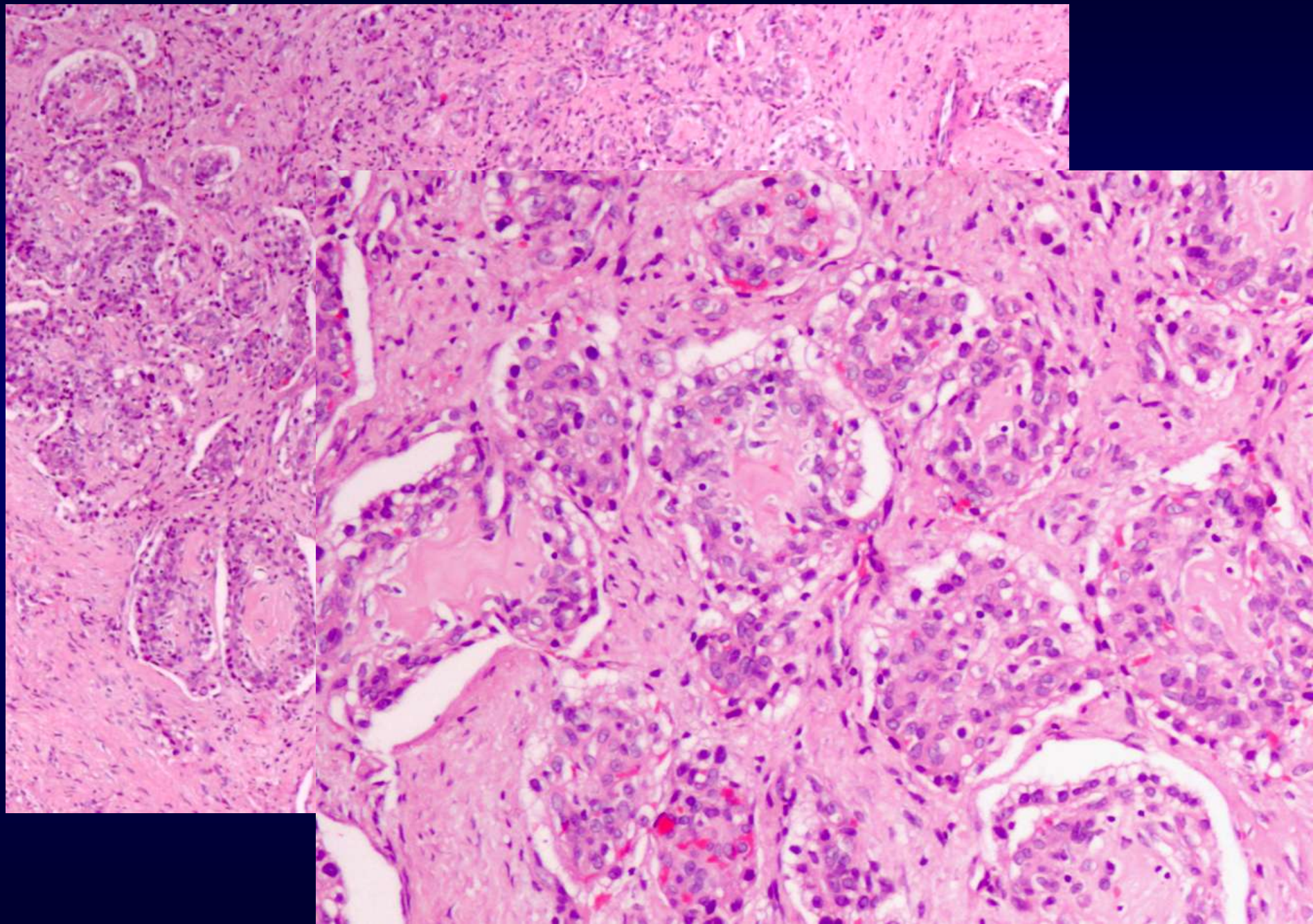

LightSpeed QX/i
Ex: CT0507672
Recon 2: POST LIVER/KIDNEYS
C: REDICAT _130CC ISOVUE
Se: 5/5
Im: 8/29
Ax: I400.0
512 x 512
STANDARD
A
C.C.N.I.H. BETHESDA, MDA
SALATA^PETER STEVEN^
026Y M 4027243
Acc: CT0507672
2005 May 31
Acq Tm: 13:50:33.0
R
L
120.0 kV
290.0 mA
5.0 mm
Tilt: 0.0
ET: 1.1 s
GP: 0.0 s
TS: 0.00 mm/s
SPR:
W:1500 L:-600
P
DFOV: 40.0 x 40.0cm

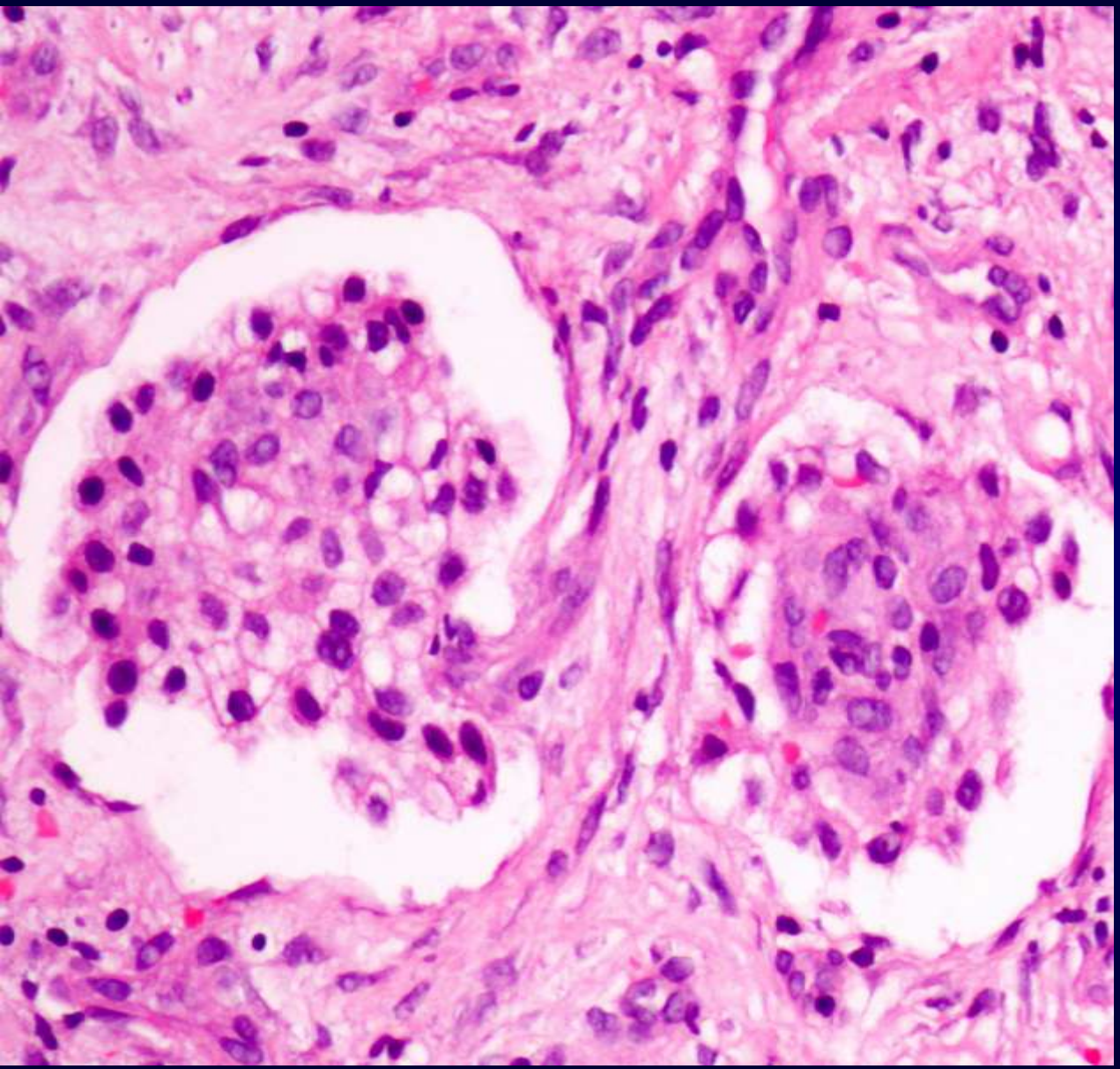





TTF1

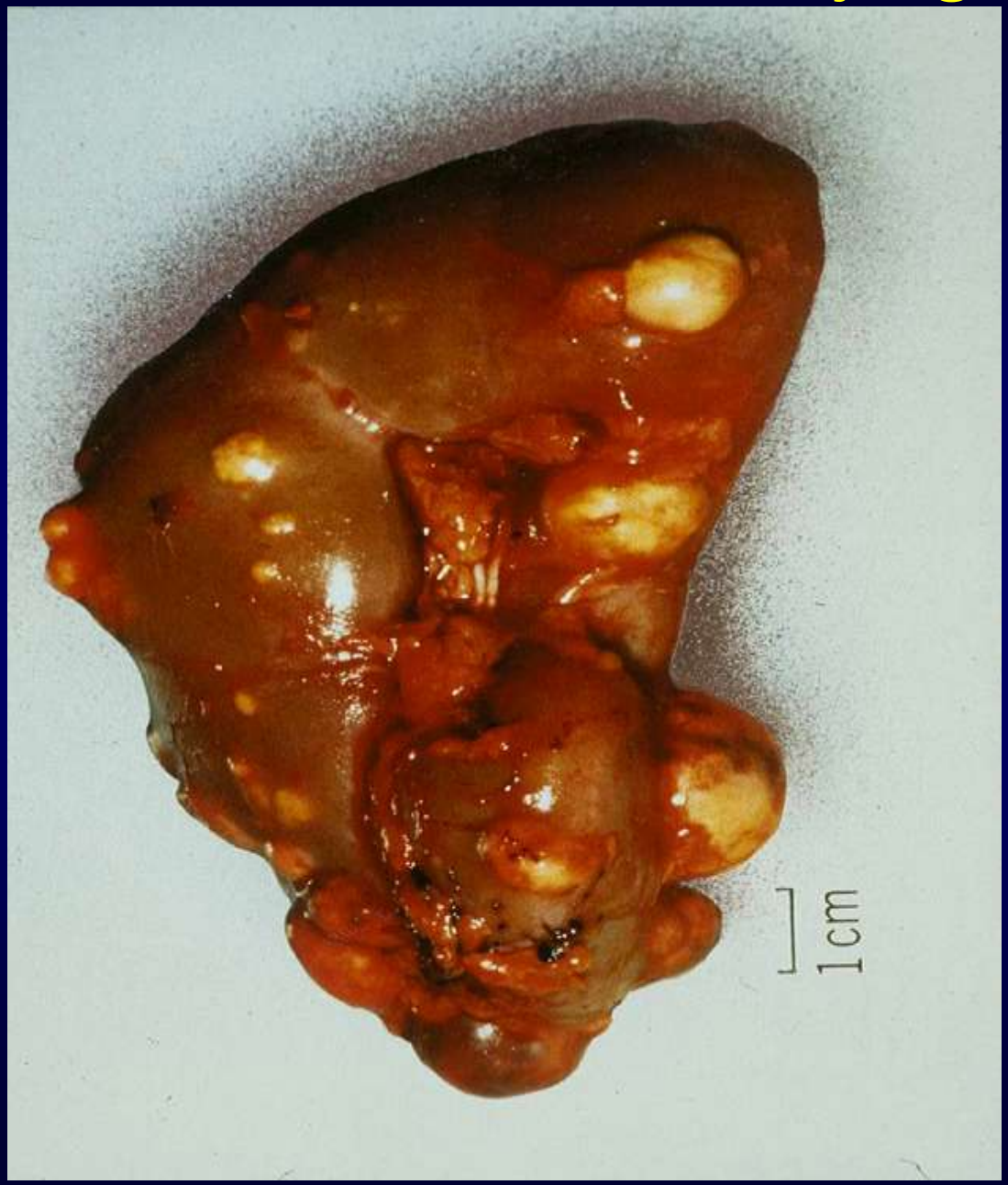
VHL Pleura





- IHC
  CK AE1/AE3 +
  Calretinin –
  CEA –
  Mucin -

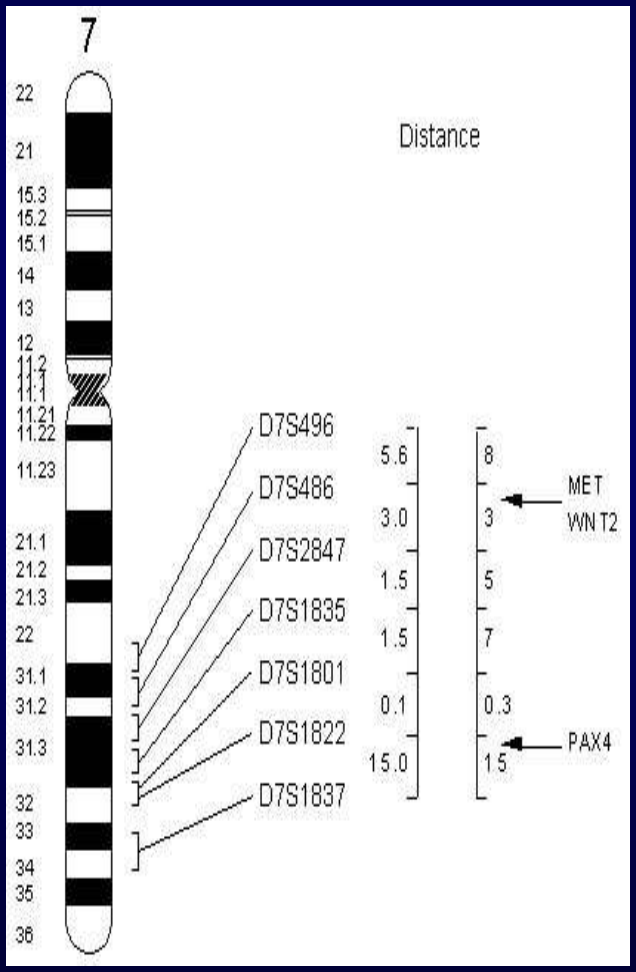
Familia con RCC multifocal y 3 generaciones afectadas.

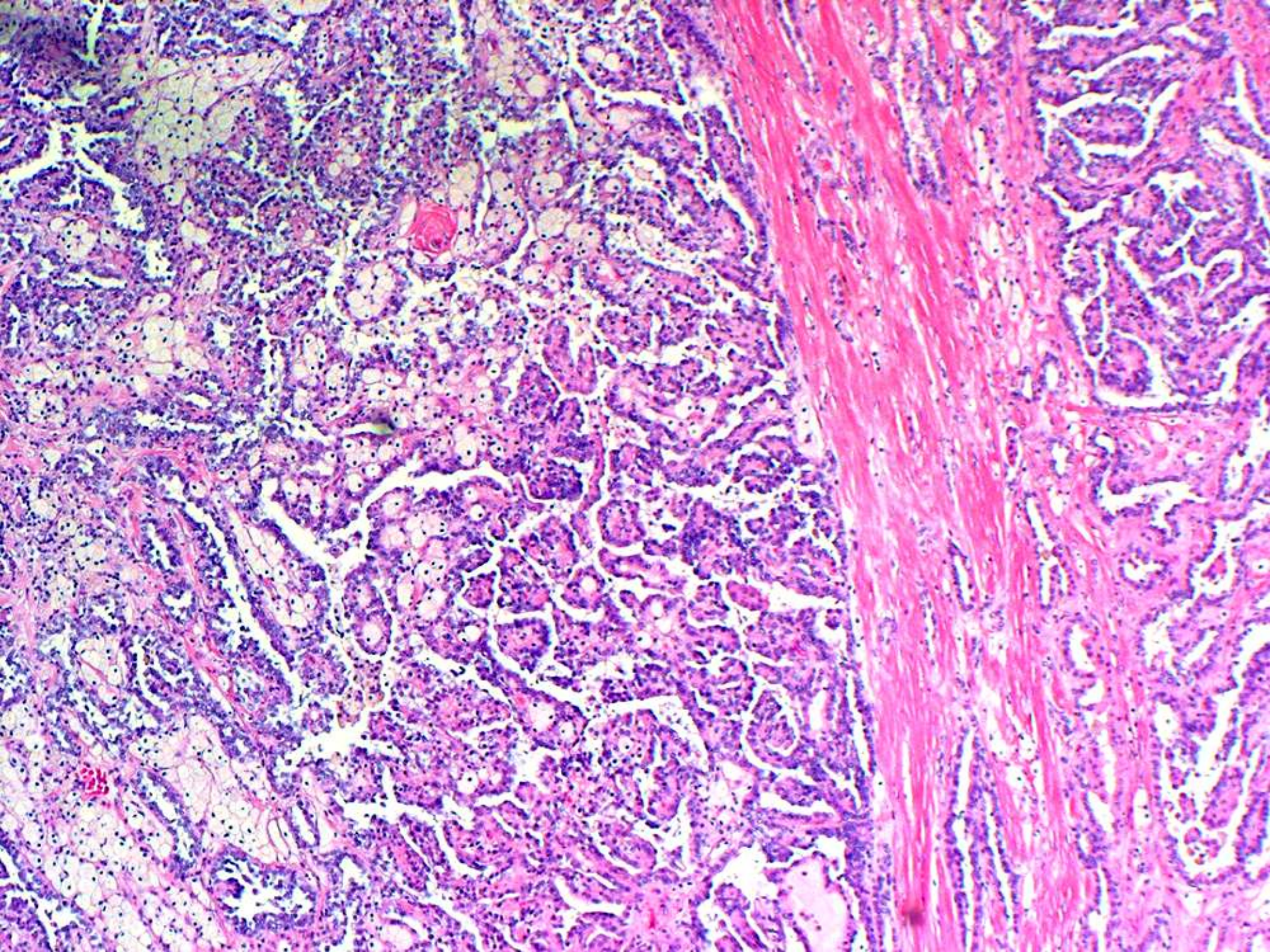


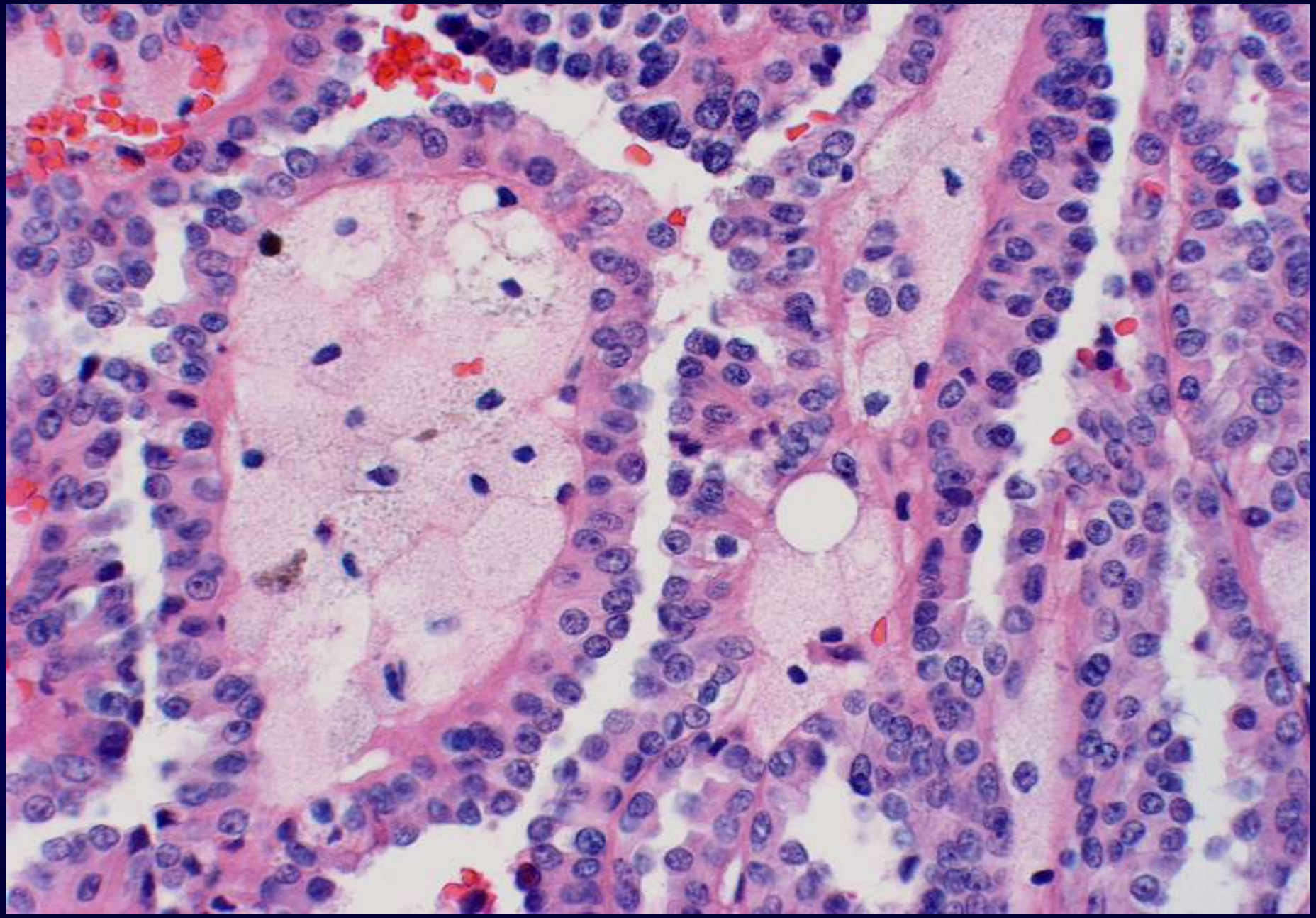
Papilar tipo 1

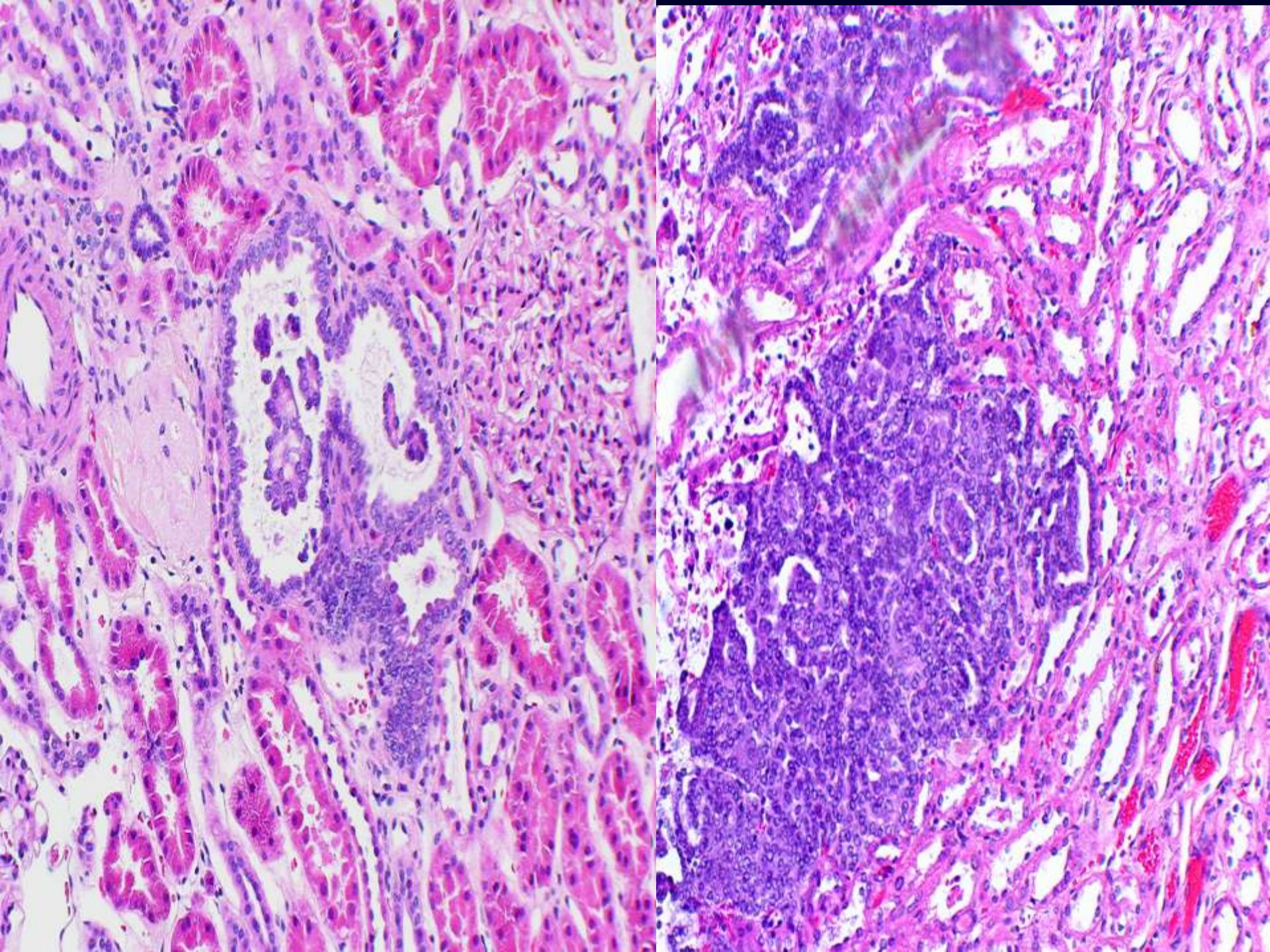
El gen esta localizdo en el cromosoma 7q31.1-34.

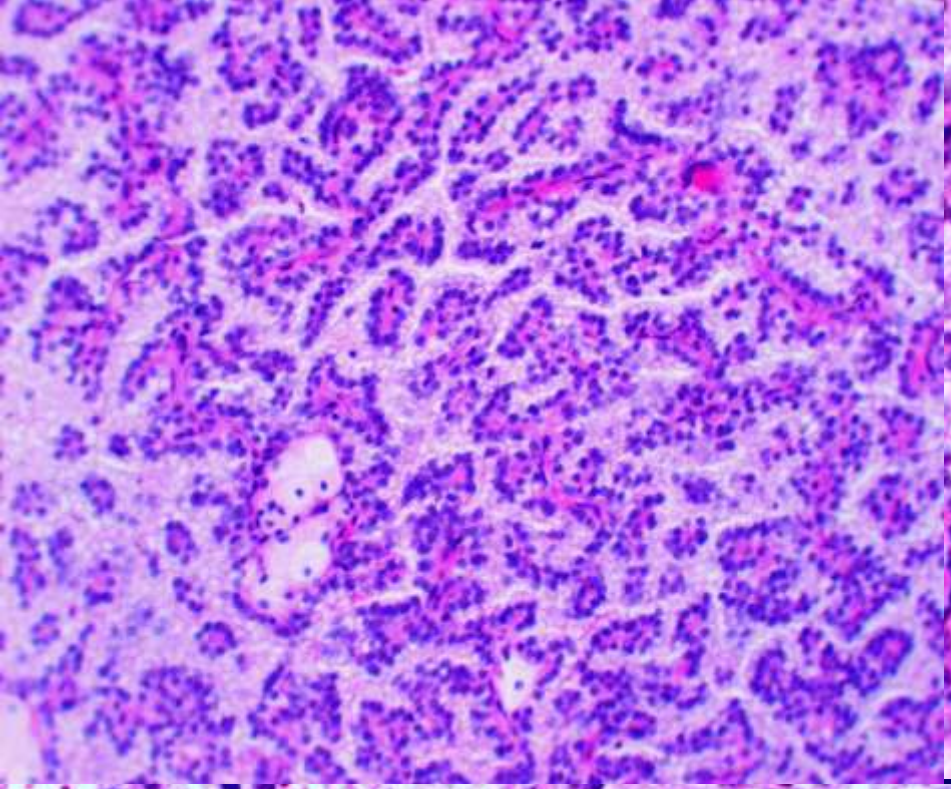
- Autosómica dominante
- Aparece tarde (50 años)
- Lesiones multiples y bilaterales de tamaño variable.
- Mutaciones en el MET oncogene (codes for a tyrosine kinase receptor)
- Hereditario y esporàdico
- Trisomias en cromosomas 7, 17

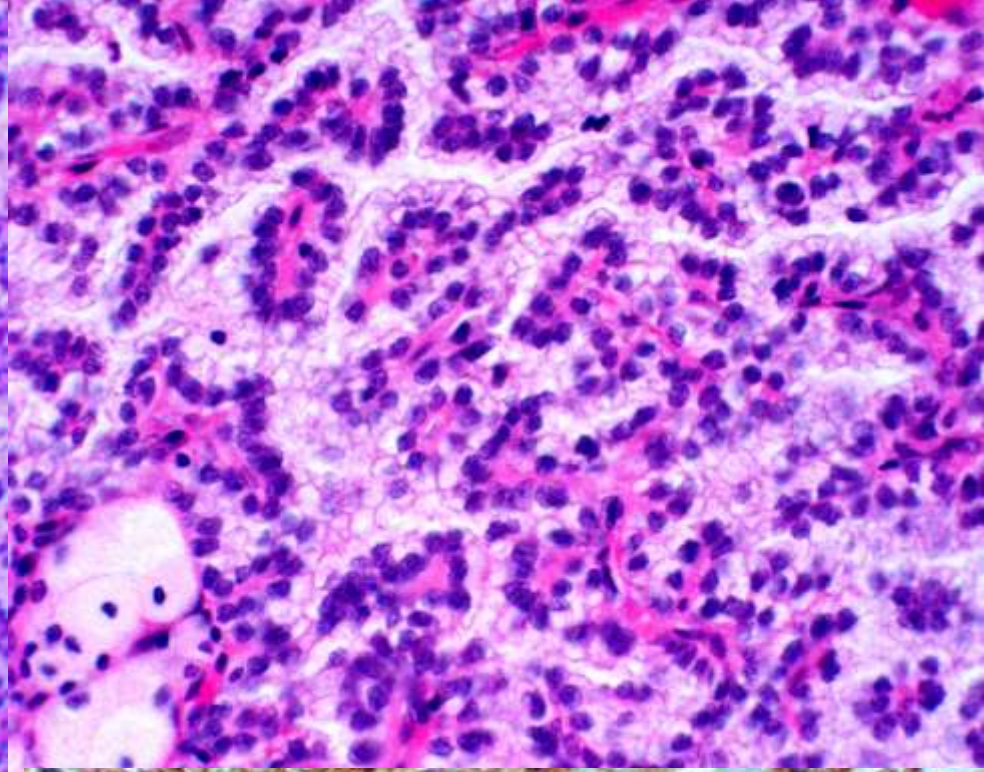


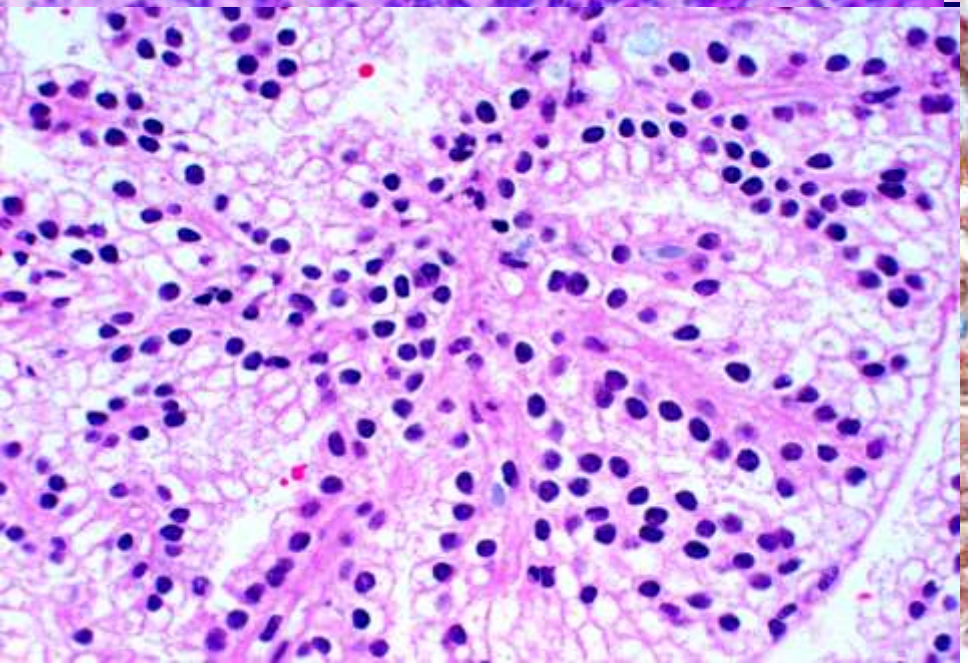


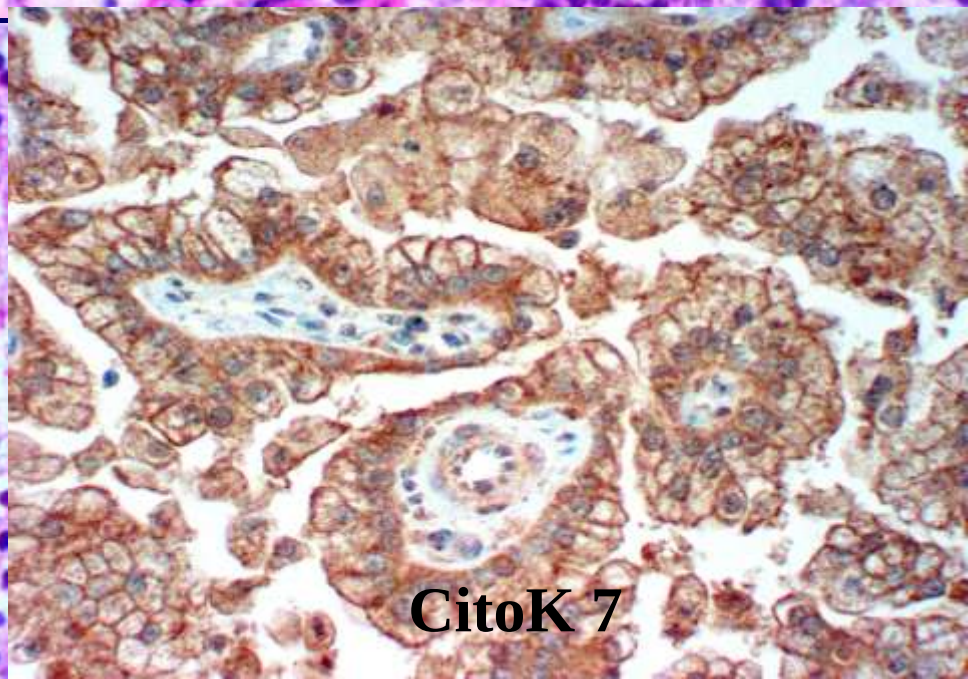


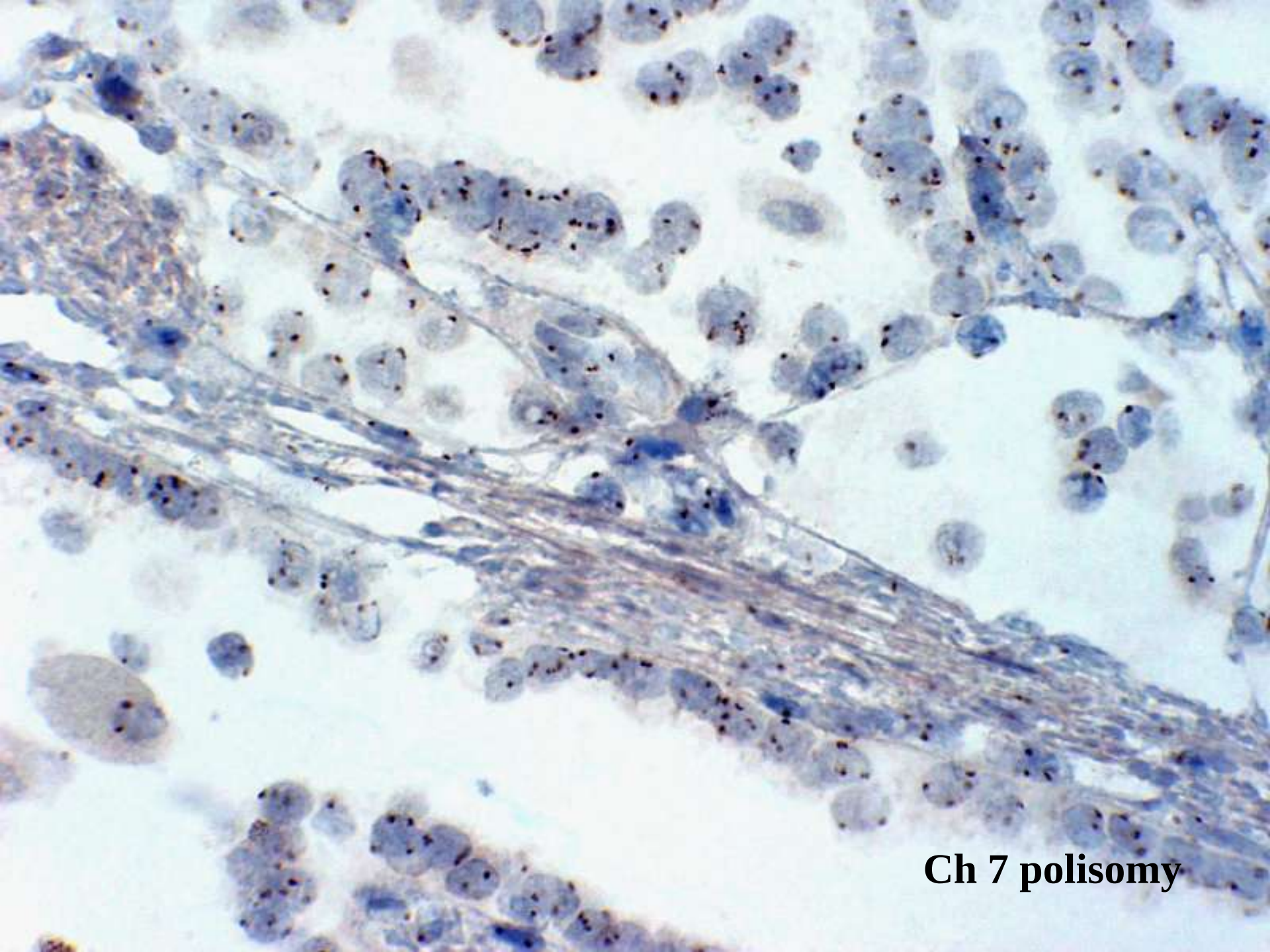









CitoK 7


Ch 7 polisomy

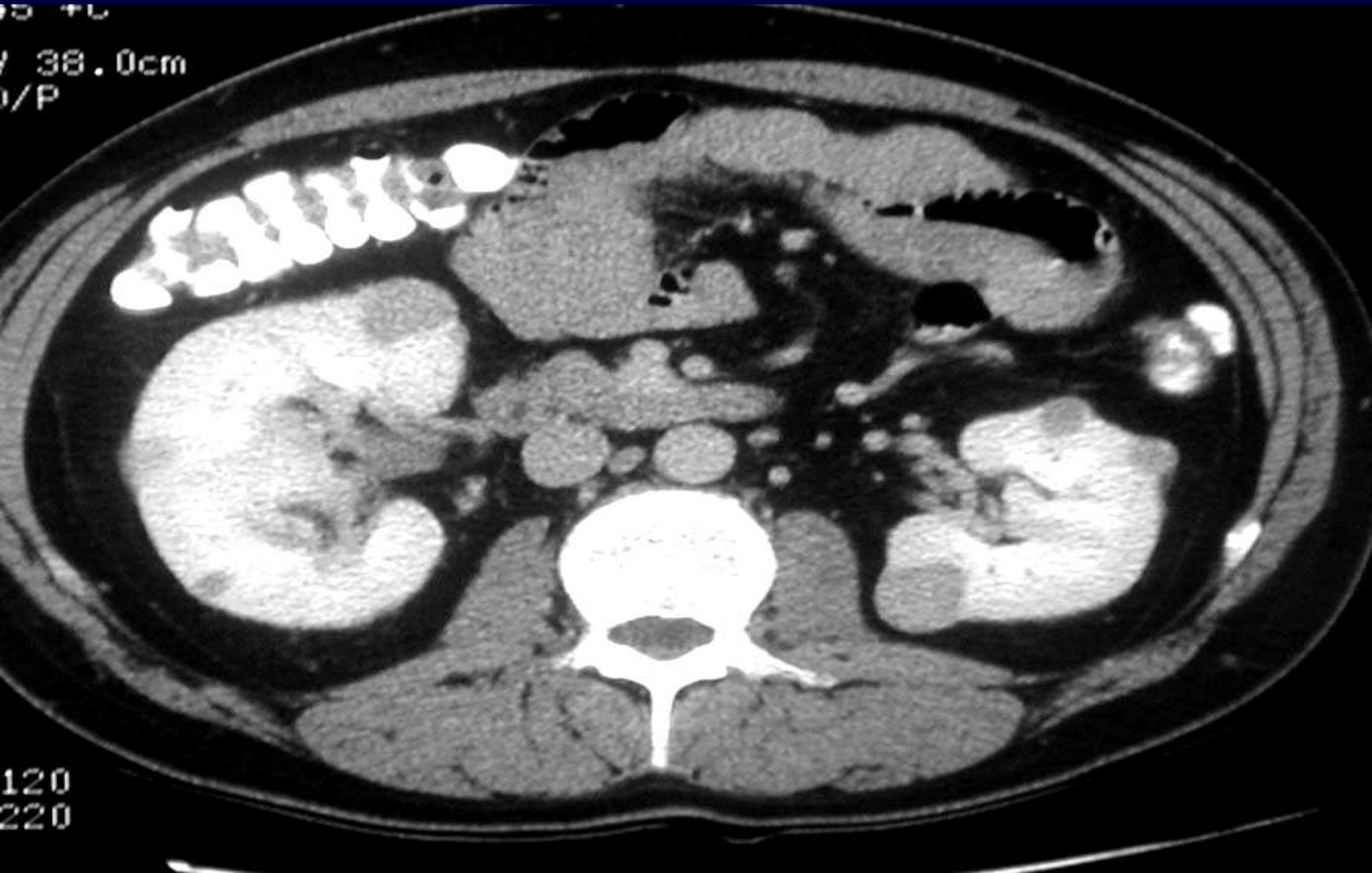
Hereditary Multiple Fibrofolliculomas With Trichodiscomas and Acrochordons

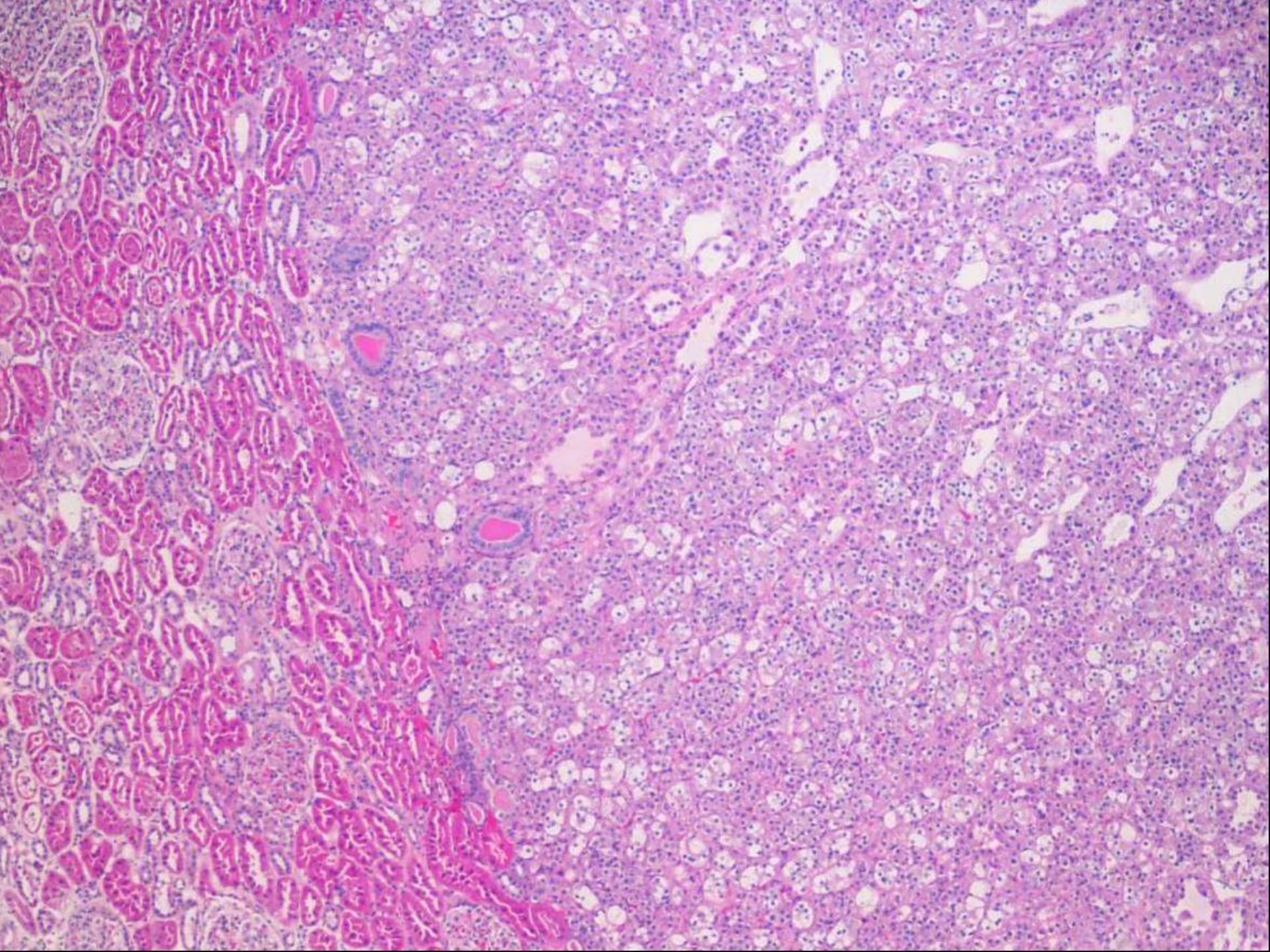
Arthur R. Birt, MD, FRCP (C); Georgina R. Hogg, MD, FRCP (C); W. James Dubé, MD

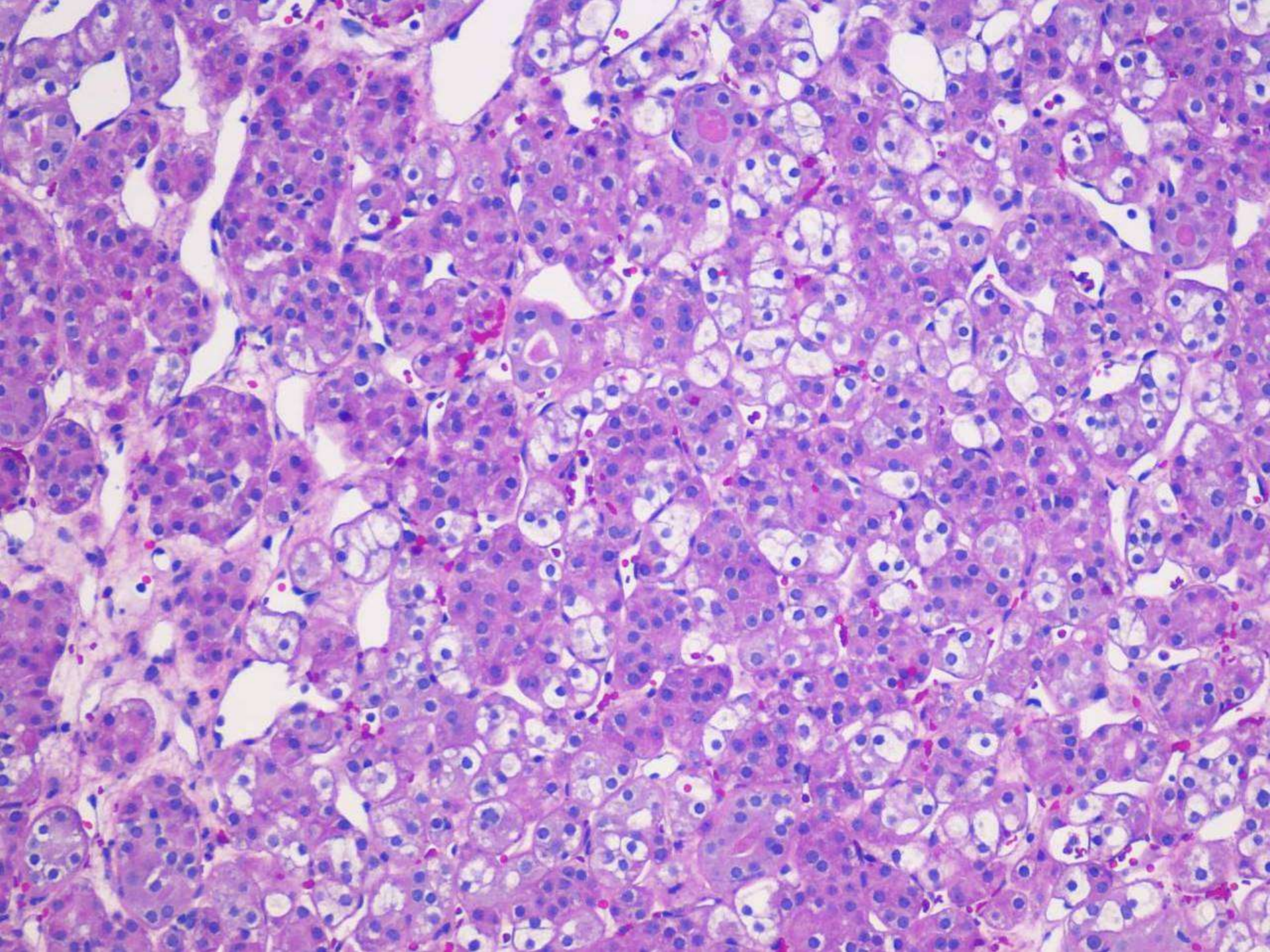
Arch Derm 113:1674-1677
Dec 1977

Arthur Birt

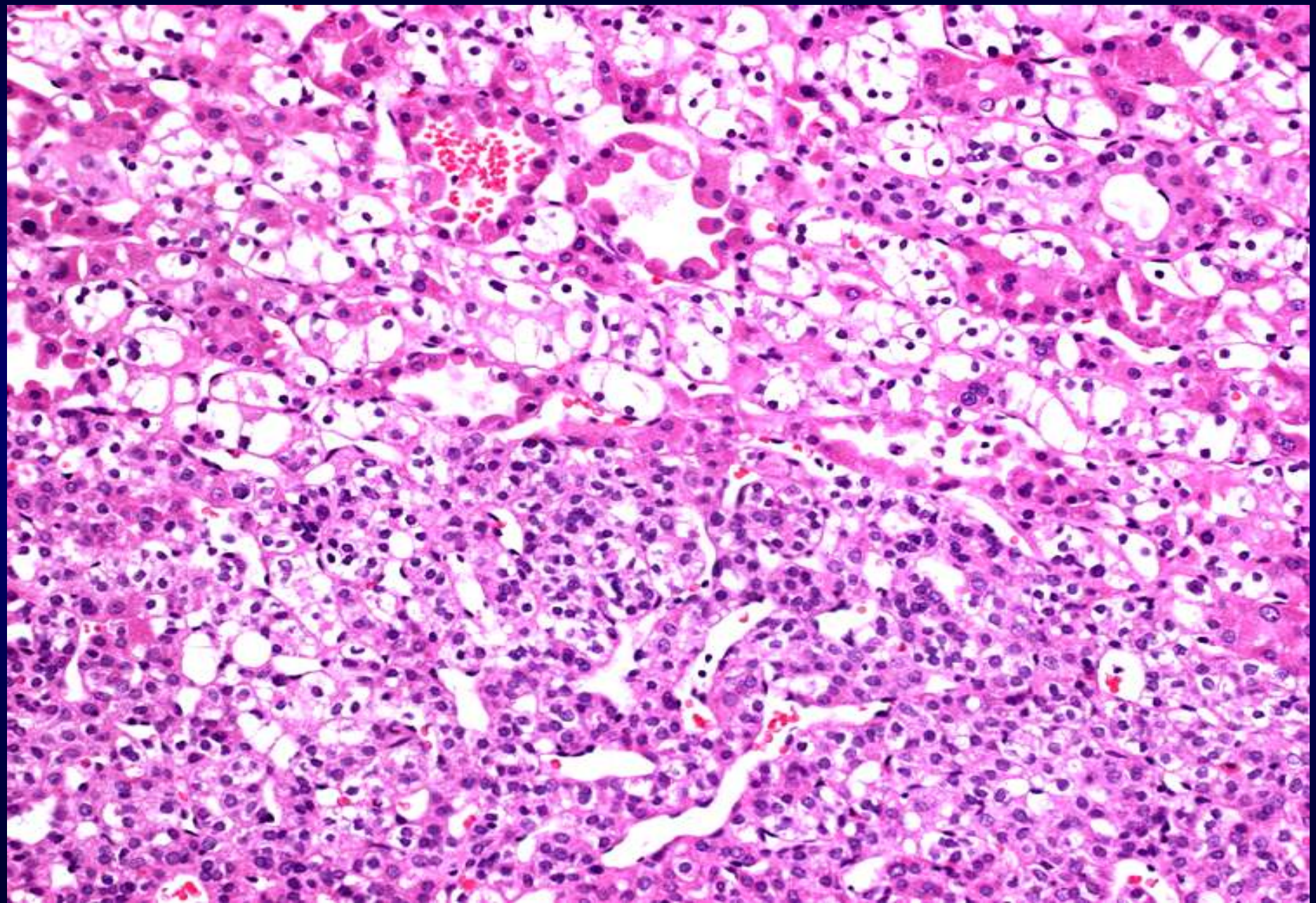
Tumores renales



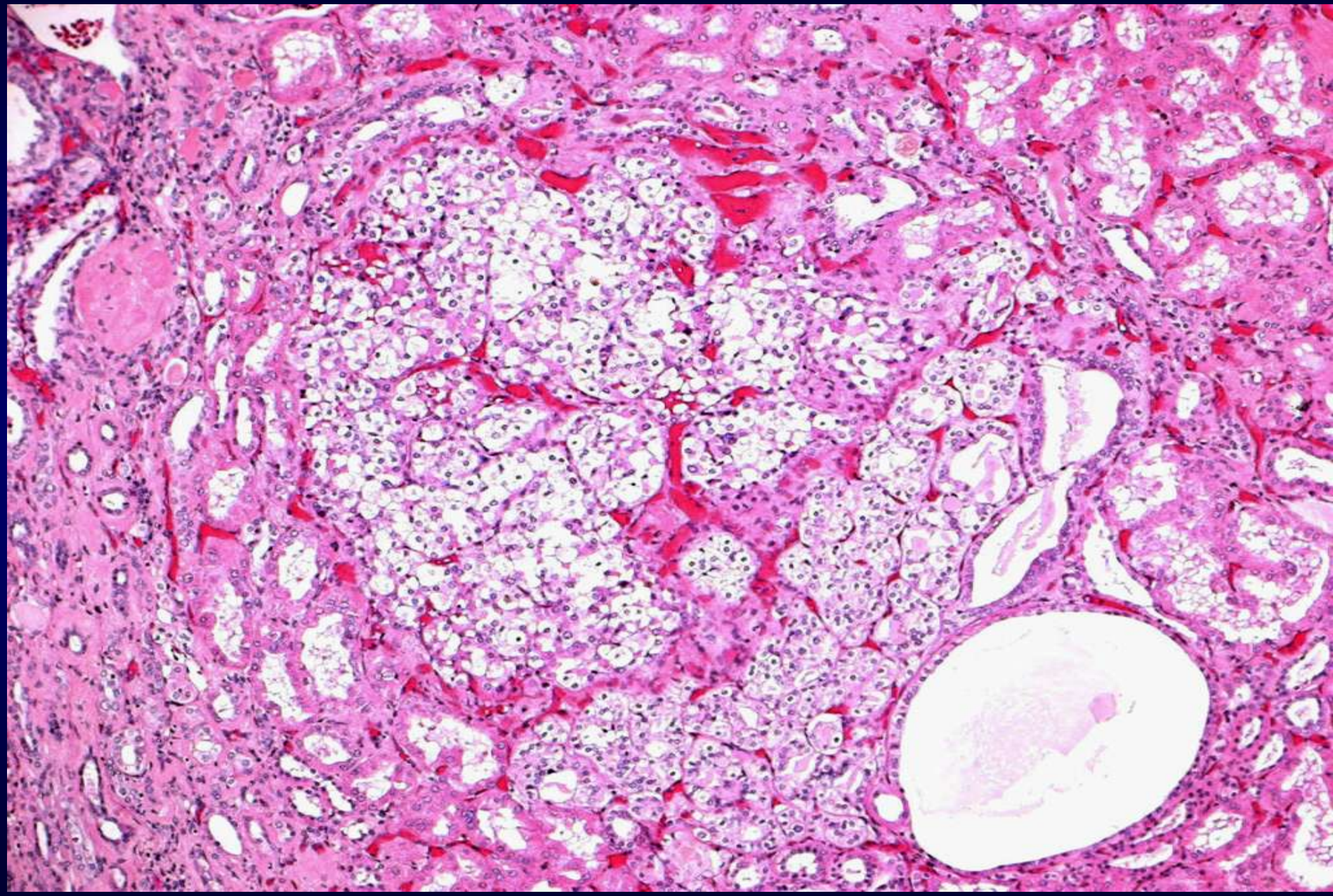




Gemelo 1



Gemelo 2



Pathology BHD renal tumors

30 patients

134 renal tumors evaluated

-65/134 (49%) chromophobe/oncocytoma hybrid

-44/134 (32%) chromophobe

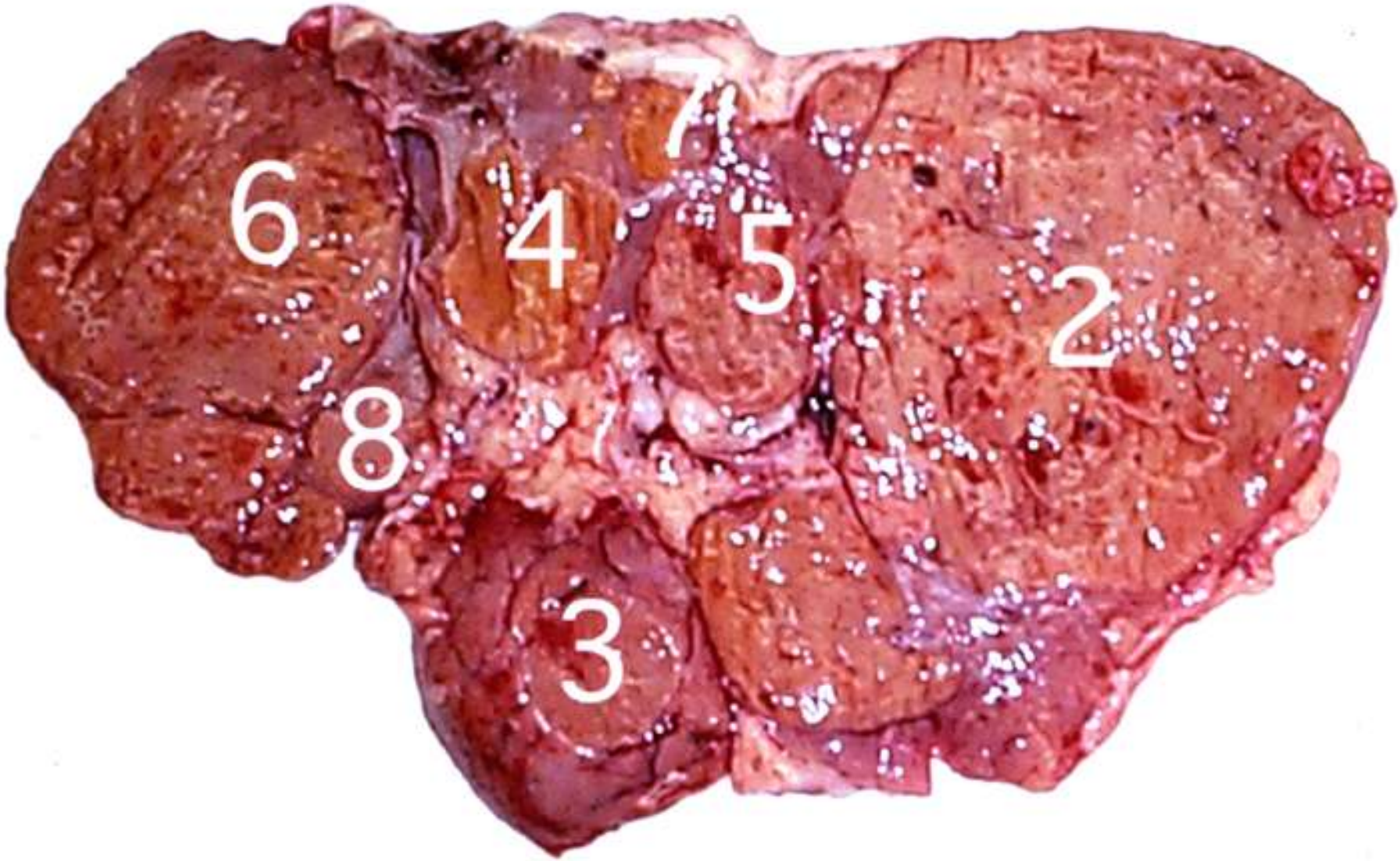
-12/134 (9%) clear cell

4 patients who developed clear cell also had multiple tumors of chromophobe, or hybrid histology.

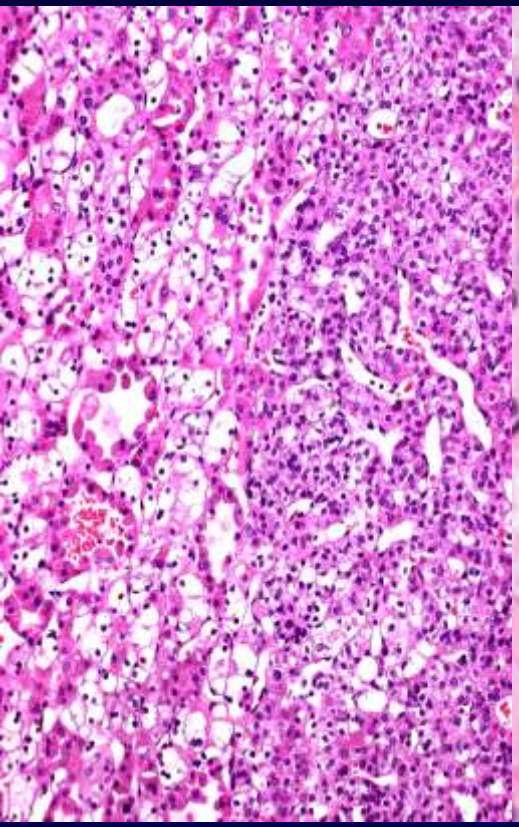
***Renal Tumors in the Birt-Hogg-Dubé Syndrome**

CP Pavlovich, M J. Merino.. AJSP02-191

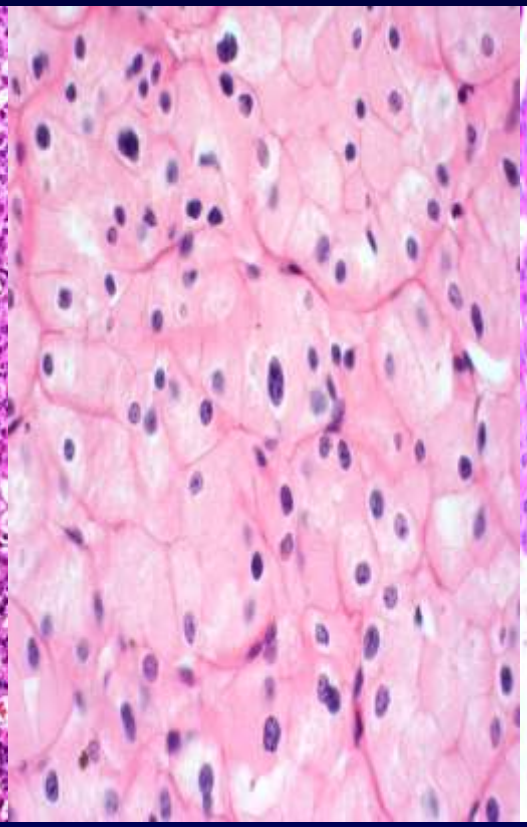
BHD



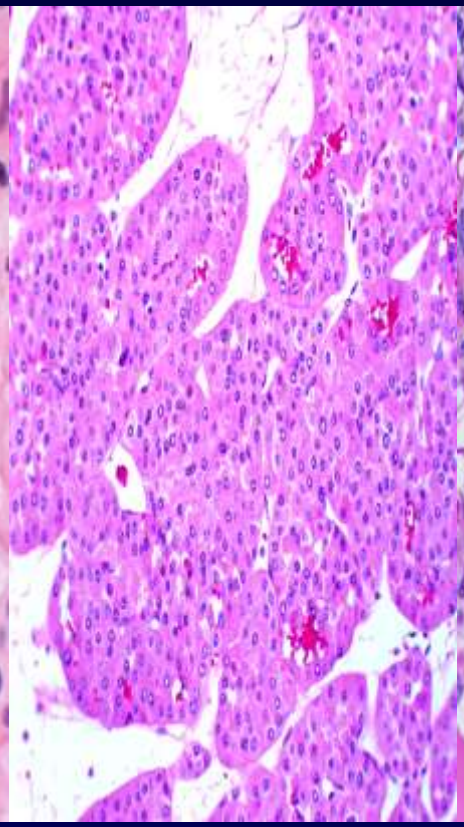
Birt Hogg Dubé: Tumores renales



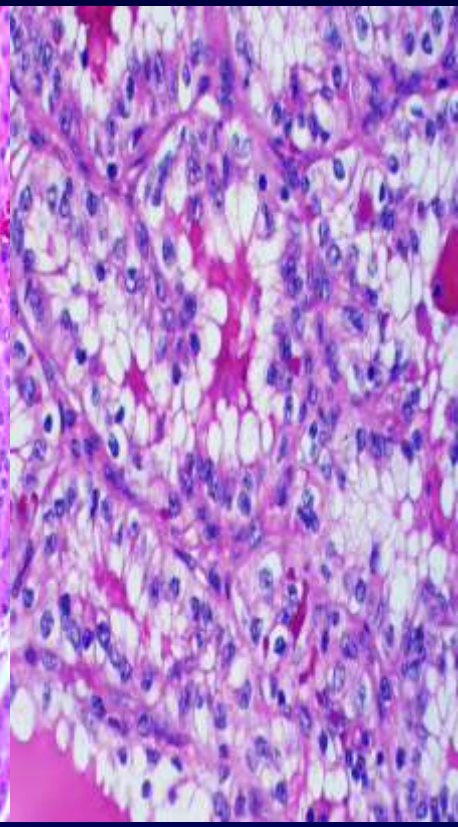
Hibrido
LOH 17



Cromofobo
LOH 17



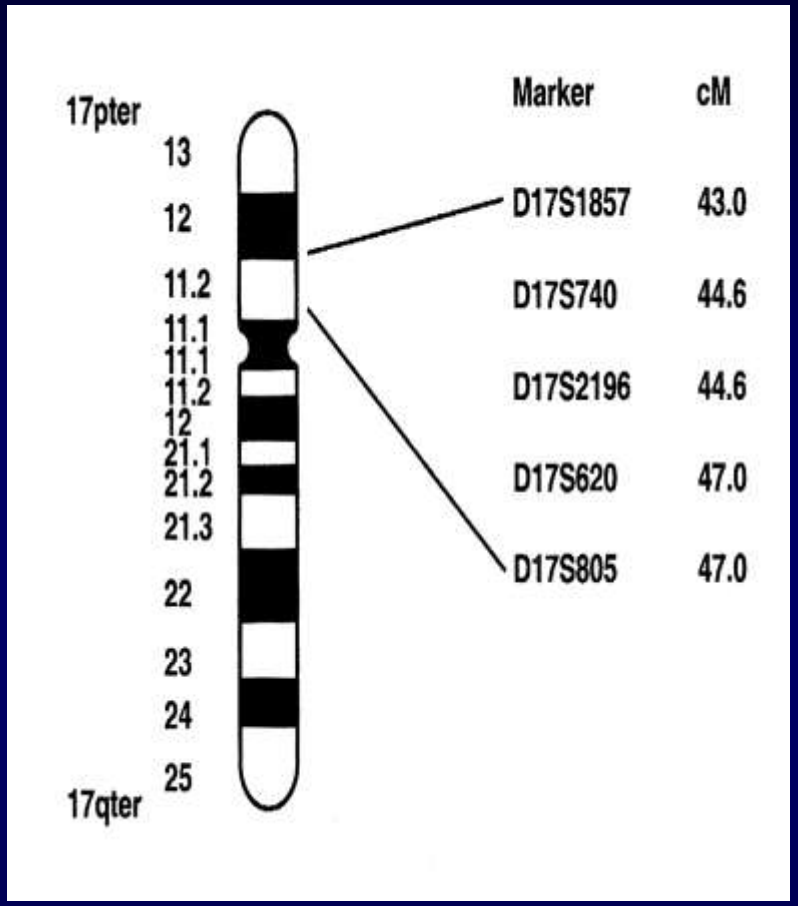
Oncocitoma
LOH 17



RCC
LOH 3p

Microdissected DNA in 88 cases

And the gene?



BHD1 Gene Locus Chromosome 17.
Encodes a protein called Folliculin

Cancer Cell. August 2002

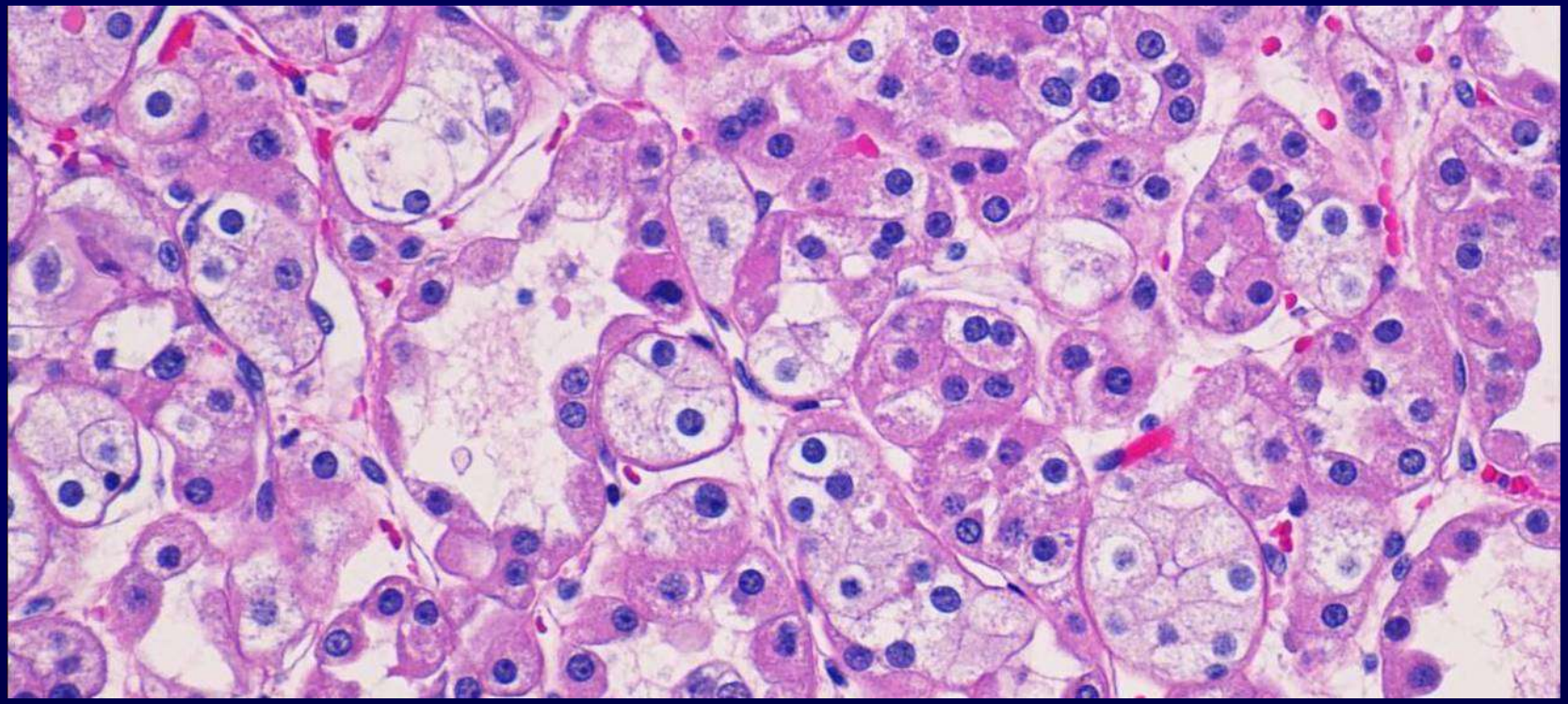
Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the Birt-Hogg-Dubé syndrome

Michael L. Nickerson,[1] Michelle B. Warren,[1] Jorge R. Toro,[4] Vera Matrosova,[1] Gladys Glenn,[4] Maria L. Turner,[5] Paul Duray,[6] Maria Merino,[6] Peter Choyke,[8] Christian P. Pavlovich,[7] Nirmala Sharma,[1] McClellan Walther,[7] David Munroe,[3] Rob Hill,[3] Eamonn Maher,[9] Cheryl Greenberg,[10] Michael I. Lerman,[1] W. Marston Linehan,[7] Berton Zbar,[1] and Laura S. Schmidt[2,11]

Hybrid oncocytic tumors (HOT) of the kidney:

Pablo Cannata

"…tumors with presence of mixed histologic features of both chromophobe renal cell carcinoma and renal oncocytoma."



Renal Oncocytosis: A Morphologic Study of Fourteen Cases
Tickoo SK,
Am J Surg Pathol; 1999

RESULTS - I

- 467 tumors from 68 patients (39 males; 29 females))
  - Evolution
  - Average age at surgery: 48.65 yrs. (range: 31-82)
  - 6.86 tumors per patient (range: 1-59)
  - Average tumor size: 2.2 cm. (range: 0.4-9)

RESULTS - III

- Great diversity of histologies:

- From the 47 patients affected with multifocal disease:

  - 17 pat. (36%) had tumors of only one histologic type
  - **30** pat. **(64%)** showed tumors of **≥2 diff. histologic types**

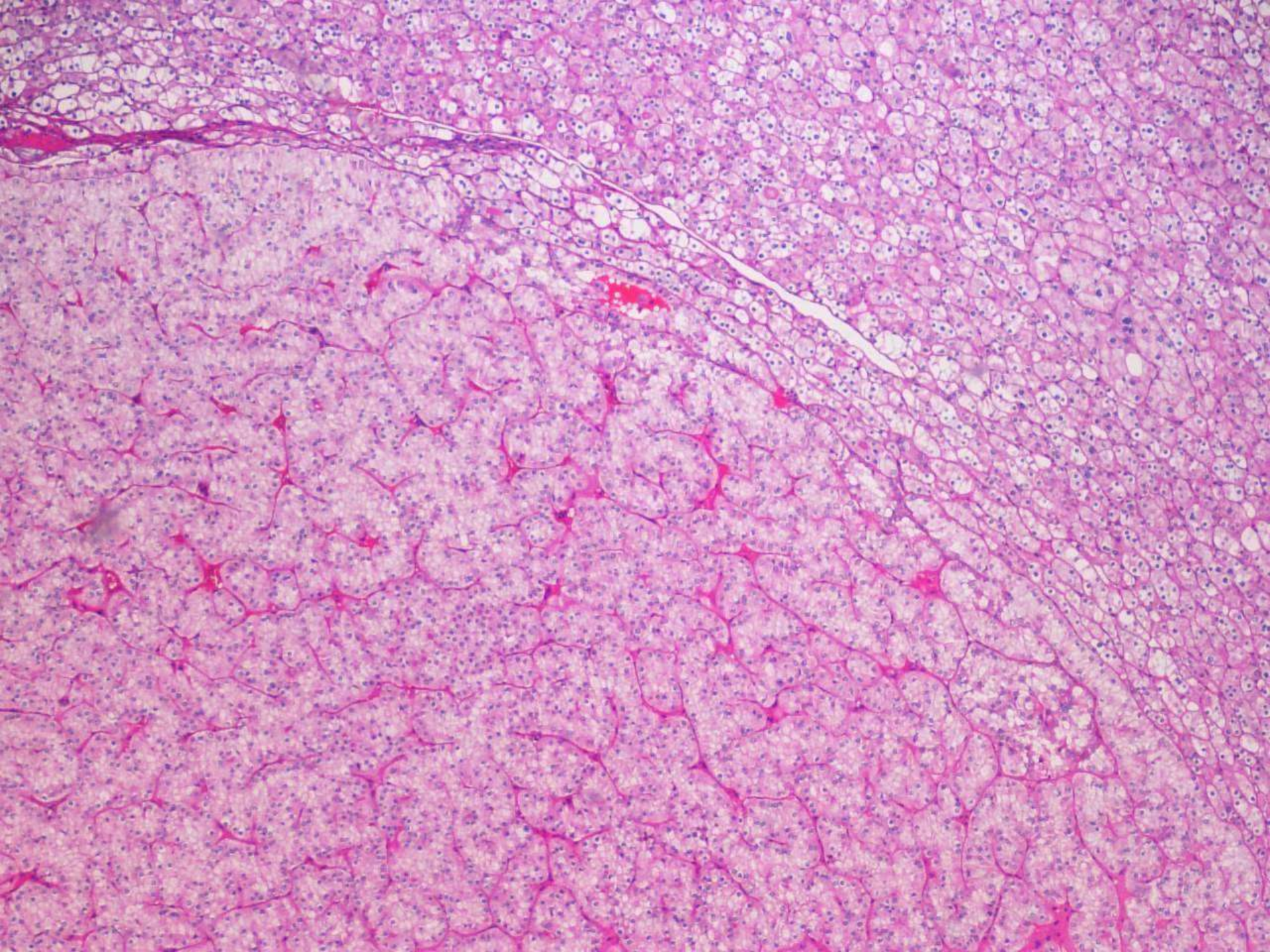
- **Hybrid Oncocytic Tumors** were seen in 50 patients (72%)

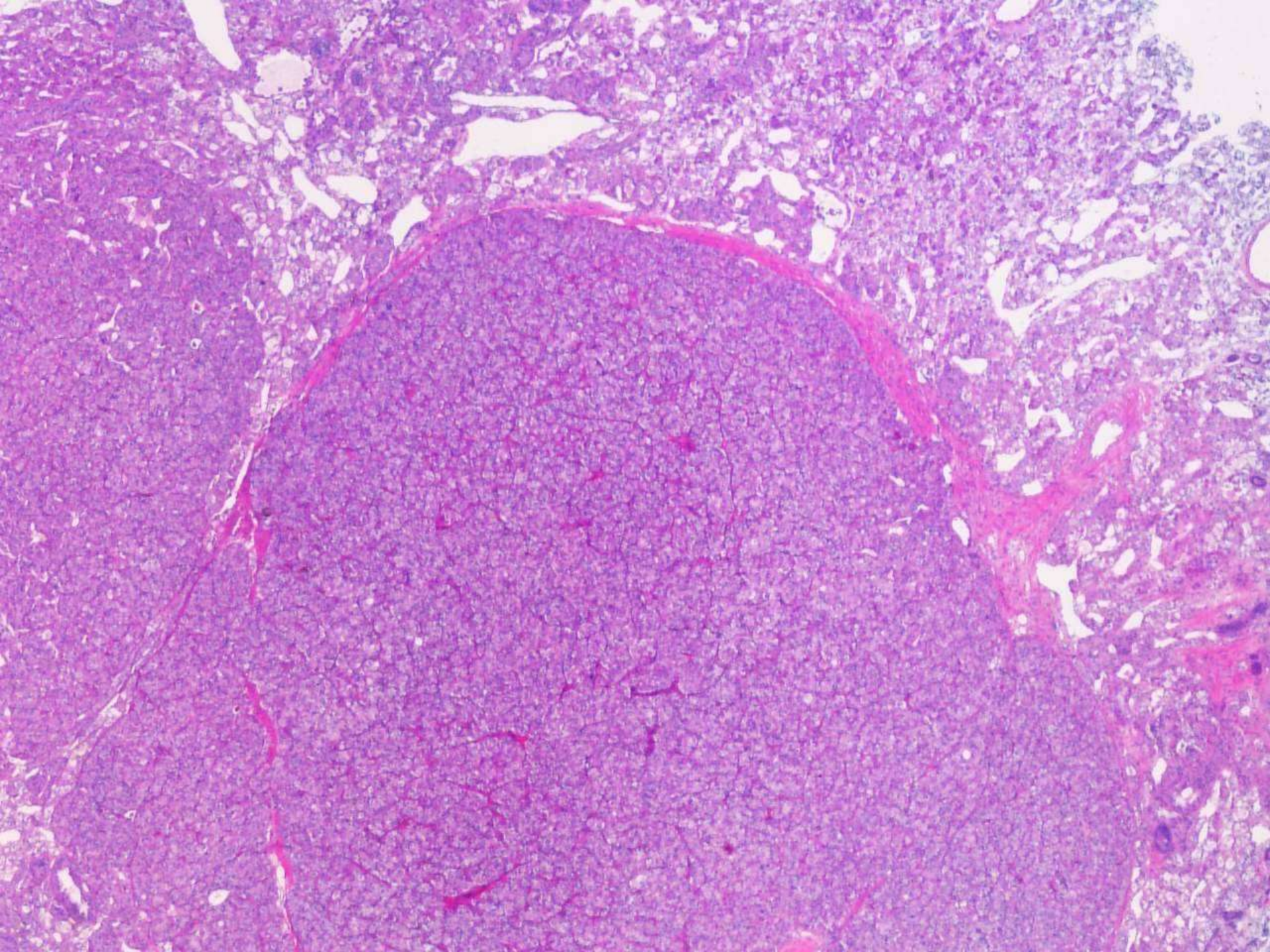
- **Chromophobe RCC** was seen in 47 patients (68%)

- ***Clear cell RCC was diagnosed in 10 patients (14.5%)*

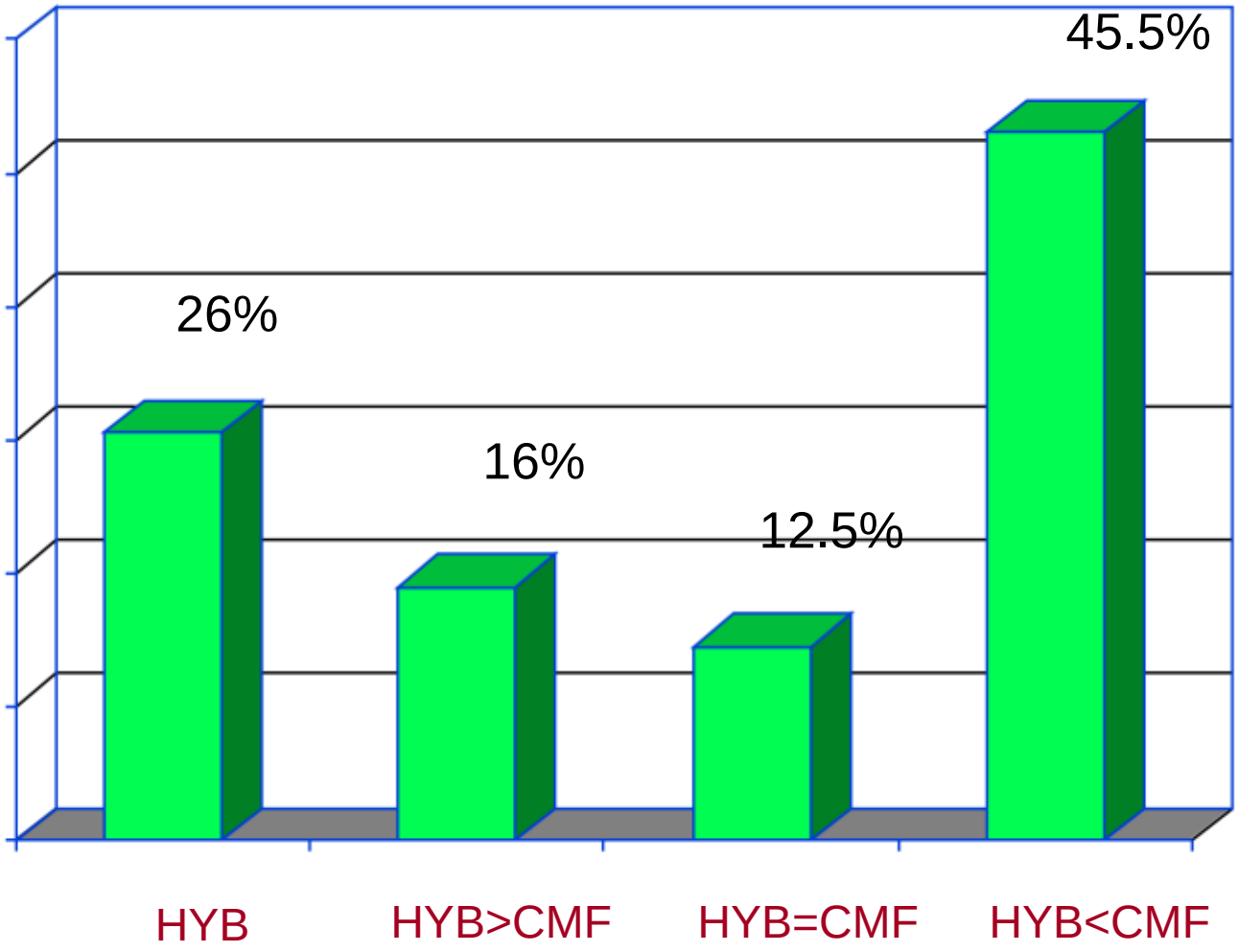
- Renal oncocytoma was seen in 6 patients (8.7%)

- A Papillary type-I RCC was seen in one patient who showed tumors of 4 different histologic types

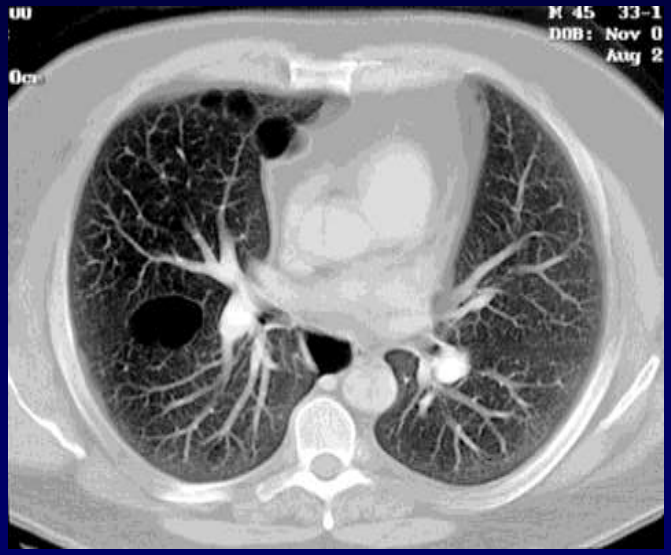


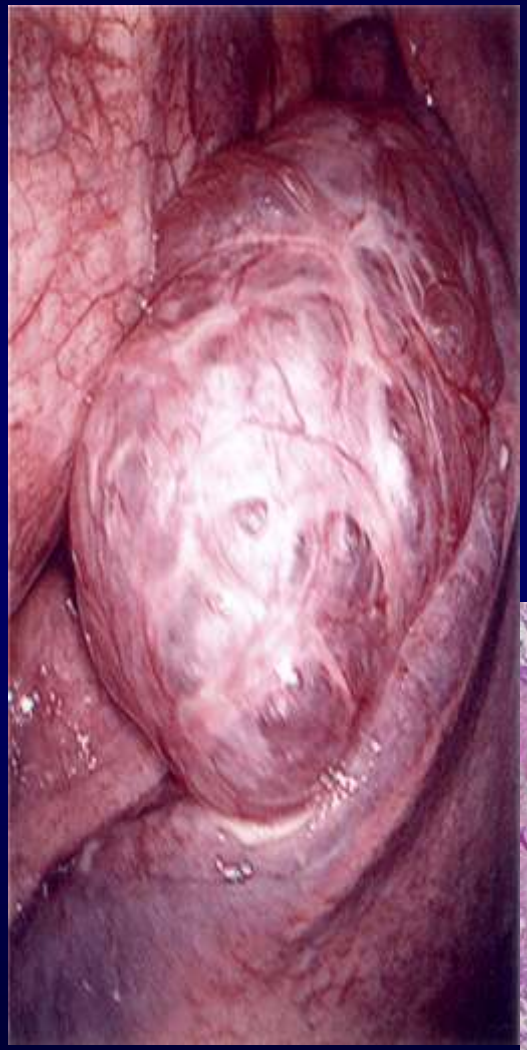


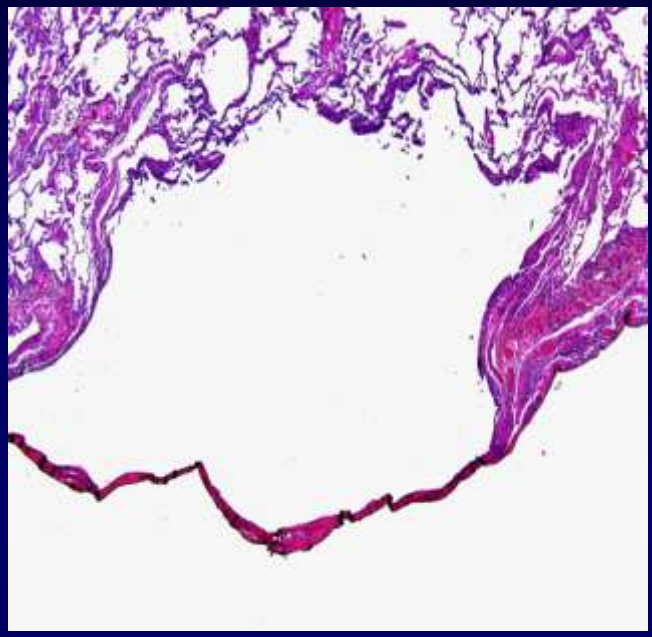
HYBRID ONCOCYTIC TUMORS

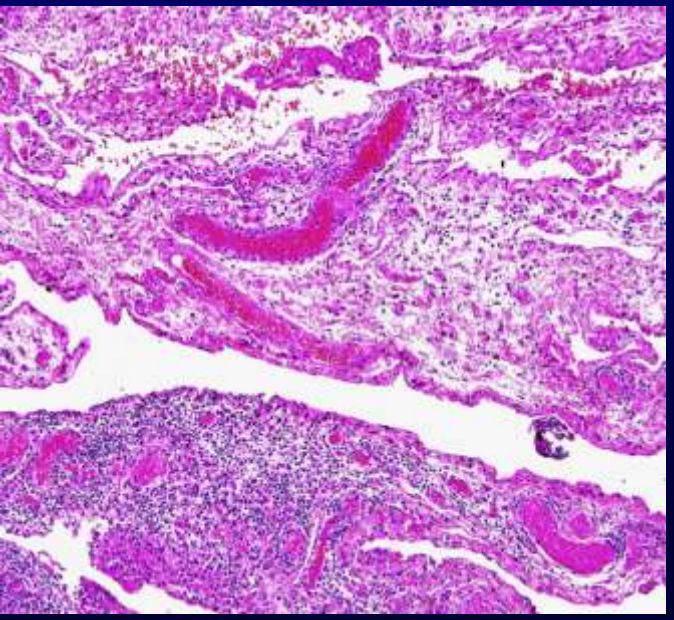


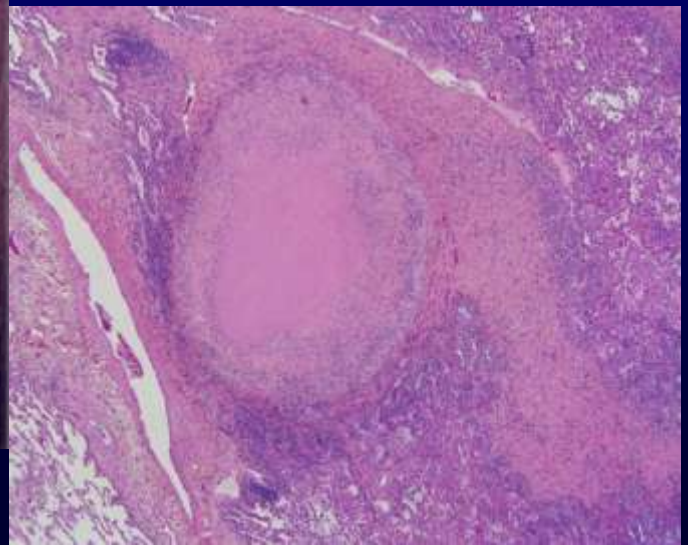
Lesiones Pulmonares BHD











CONCLUSIONS

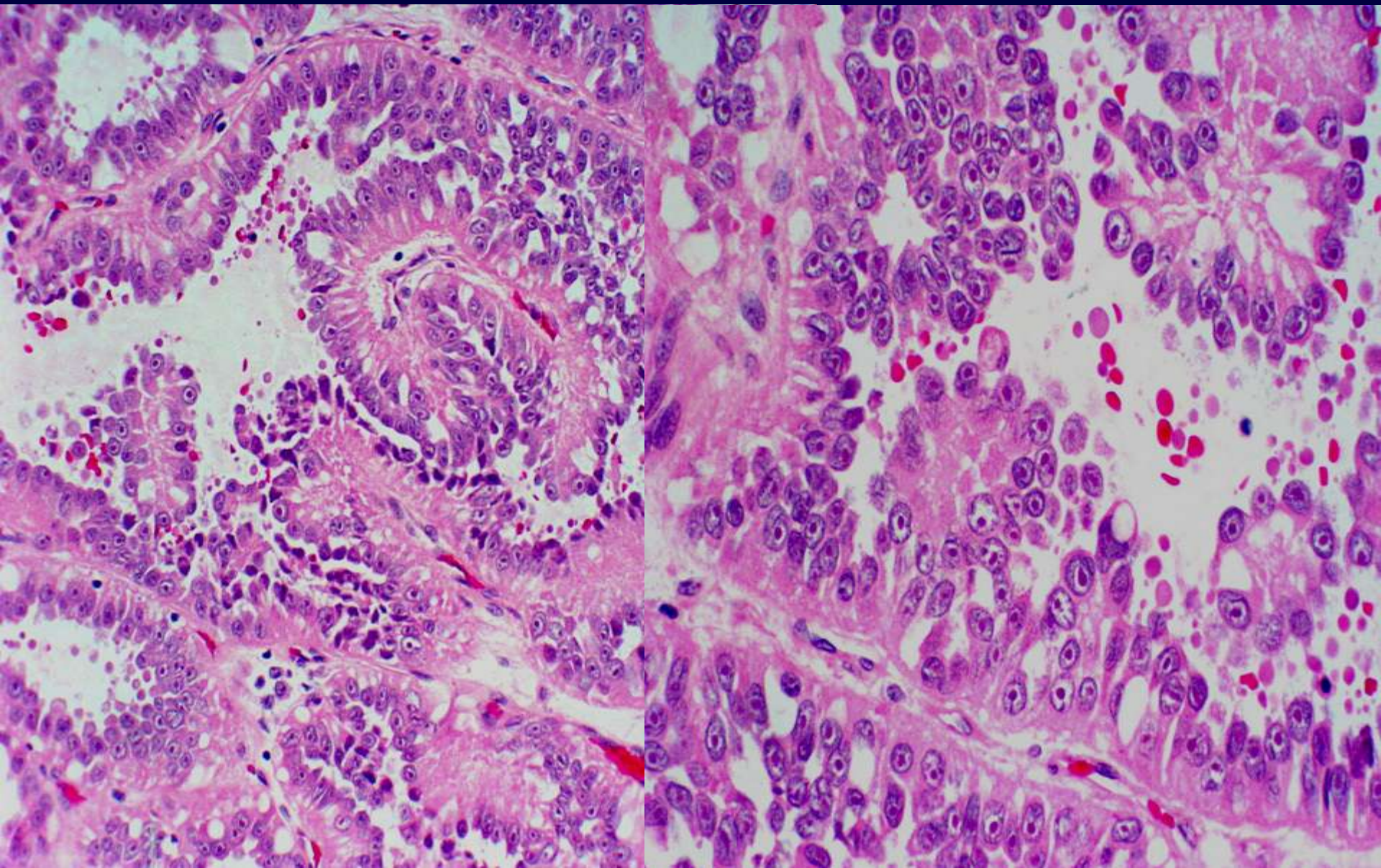
- Patients with multiple skin lesions consistent with *fibrofolliculomas* should be screened for renal tumors
- **Hybrid oncocytic tumors** are the most frequent renal neoplasias among BHD patients (58.7%)
- BHD predisposes to tumors derived from the distal nephron (97%)
- It is not uncommon to find solid nodules of ‘classic’ ChRCC growing inside hybrid tumors
- Hybrid tumors show an excellent oncologic outcome
- The question why do some of these patients develop more aggressive tumors (clear cell RCC) still remains unanswered
- *Remember lung cysts*

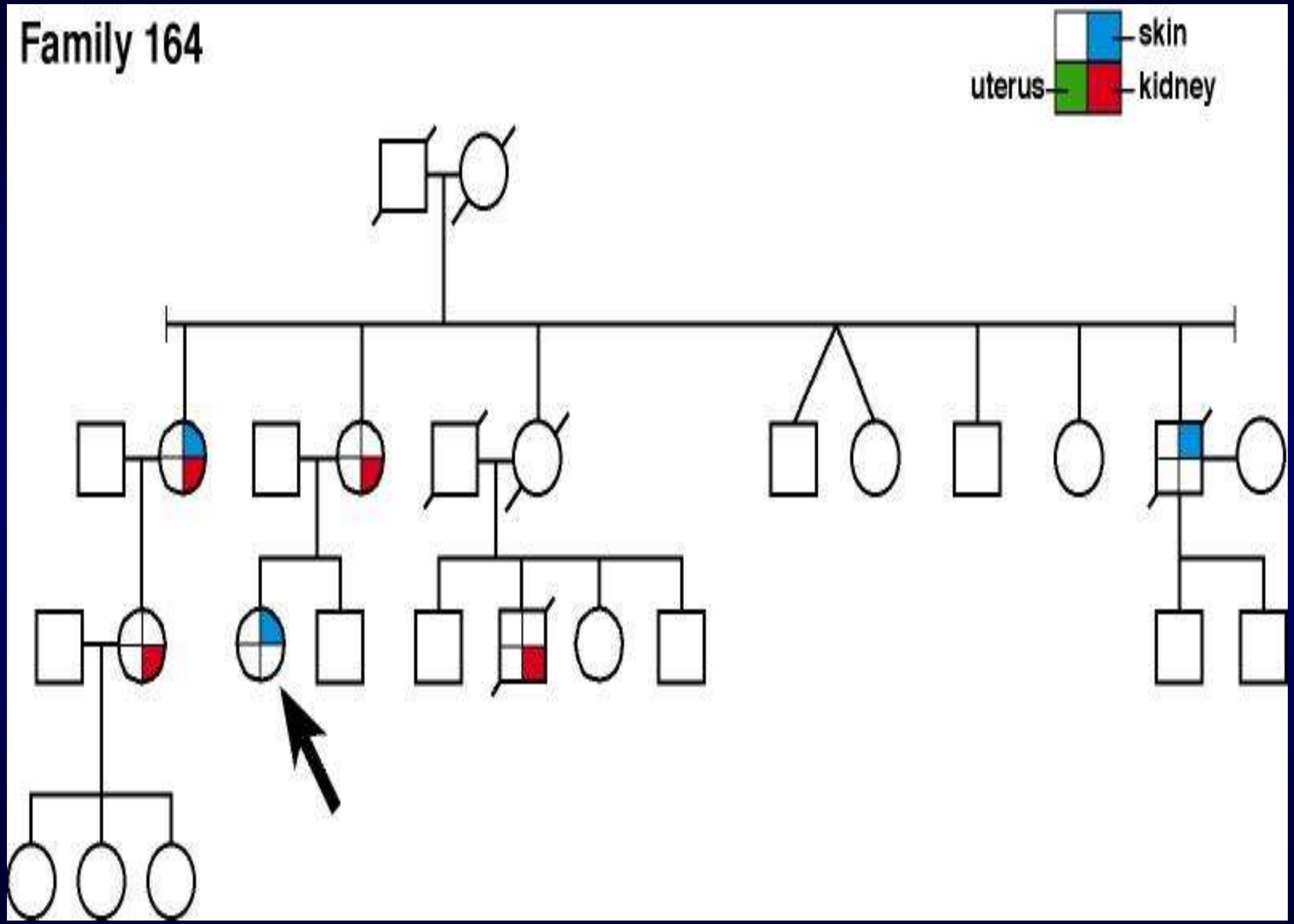
Terapia (Hereditarios)

- Morfología … VHL, Pap tipo I, BHD …. Estudio genético……
- Nefrectomia parcial para tumores menores de 3 cm con resección de quistes y lesiones pequeñas.
- Seguimiento cercano de lesiones pequeñas.
- Evaluación de miembros familiares, estudios genéticos y counseling
- Pacientes con tumores menores de 3-4 cm tienen excelente prognóstico con largas sobrevida. (10-15)

Recordar que estos pacientes se trataban con nefrectomia..

Mujer de 21 años con RCC stadio IV




Family 164
skin
uterus
kidney

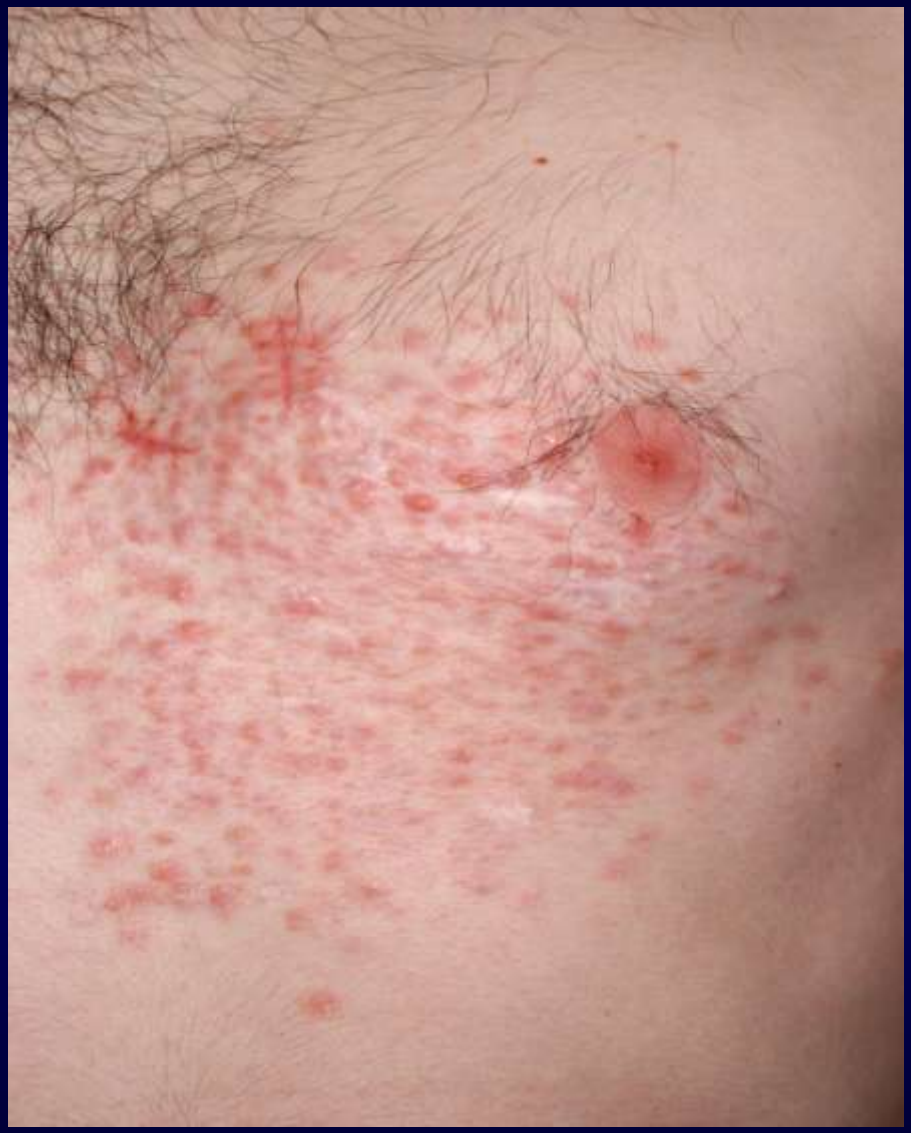
HLRCC

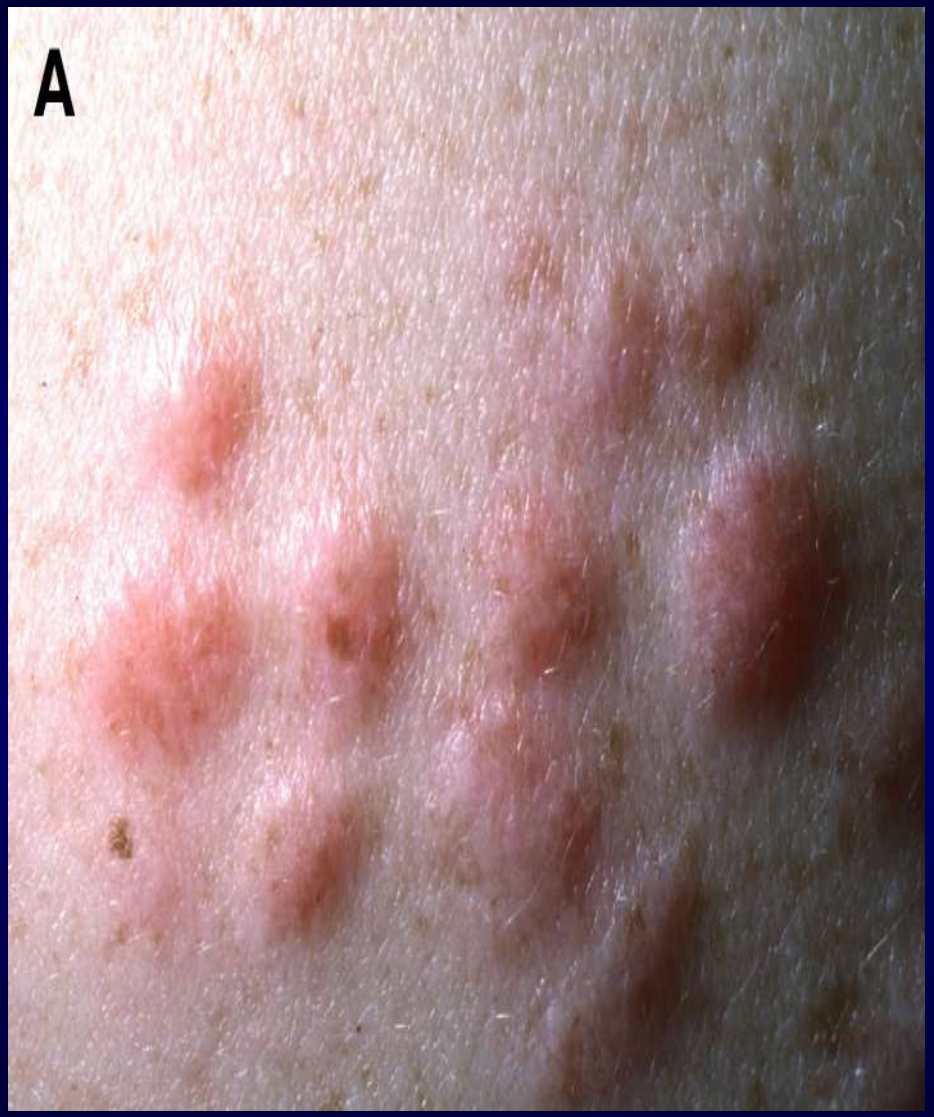
Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome (HLRCC) ha sido descrito (Launonen *et al*, 2001).

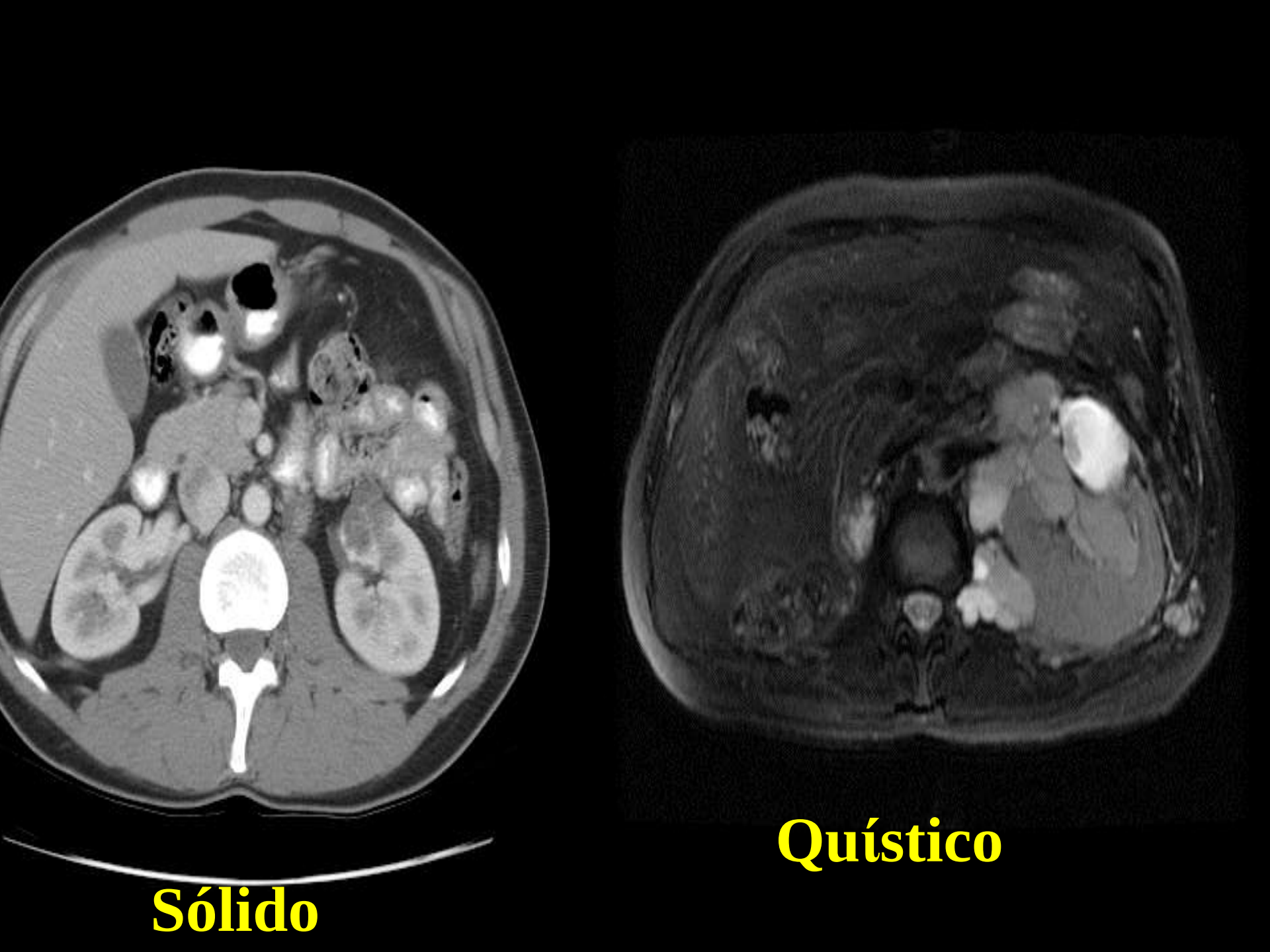
- HLRCC es autosómico dominante
- Es caracterizado por una predisposición a leiomiomas uterinos y a carcinomas de células renales.
- Mutaciones en linea germinal en el gen fumarate hydratase (FH, 1q42.3-q43)

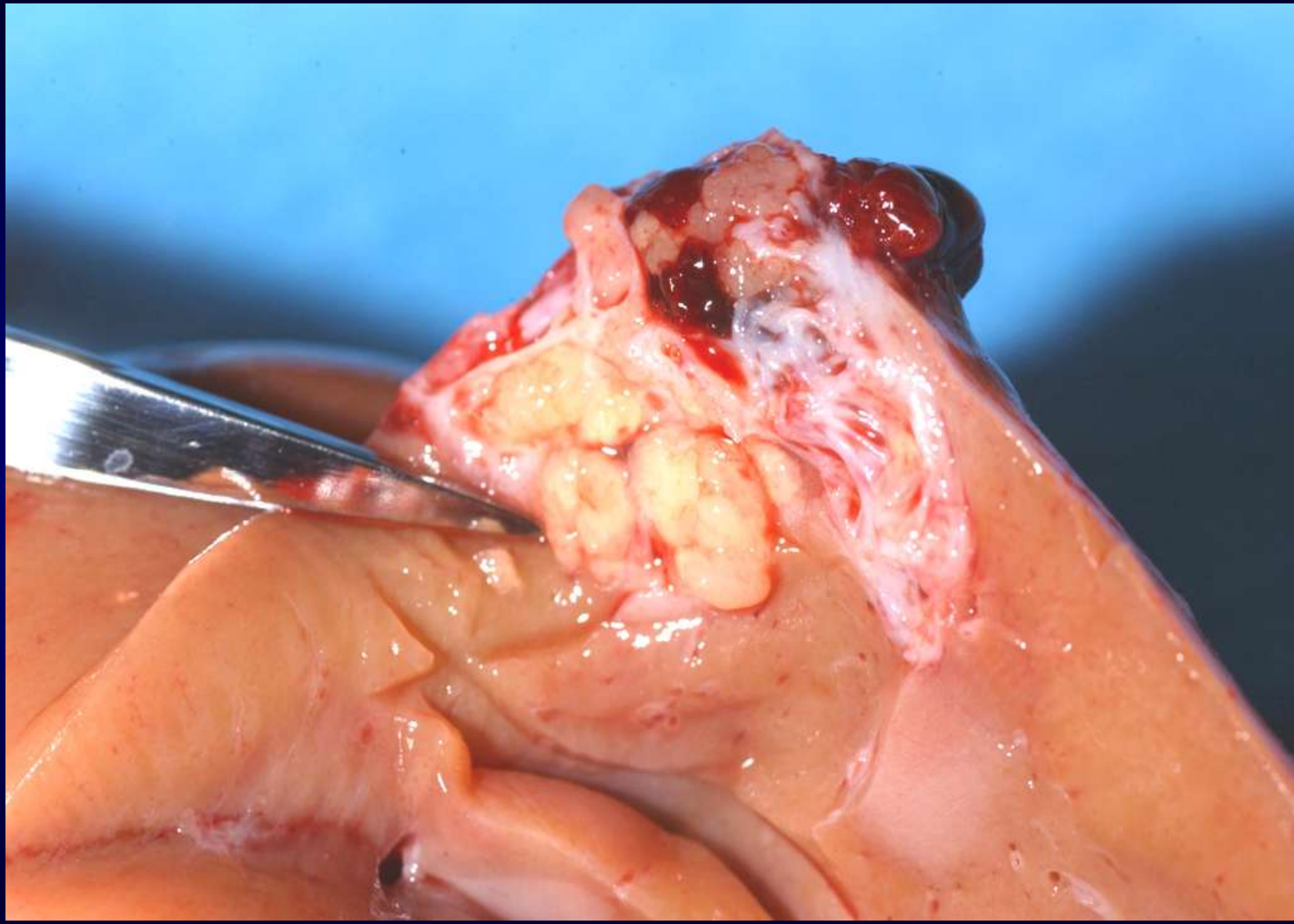
(The Multiple Leiomyoma Consortium, 2002).

Brother

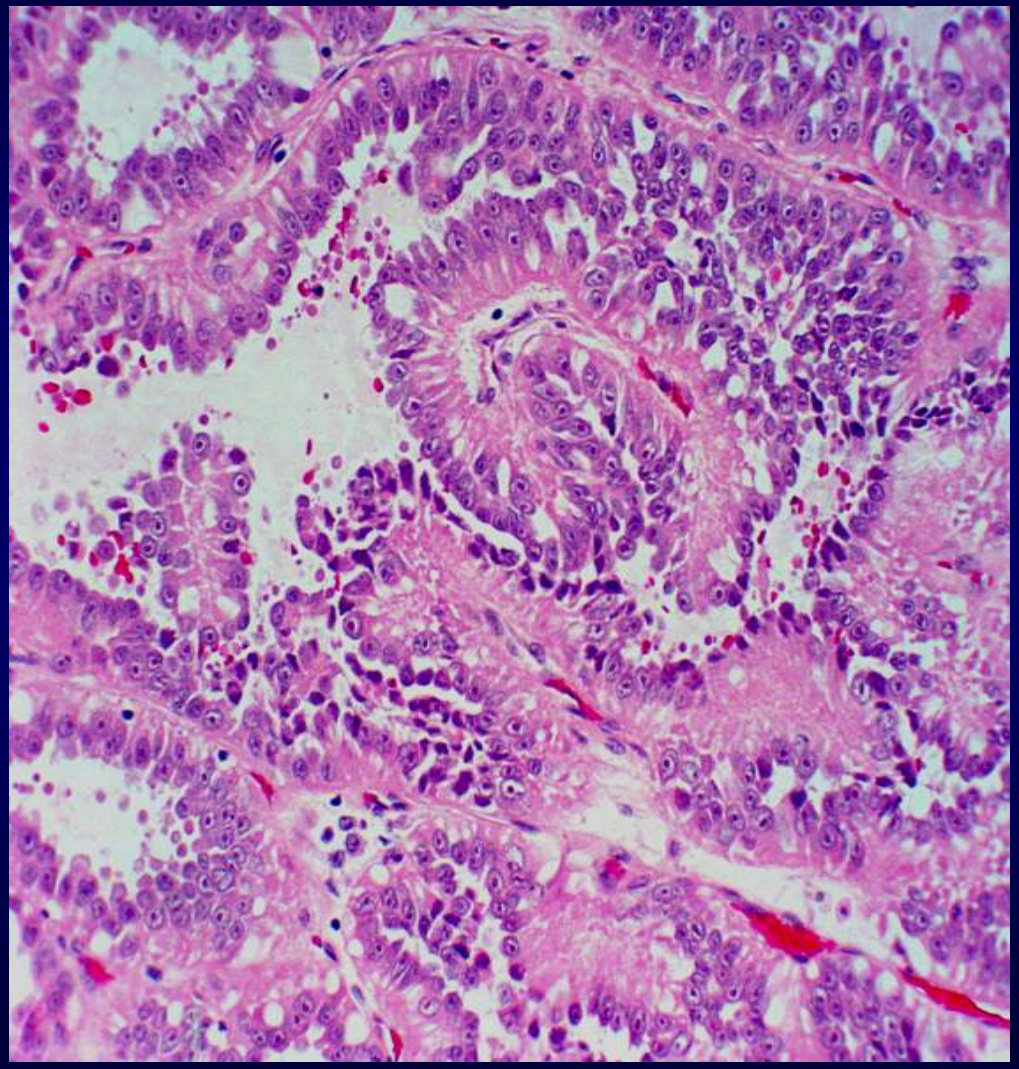





Sólido
Quístico

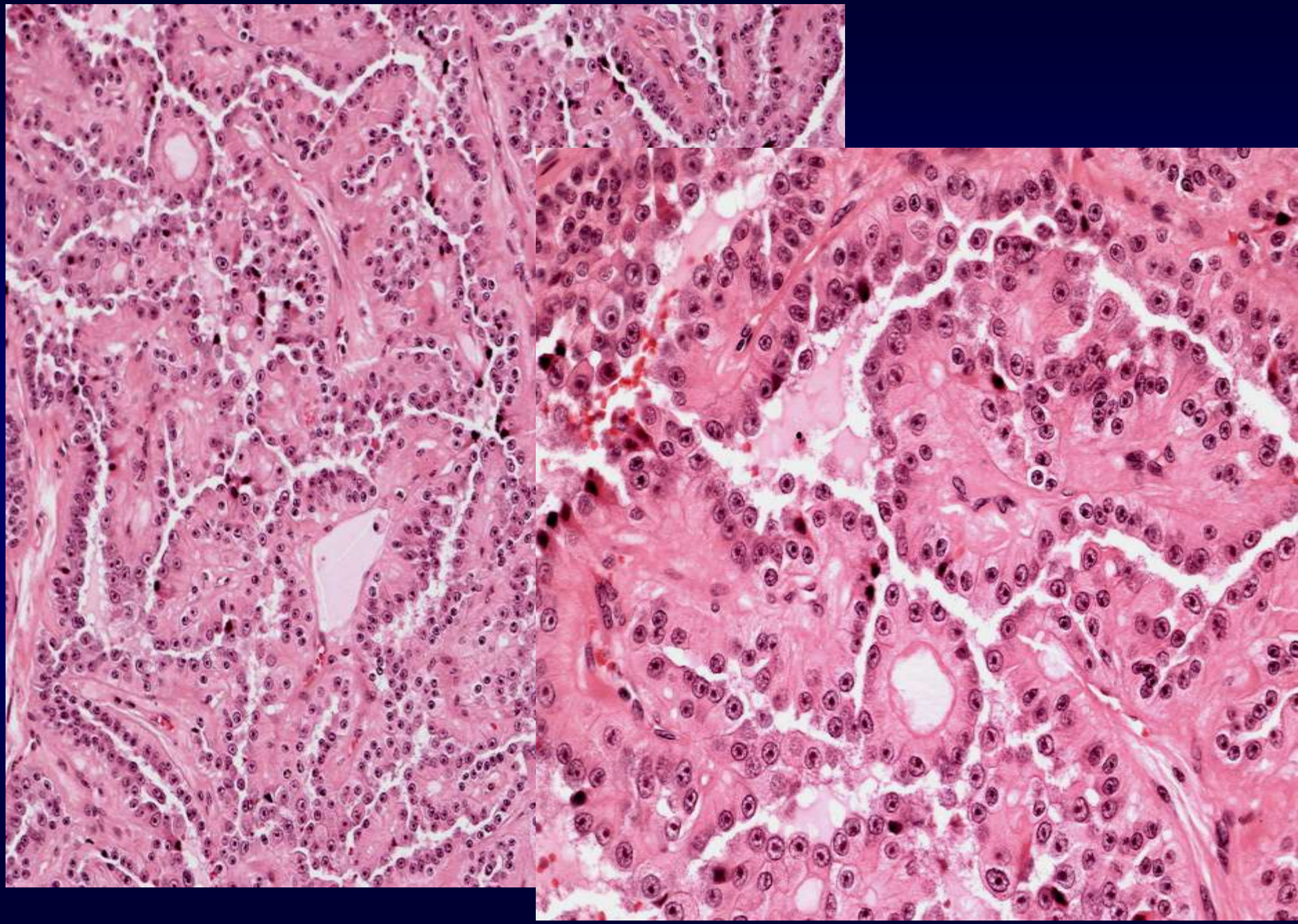


Patrones Histológicos

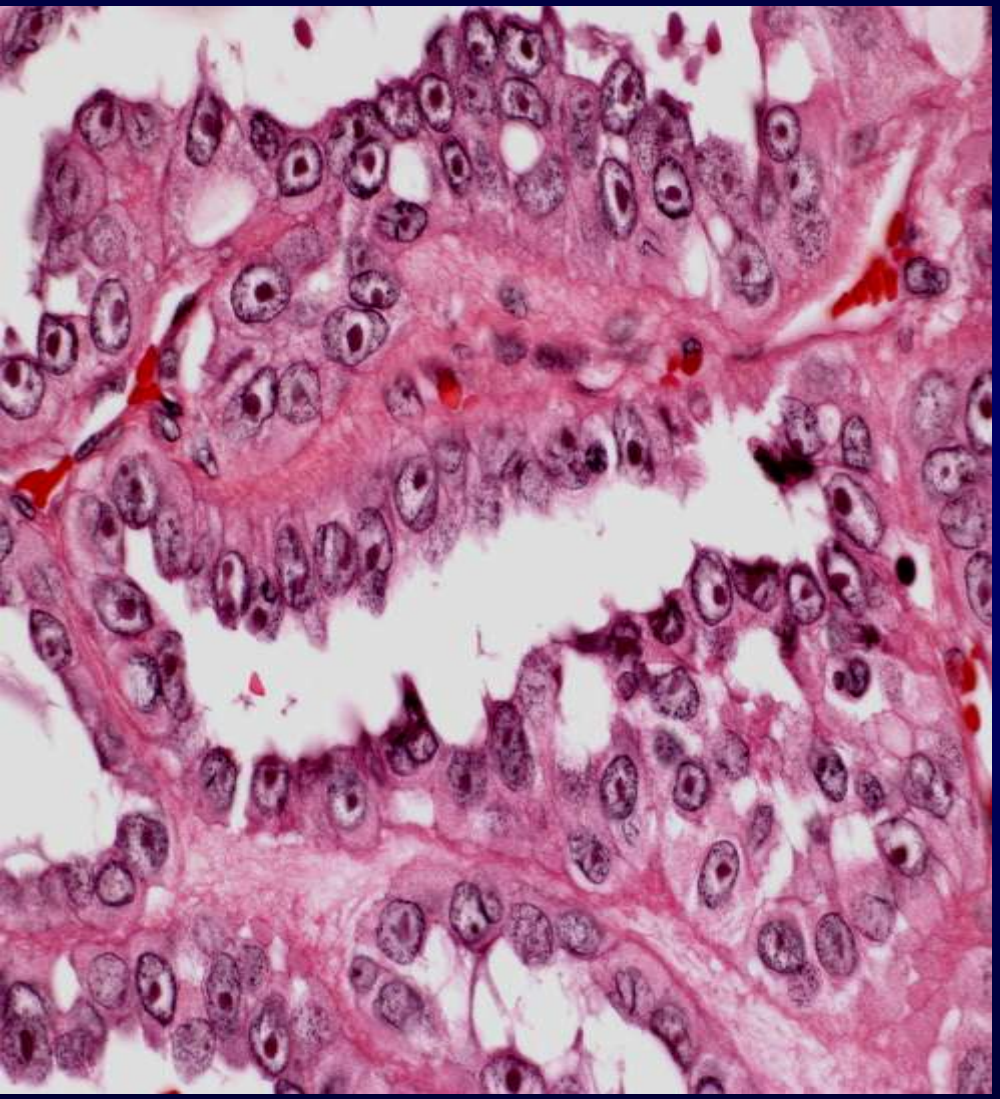


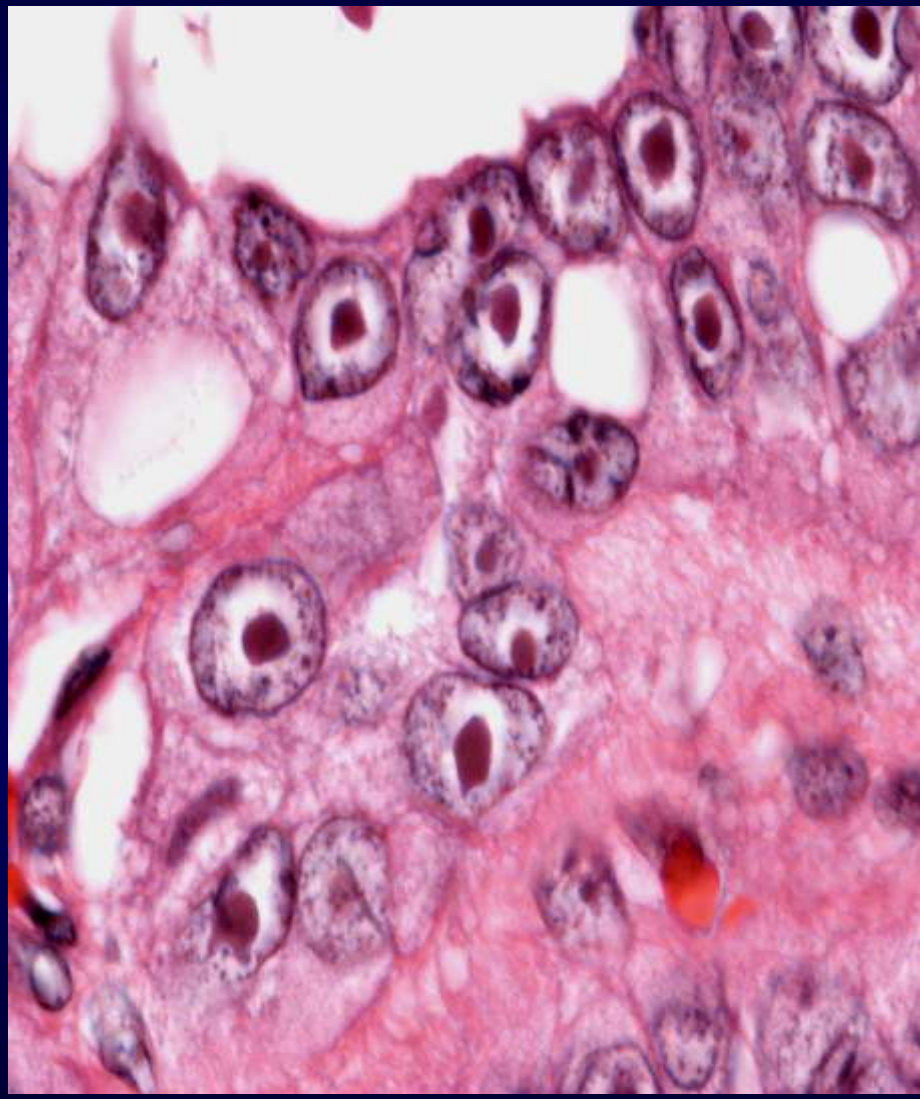
- Papilar
- Quistico
- Tubular
- Solid
- Cribriforme
- Mixto, con celulas claras

Merino MJ, Am J S P

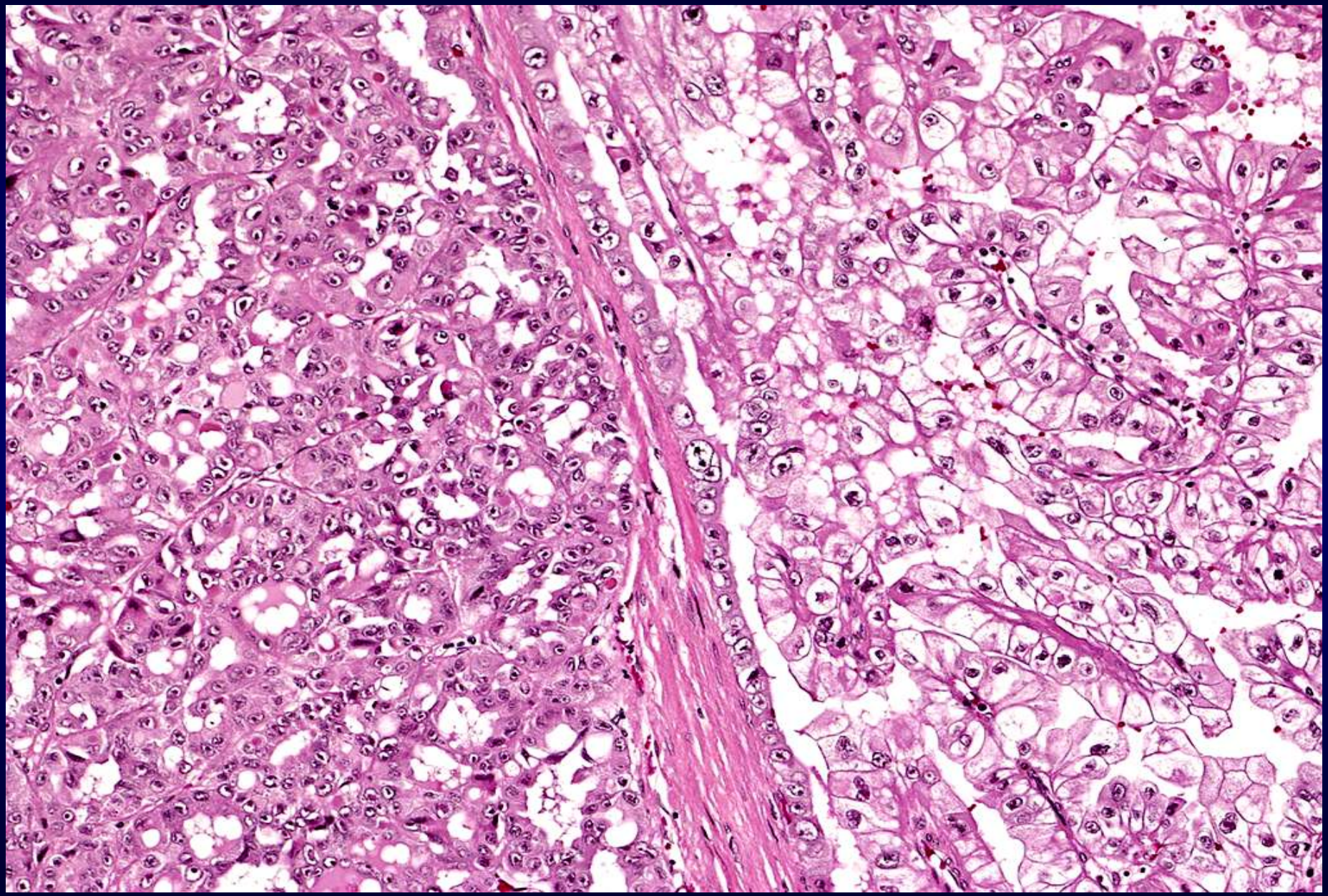


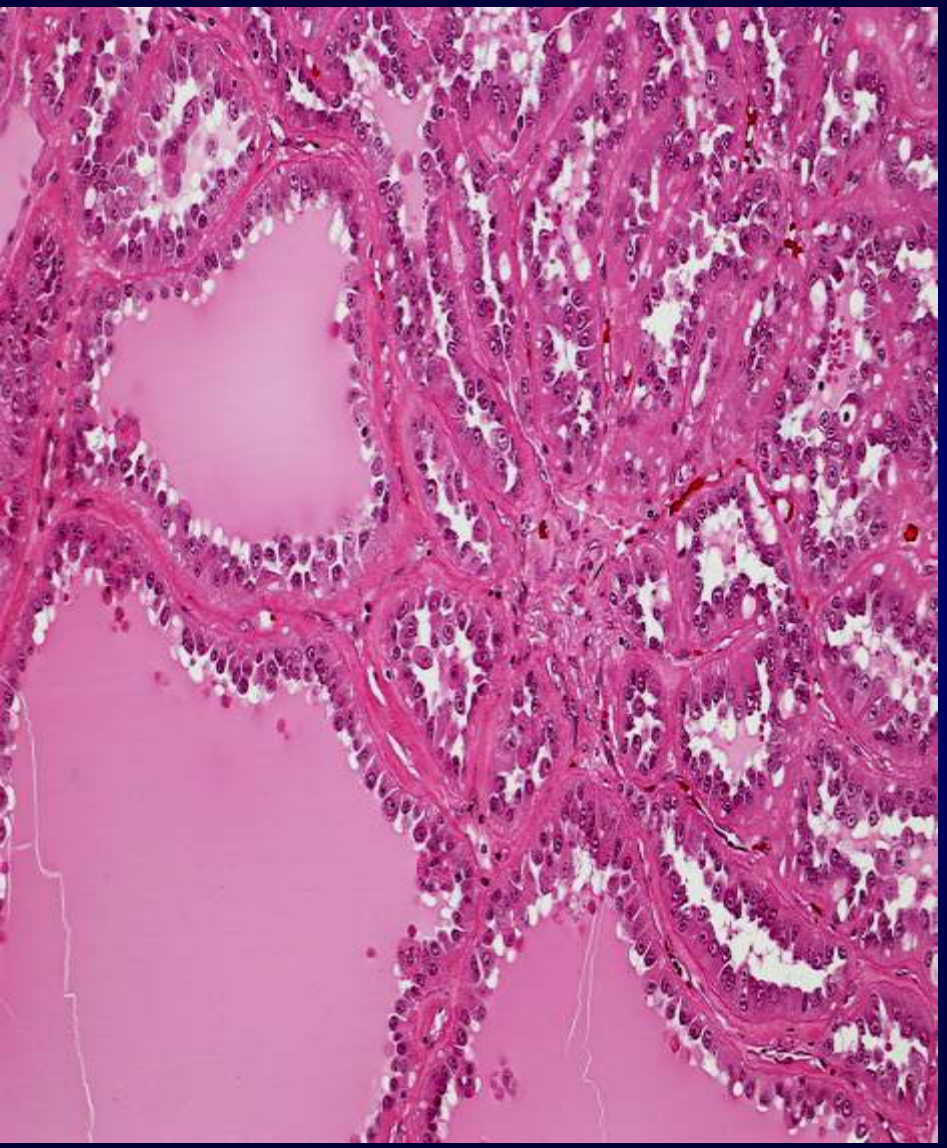
HLRCC

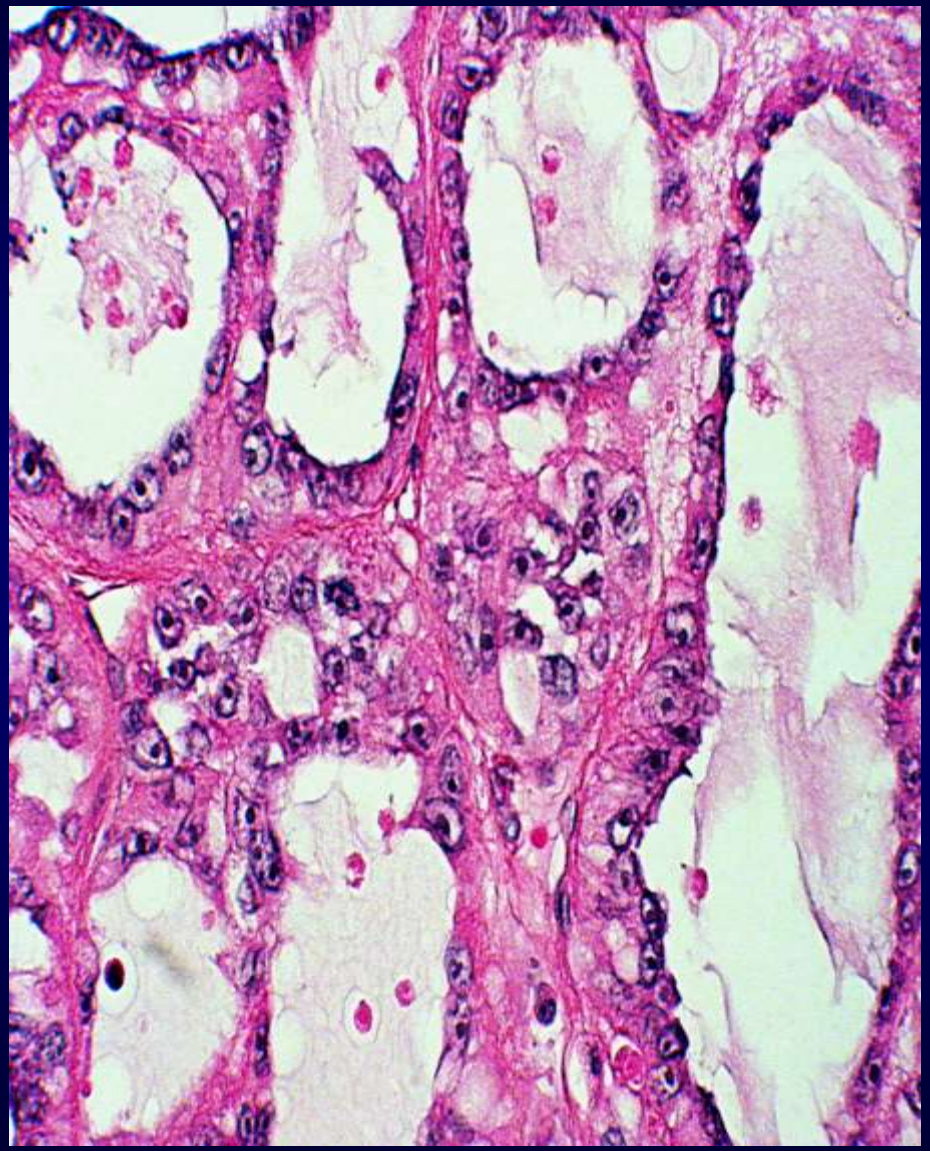




Mixed



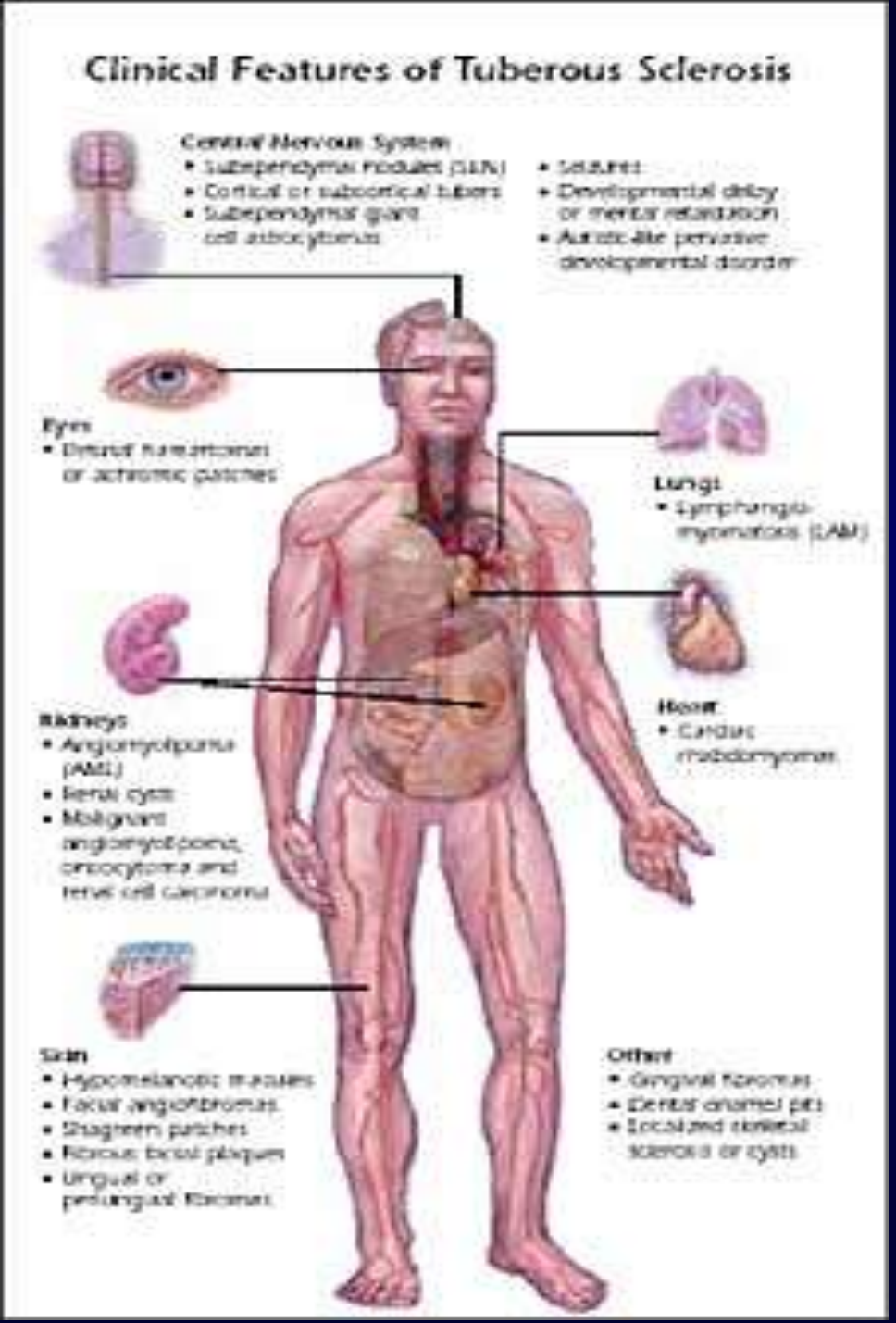


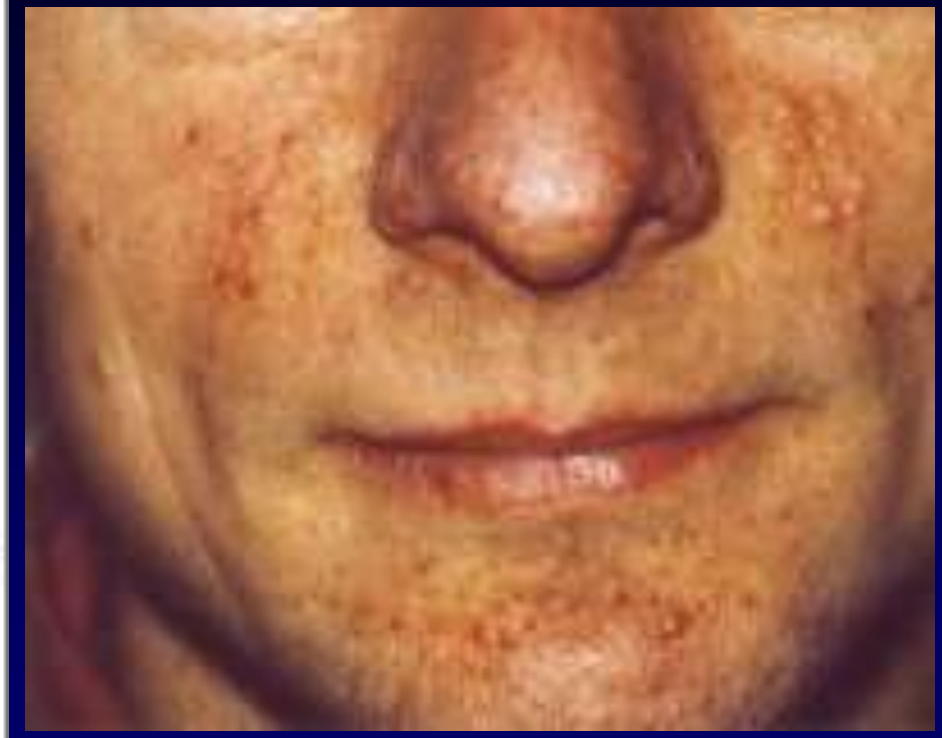


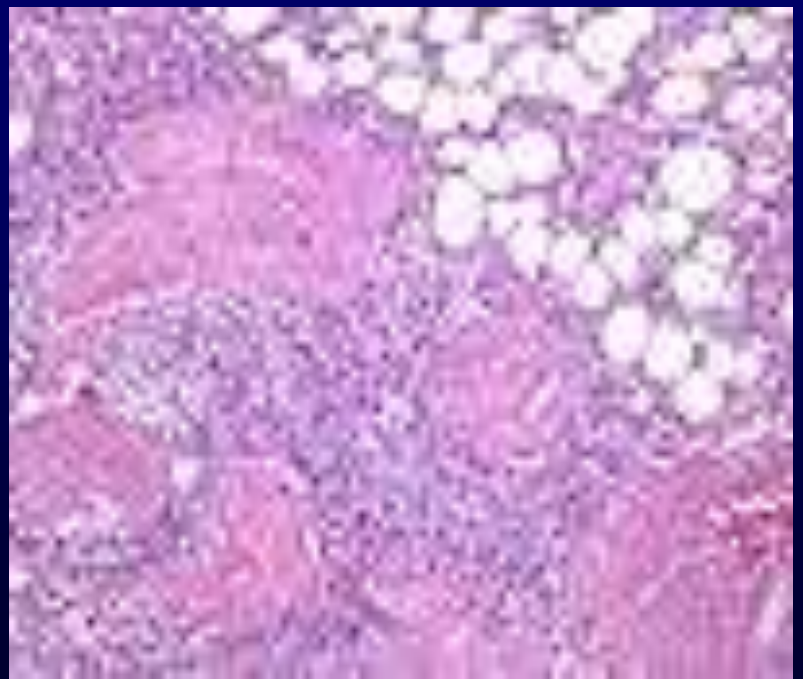
Terapia

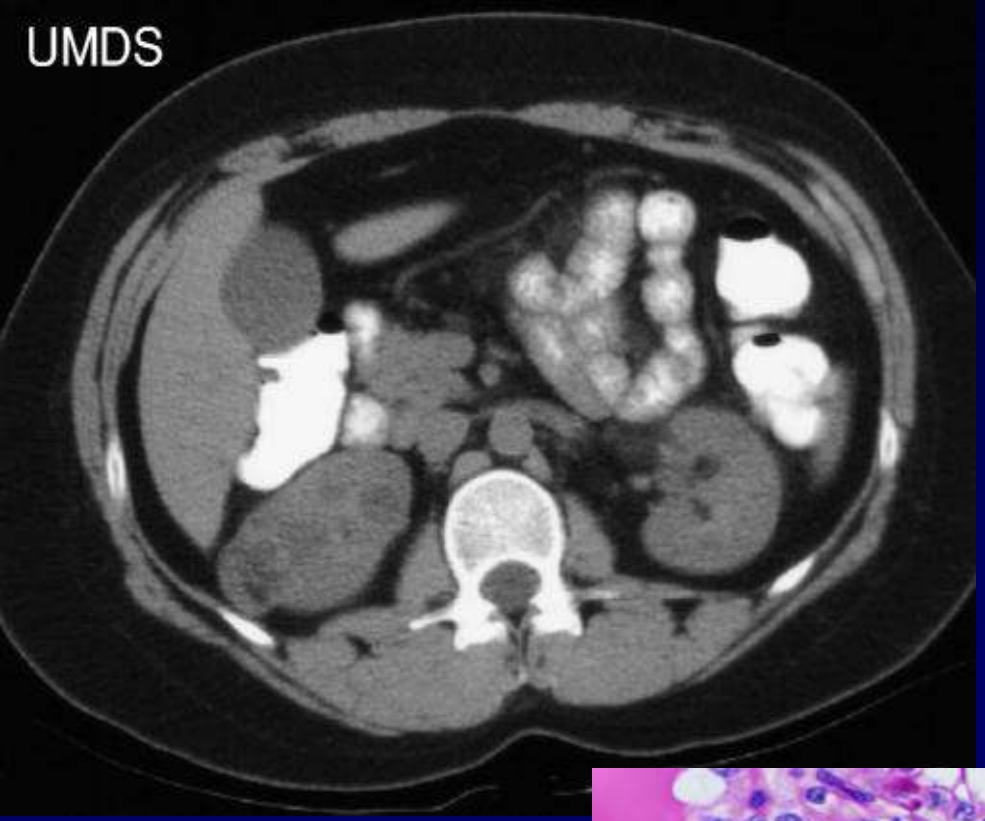
- Pacientes con HLRCC no responden a IL2. No hay buenas terapias, pero estos pacientes son candidatos para terapias experimentales.
- Reconocimiento de HLRCC con lleva a estudios geneticos y detección and resección de tumores en otrs miembros familiares.
- Prognostico pobre, 11/16 patients fallecieron en menos de tres años.

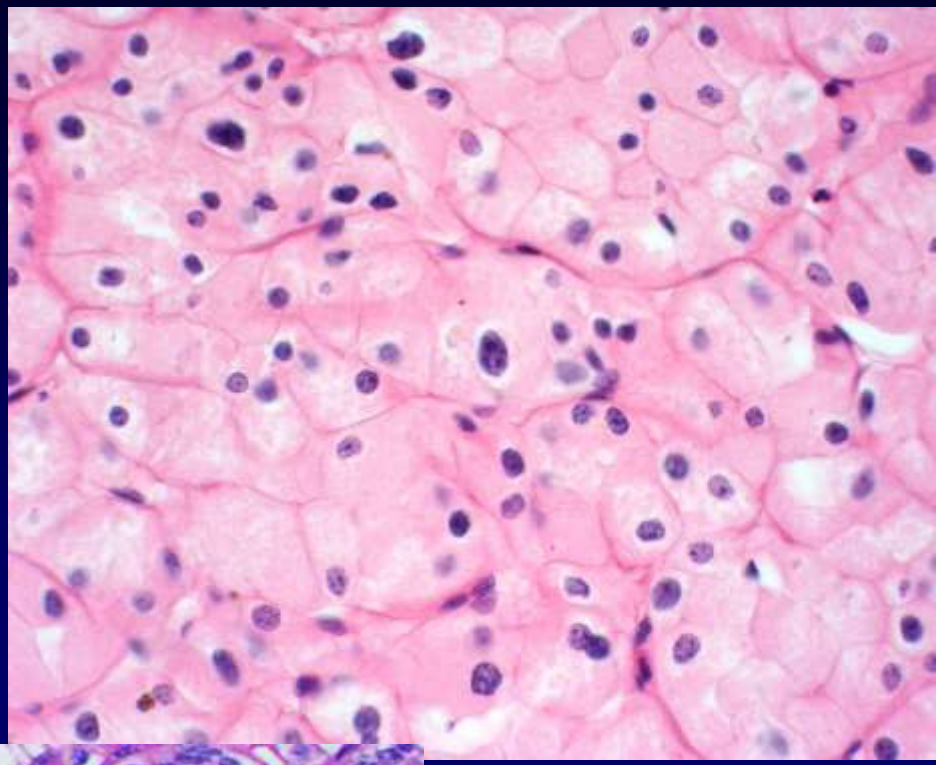
Clinical Features of Tuberous Sclerosis

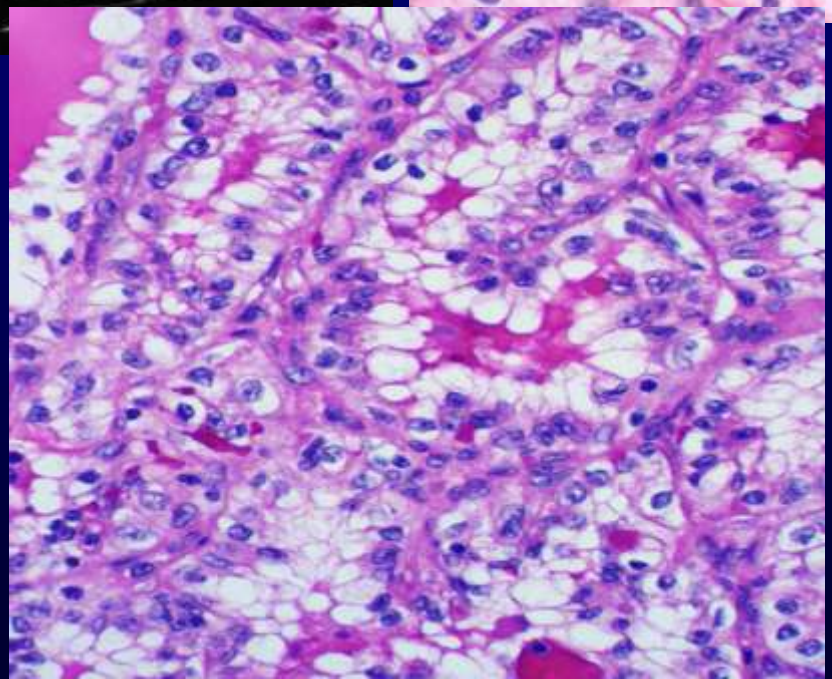







UMDS

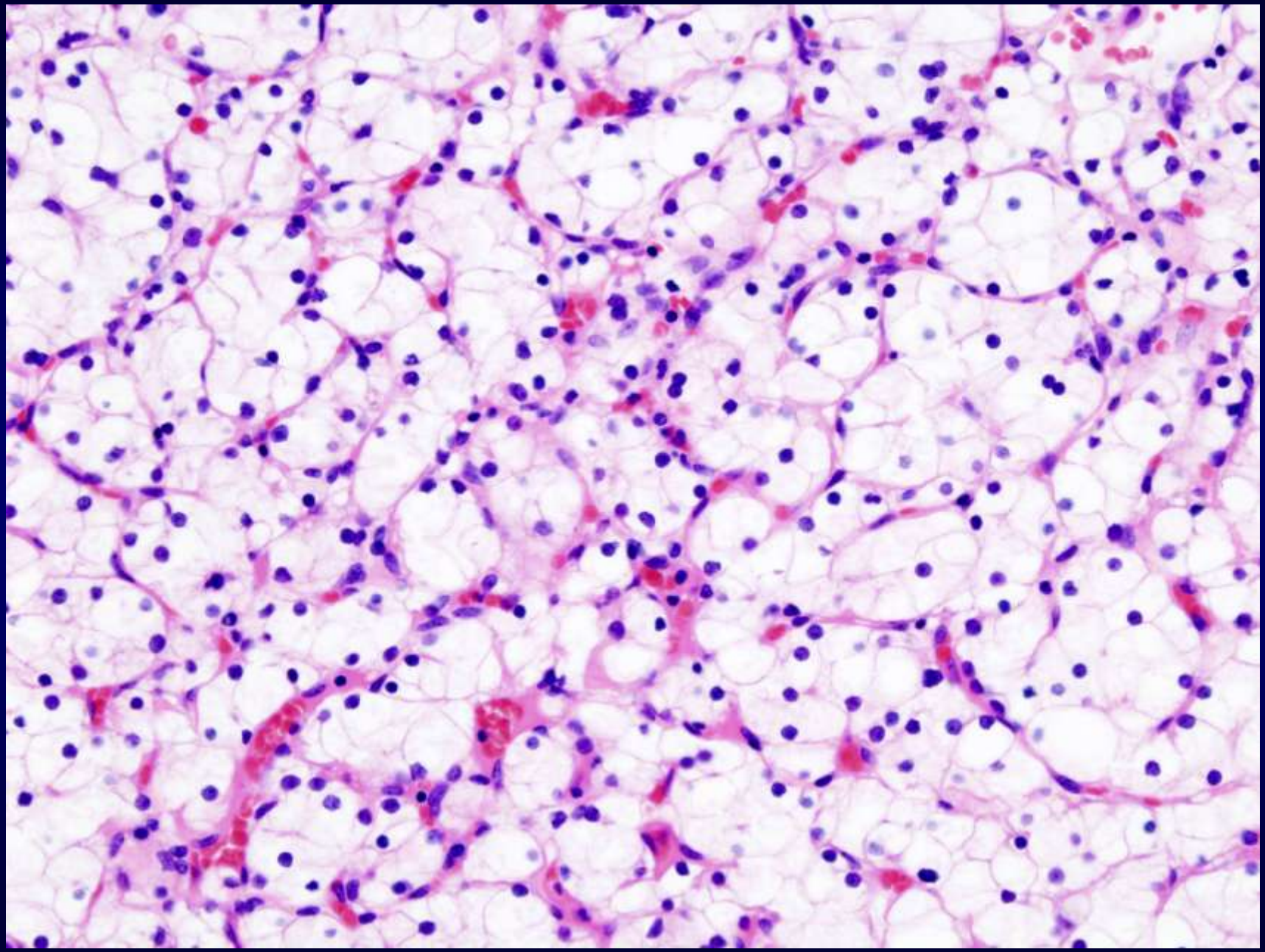


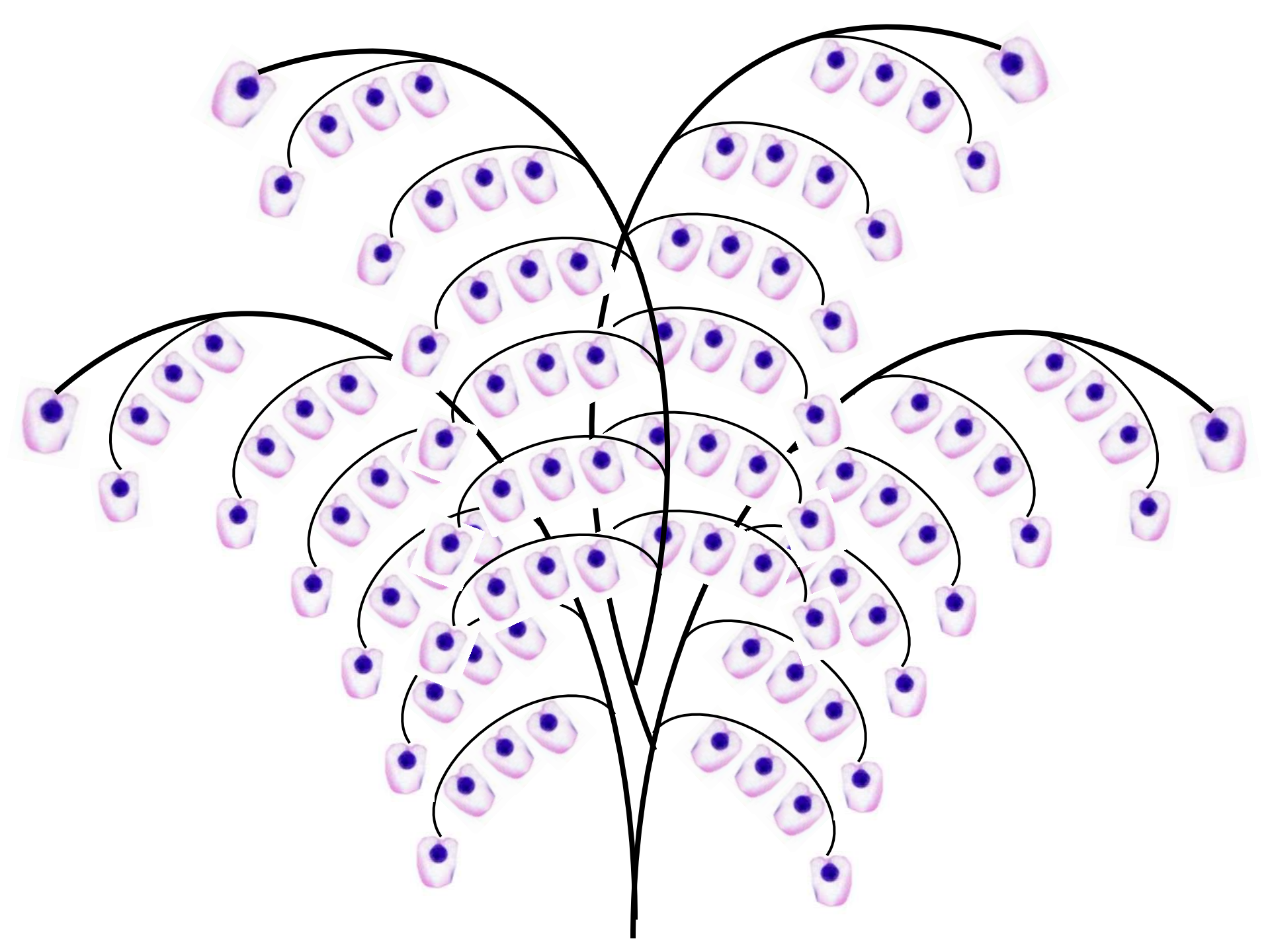


***The first step in the evaluation of families with FRC is a careful review of renal tumor pathology. Germline mutation analysis of renal carcinoma genes and clinical evaluation are guided mainly by the results of tumor pathology review*.**

BZbar

"Phenotype precedes genotype"





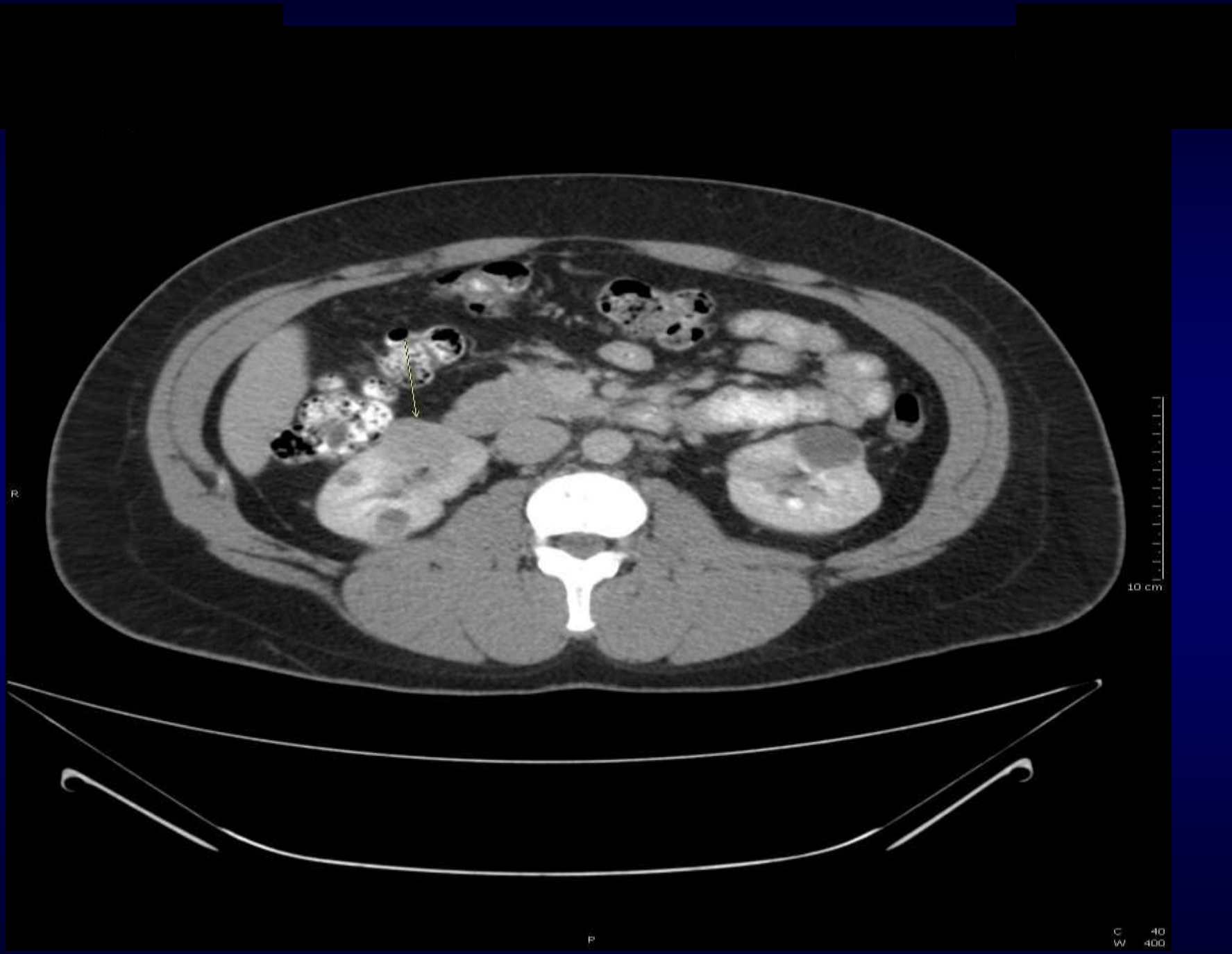
Disruption of the *TSC1 or TSC2 gene leads*

Sindromes Hereditarios

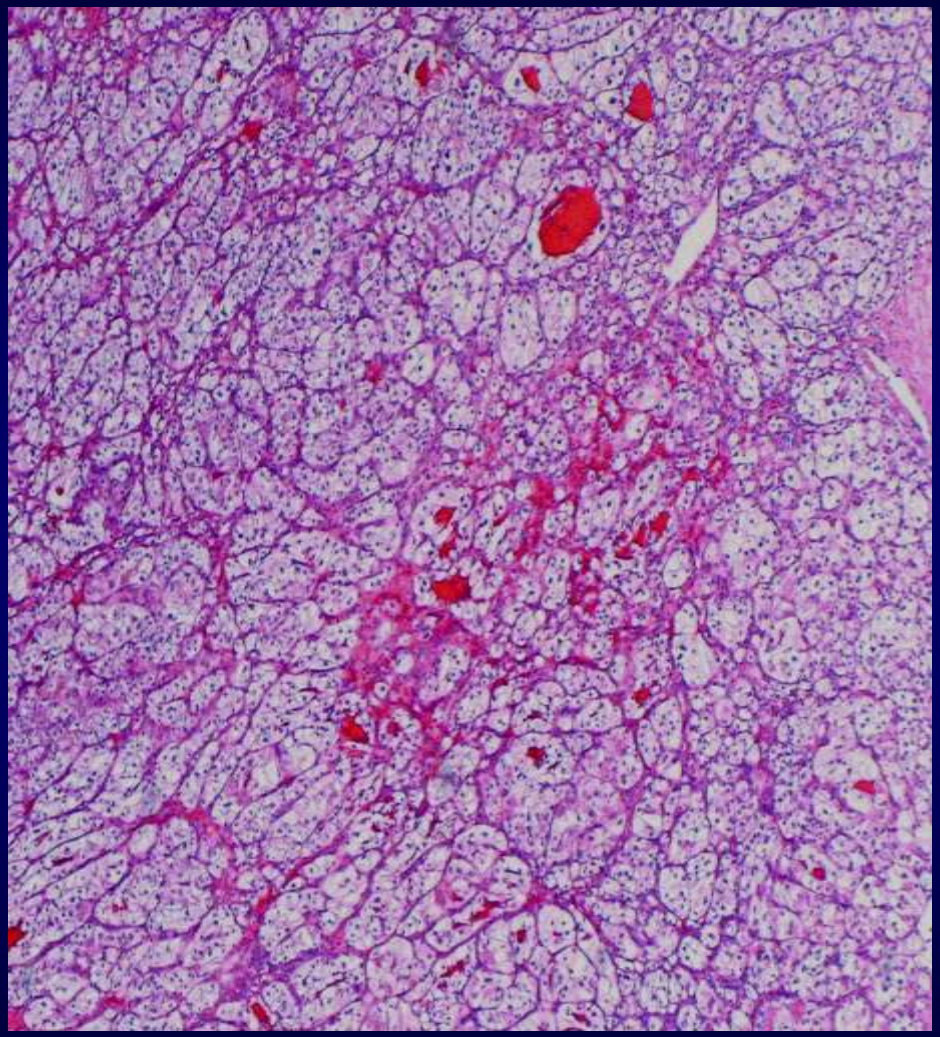
- Von Hippel-Lindau
- EsclerosisTuberosa
- Sindromes asociados a Wilm's

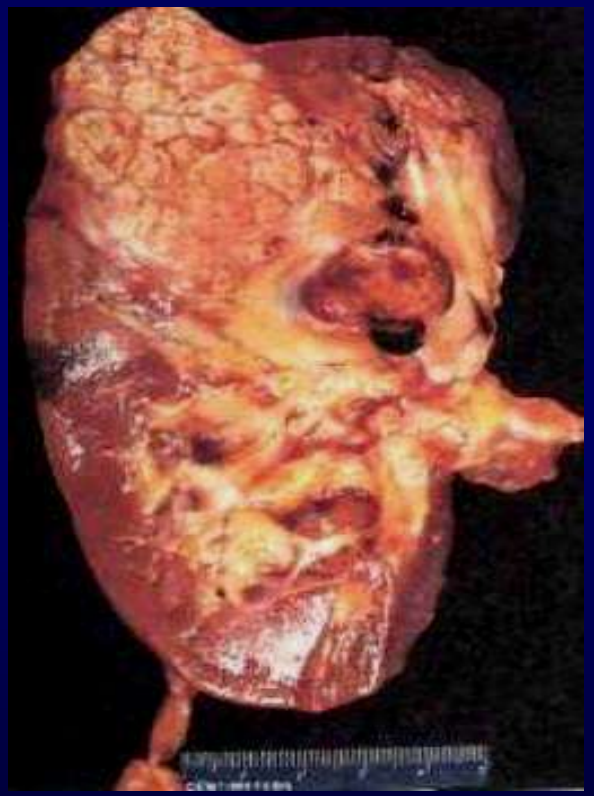
- Von Hippel-Lindau disease
- Papillary tipo I
- Birt-Hubb-Dube
- HLRCC
- Esclerosis Tuberosa
- SDH
- Sindromes asociados con Wilm's

Cancer de riñon es una enfermedad compleja

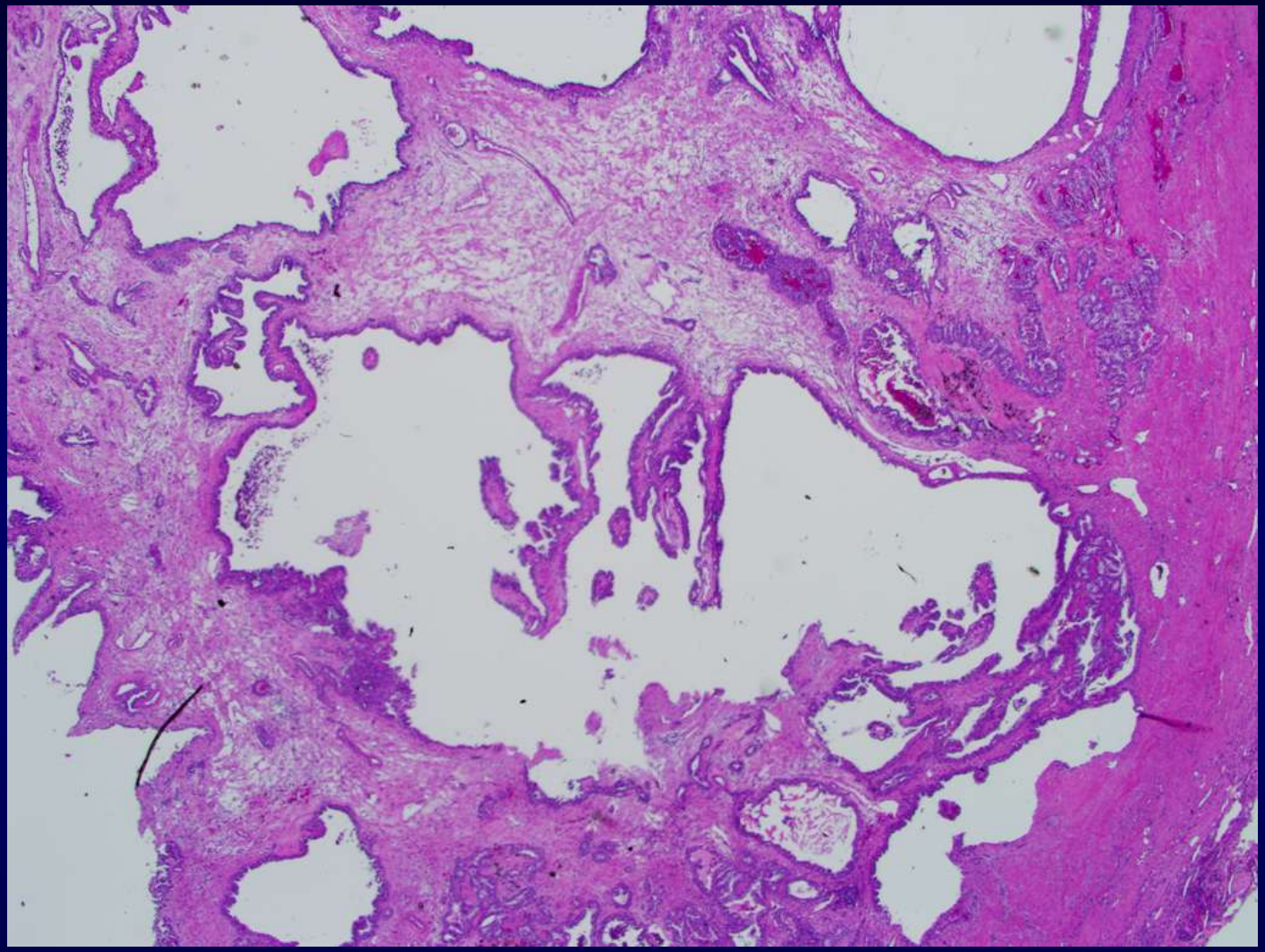

R
10 cm
P
C 40
W 400

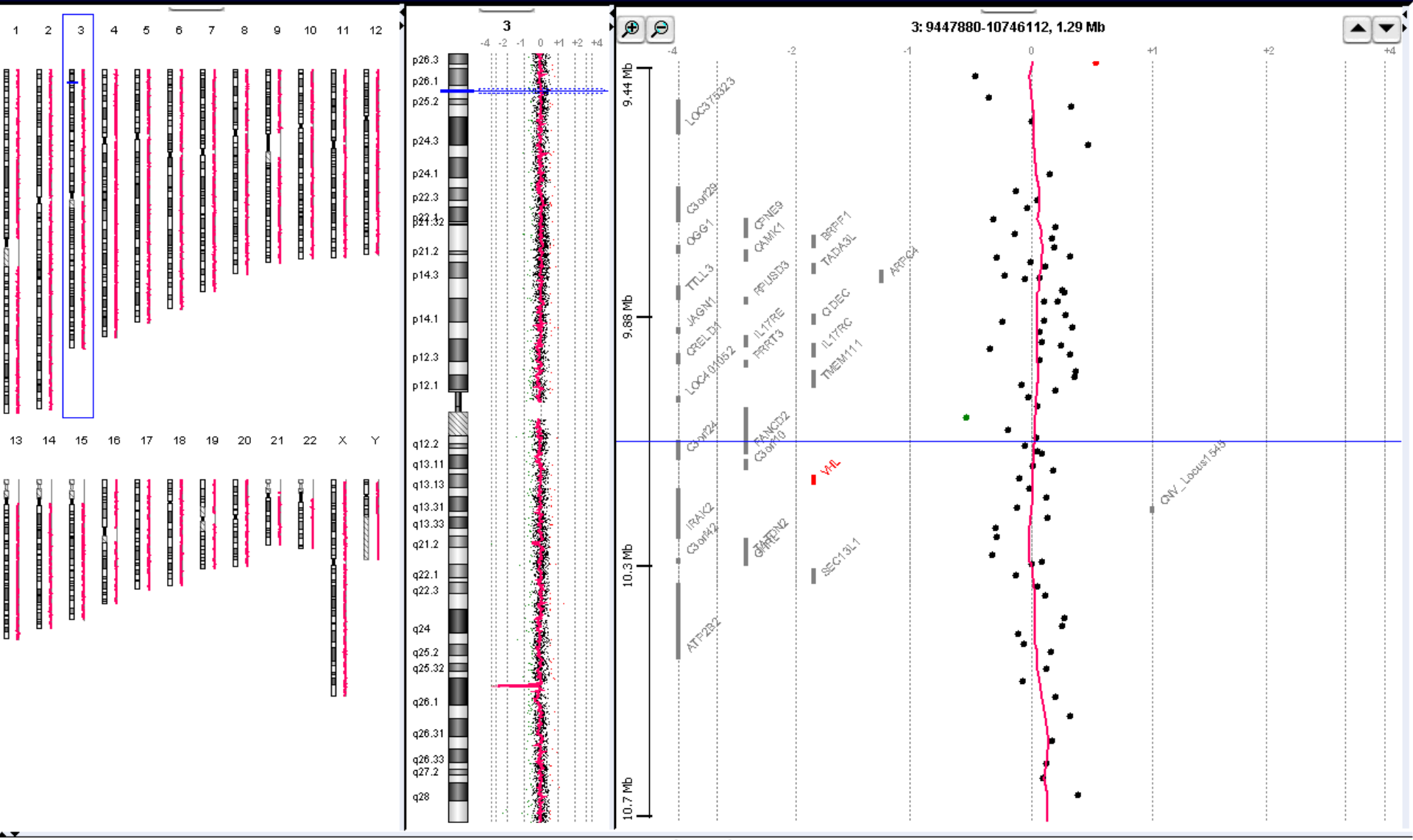
RCC Cel Claras





Identificar terapias nuevas



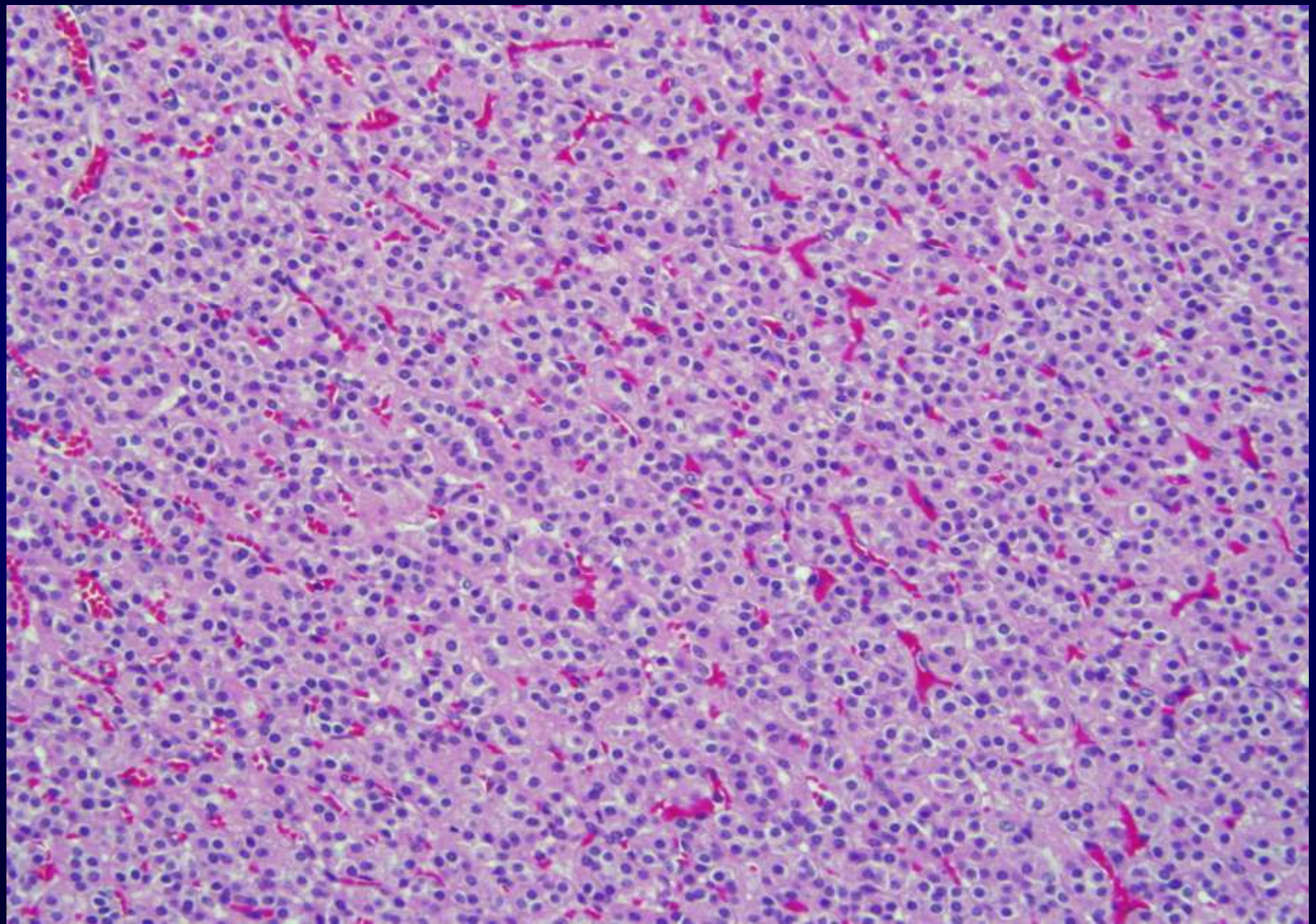


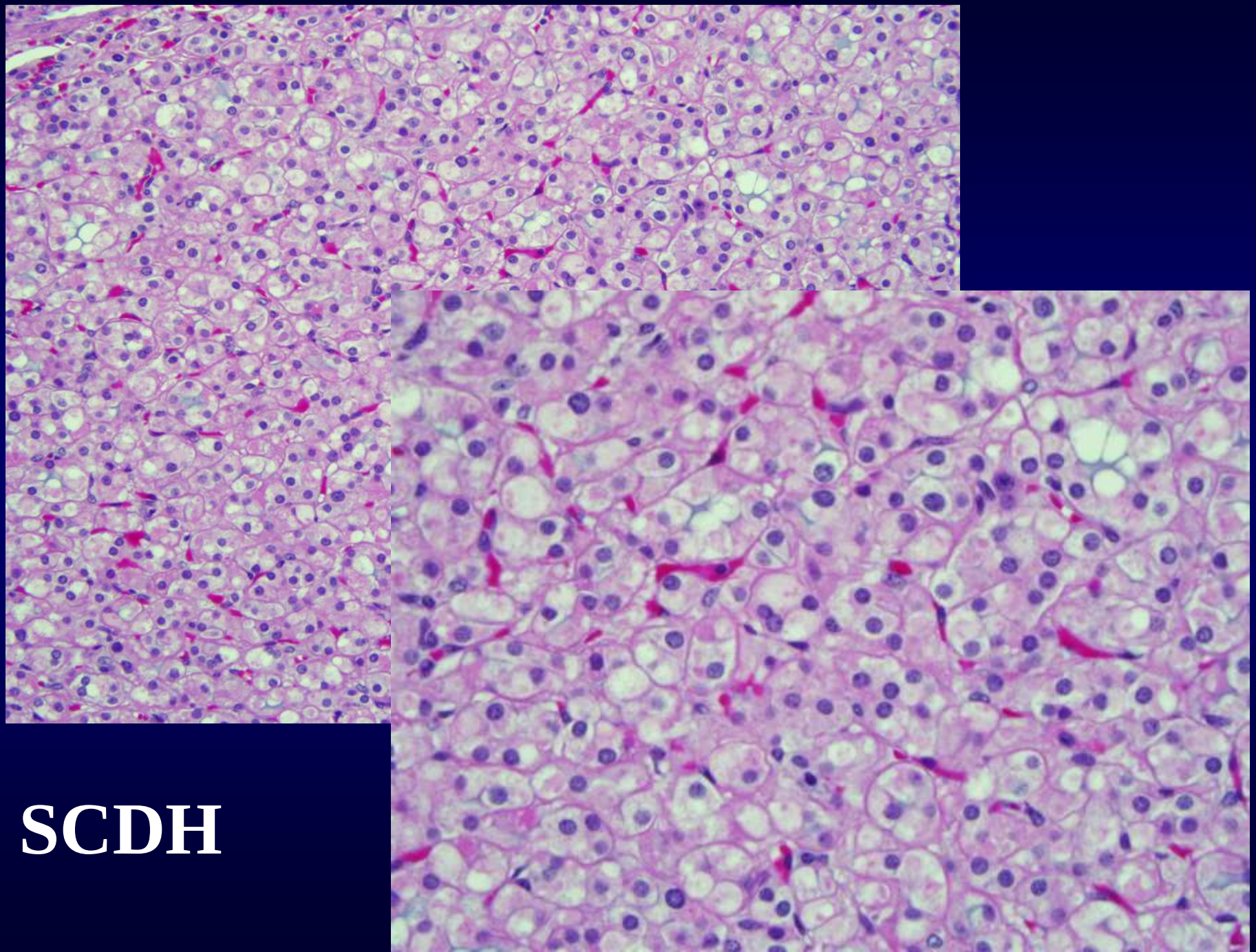
Arrays | Calibration Arrays

ProbeName	ChrName	Start	Stop	FeatureNum	Description	Name of Gene	Accession	US82400122_251469812749_Kidney
A_16_P361...	chr3	10103763	10103822	97734	Homo sapie...	FANCD2	ref|NM_001...	-0.039056923

CGH 014698 | Selected Arrays

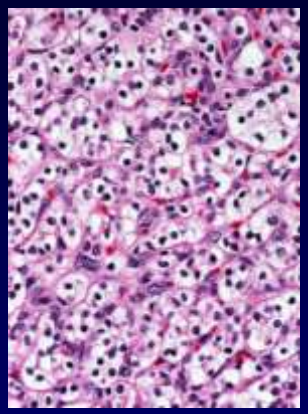
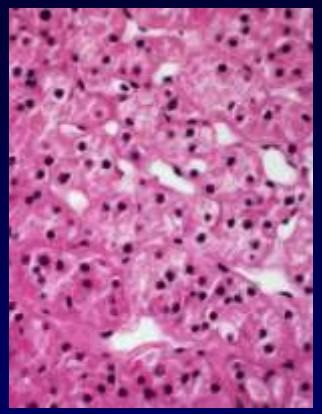
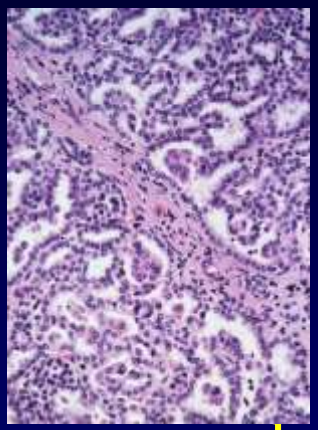
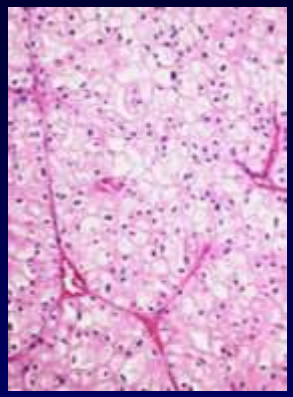
Paciente femenina de 35 años



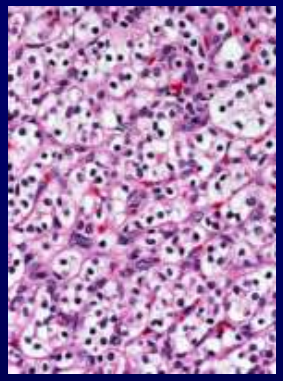
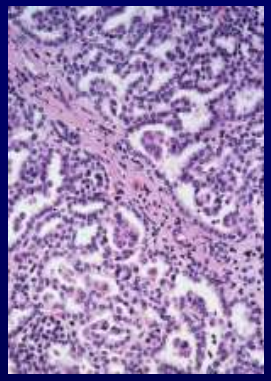
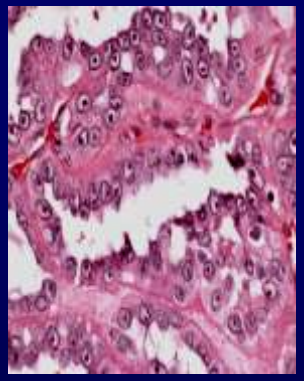
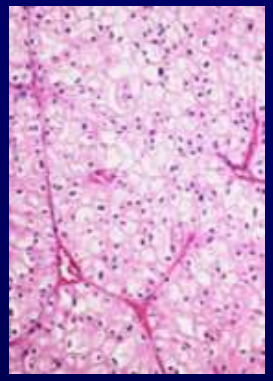
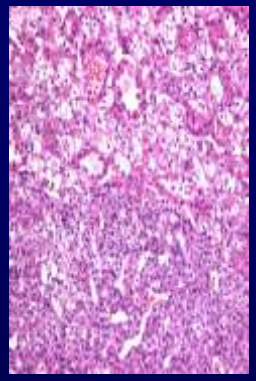
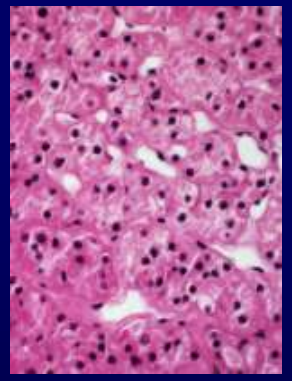


SCDH

En el comienzo…el cancer de riñon era sencillo

Necesitaremos clasificaciones nuevas basadas en cambios geneticos

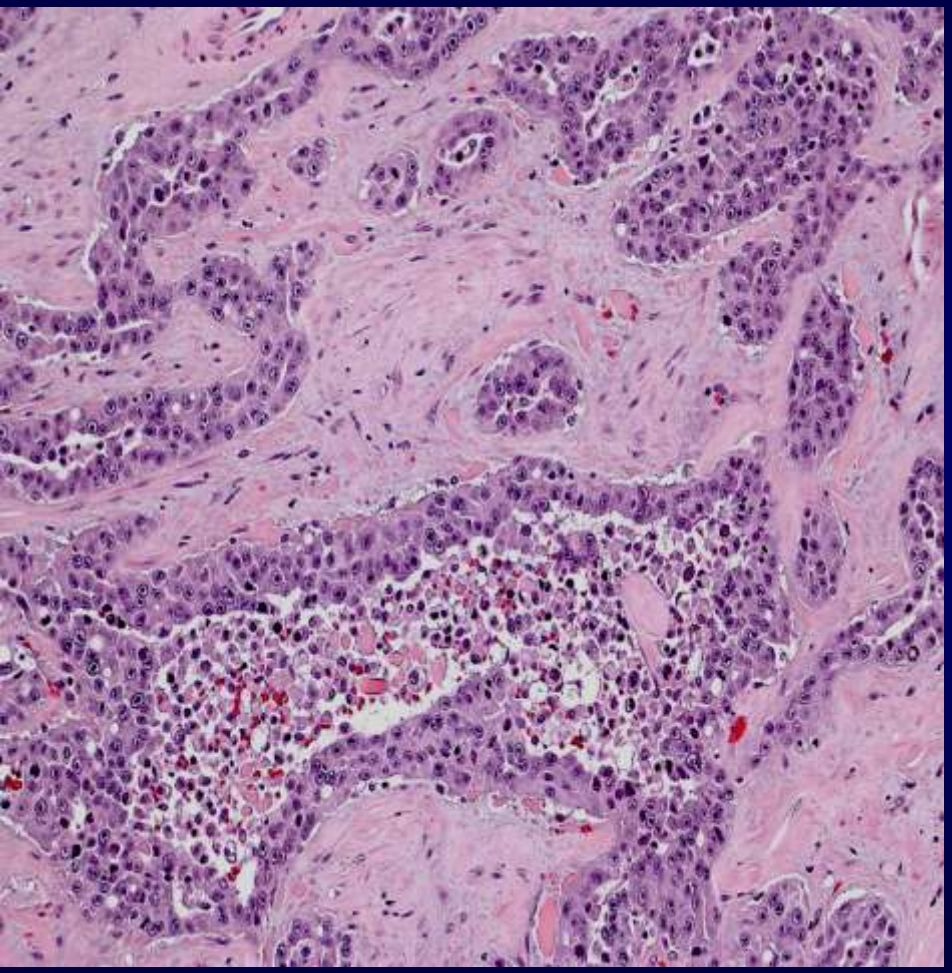







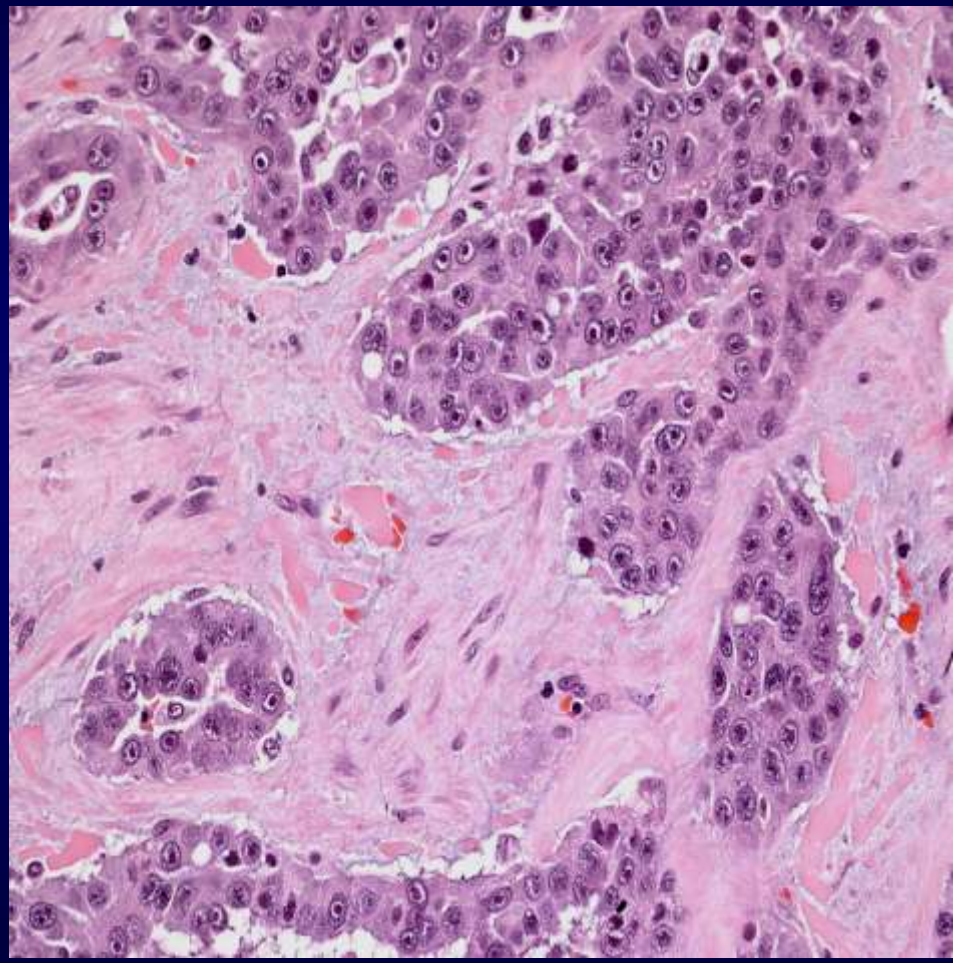
?

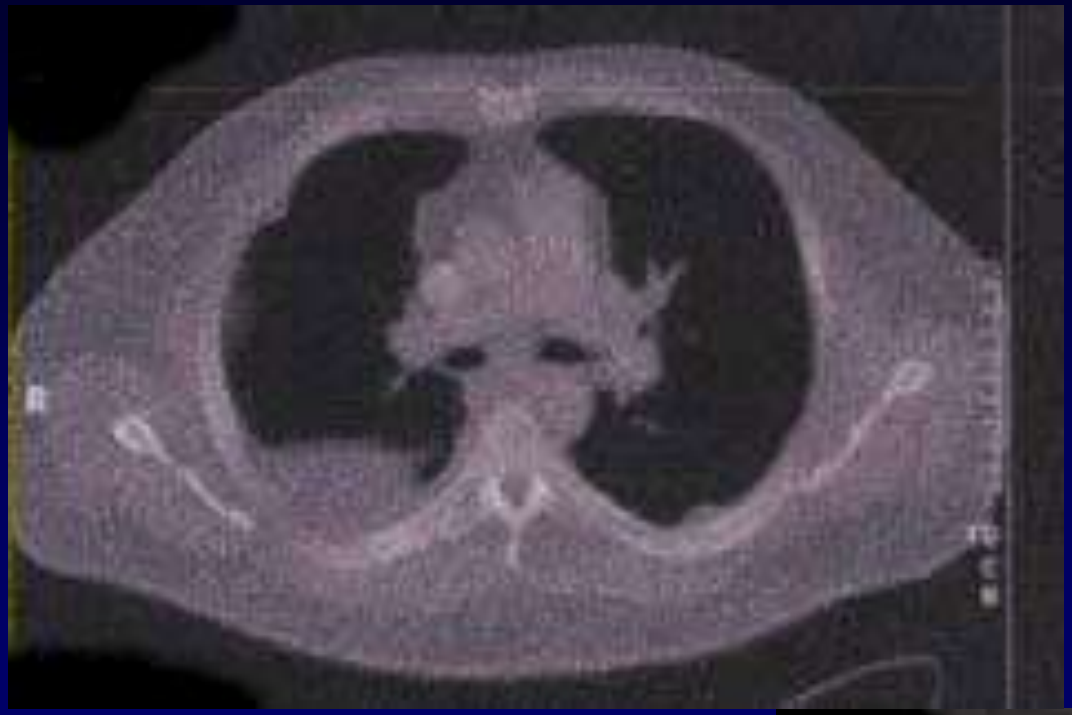
Clear Cell	Pap Type 1	HLRCC	Chromo	Hybrid	Oncocyto
H → VHL	Met	FH	BHD	BHD	BHD
E → VHL	Met	FH?	BHD?		BHD?

50 familias con

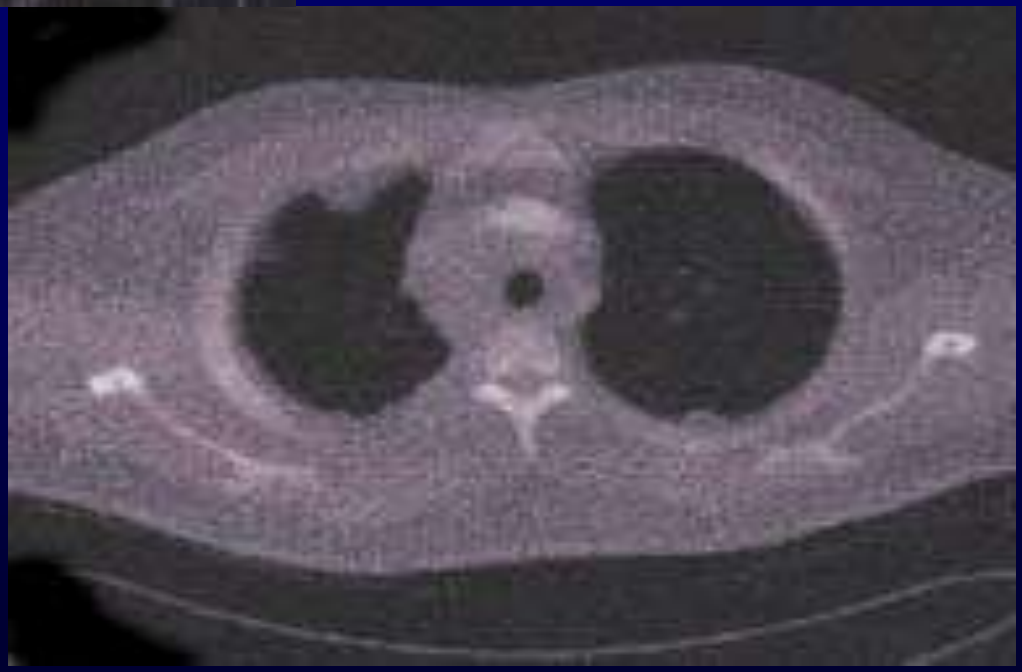
38 year old male with diffuse metastatic disease, diagnosed as RCC in Feb 2004.







MAY
Received therapy with Iressa (targets the receptor of the tyrosine Kinase activity of the EGF receptor



August 2005

Patient still doing well with disease June 2006