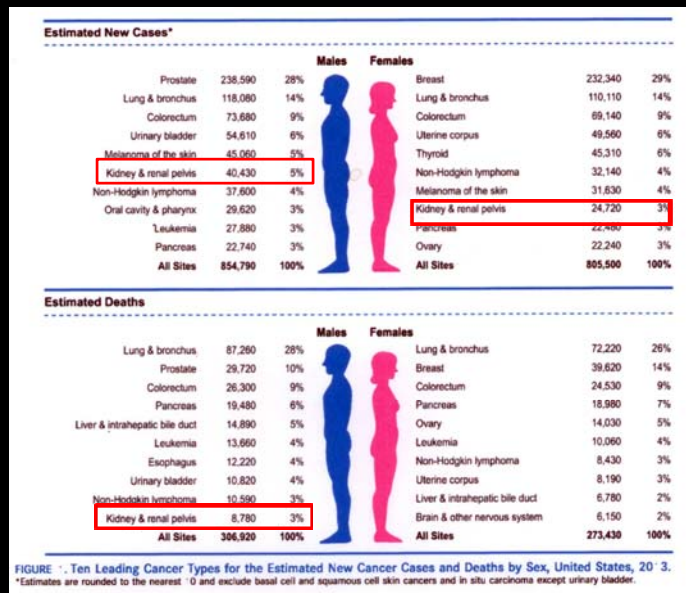


RENAL CELL CARCINOMA: THE 2012 ISUP VANCOUVER CLASSIFICATION



David Grignon MD, Indiana University, Indianapolis, IN

RENAL CELL CARCINOMA EPIDEMIOLOGY

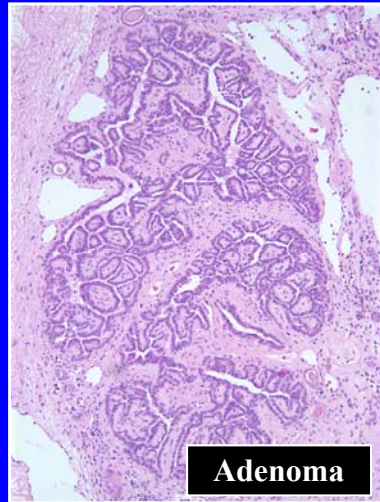


Siegel et al. CaA Cancer J Clin 63:11-30, 2013

EPITHELIAL KIDNEY TUMORS CLASSIFICATION (2004)

BENIGN

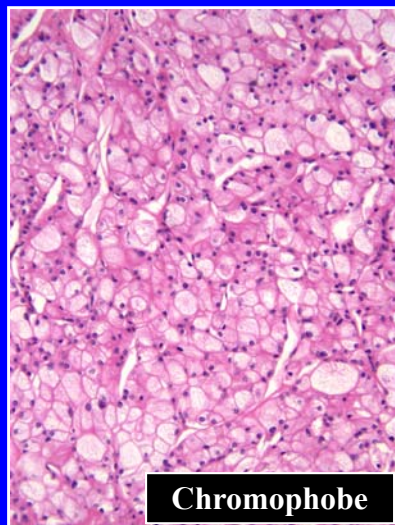
Papillary adenoma
Metanephric
adenoma
Metanephric
adenofibroma
Oncocytoma



EPITHELIAL KIDNEY TUMORS CLASSIFICATION (2004)

MALIGNANT

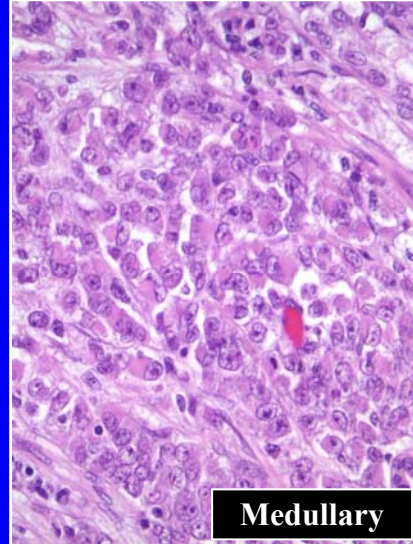
Clear cell
Multilocular cystic
Papillary
Type 1
Type 2
Chromophobe
Classic
Eosinophilic



EPITHELIAL KIDNEY TUMORS CLASSIFICATION (2004)

MALIGNANT

Collecting duct
Medullary
Mucinous tubular
and spindle cell
Xp11 translocation
carcinomas
Other specified
Unclassified



Medullary

2012 ISUP/VANCOUVER CLASSIFICATION

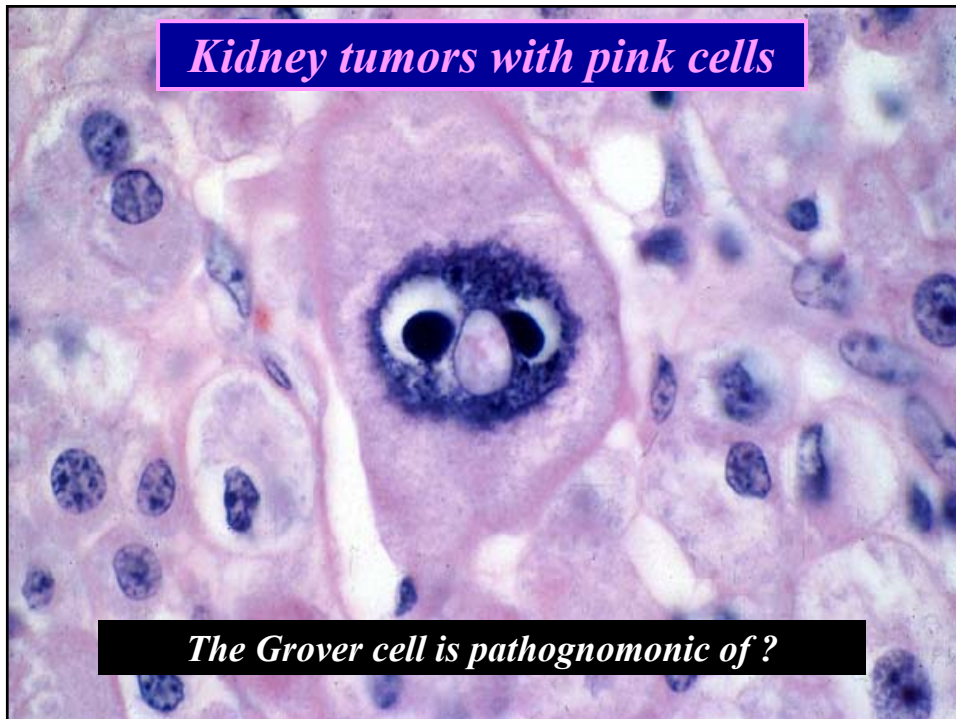
New Tumors Added - Modified

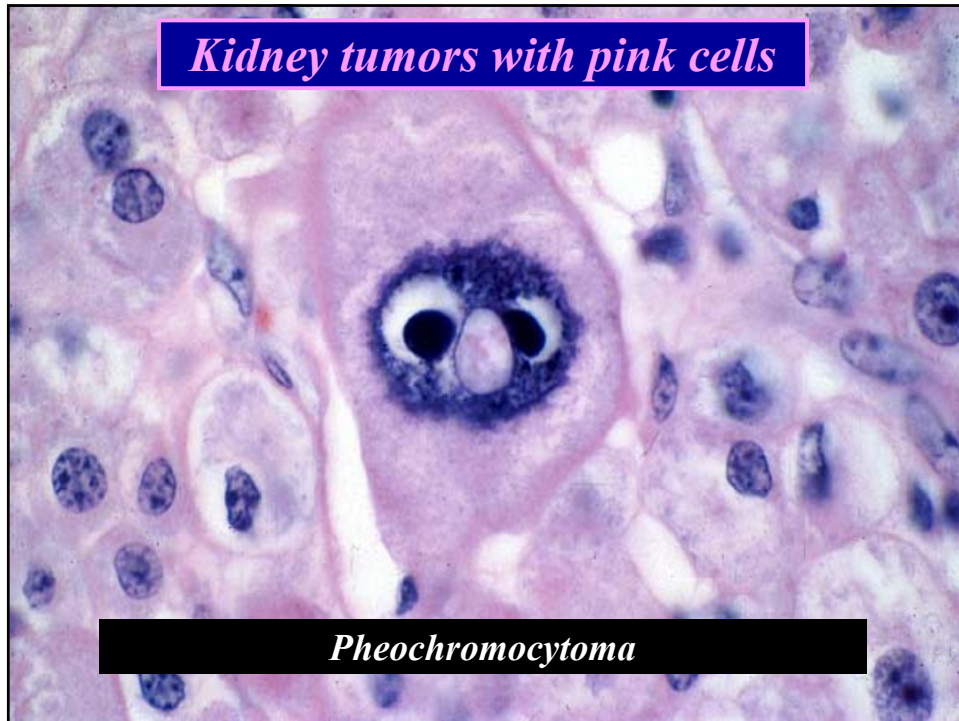
- Tubulocystic carcinoma
- Acquired cystic disease associated RCC
- Clear cell papillary RCC
- Specific hereditary types of RCC
 - Hereditary leiomyomatosis and RCC syndrome
- RCC with angioleiomyoma-like stroma (renal angioadenomatous tumor - RAT) – include in clear cell papillary RCC category
- t(6:11) RCC – include with other translocation associated carcinomas in the MiTF family
- Hybrid oncocytoma-chromophobe tumors – include as subset of chromophobe RCC

2012 ISUP CLASSIFICATION

Tumors Not Ready to be Added

- Specific hereditary types of RCC
 - Birtt-Hogg-Dube Syndrome
 - Succinate dehydrogenase related RCC
- Oncocytic papillary RCC
- ALK-translocation associated
- Thyroid-like follicular carcinoma
- Others

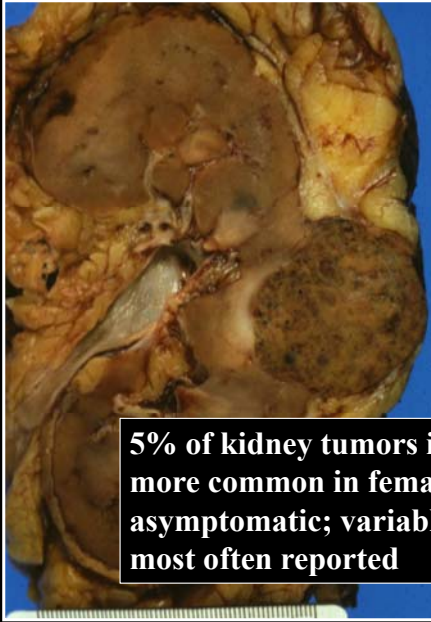




DIFFERENTIAL DIAGNOSIS

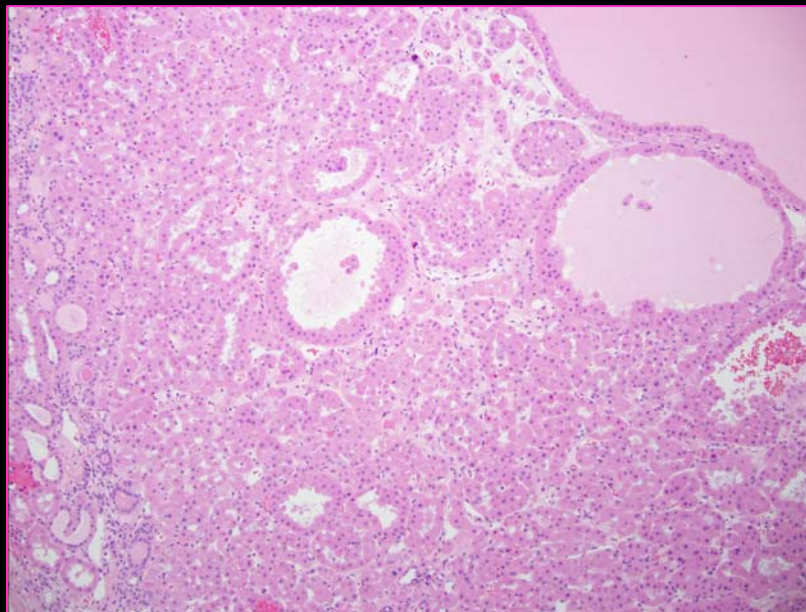
ONCOCYTOMA
CHROMOPHOBE RCC
CLEAR CELL RCC
UNCLASSIFIED RCC
PAPILLARY RCC
COLLECTING DUCT CA
TRANSLOCATION CARCINOMAS
SDHB ASSOCIATED RCC
EPITHELIOID ANGIOMYOLIPOMA

RENAL ONCOCYTOMA

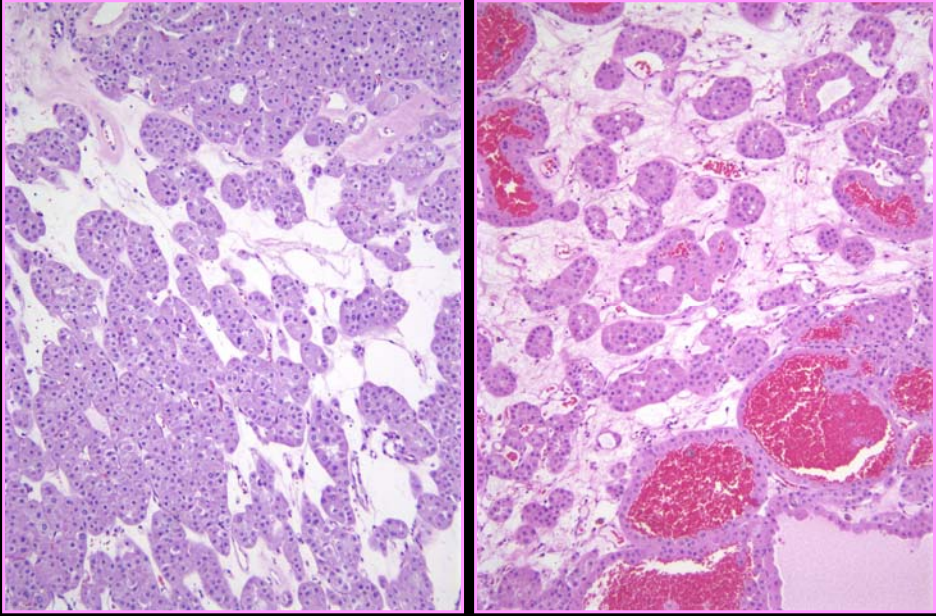


5% of kidney tumors in adults; wide age range; more common in females (2-3:1); majority are asymptomatic; variable cytogenetics: -1 and -Y most often reported

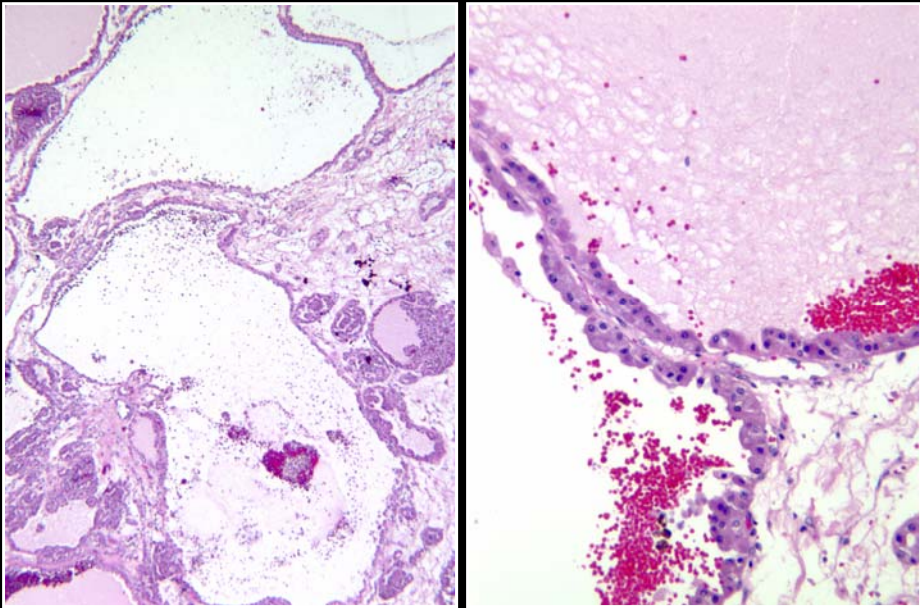
RENAL ONCOCYTOMA



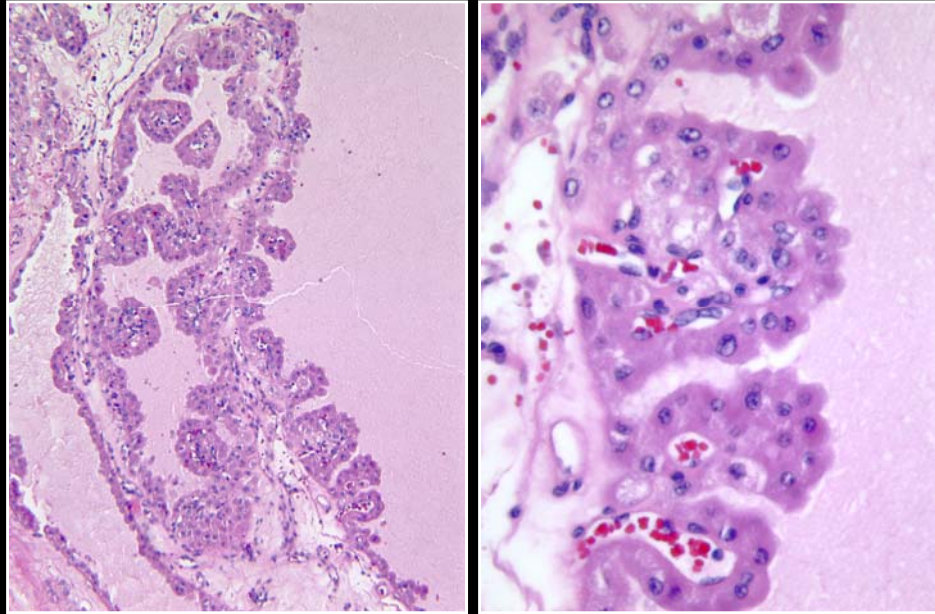
RENAL ONCOCYTOMA



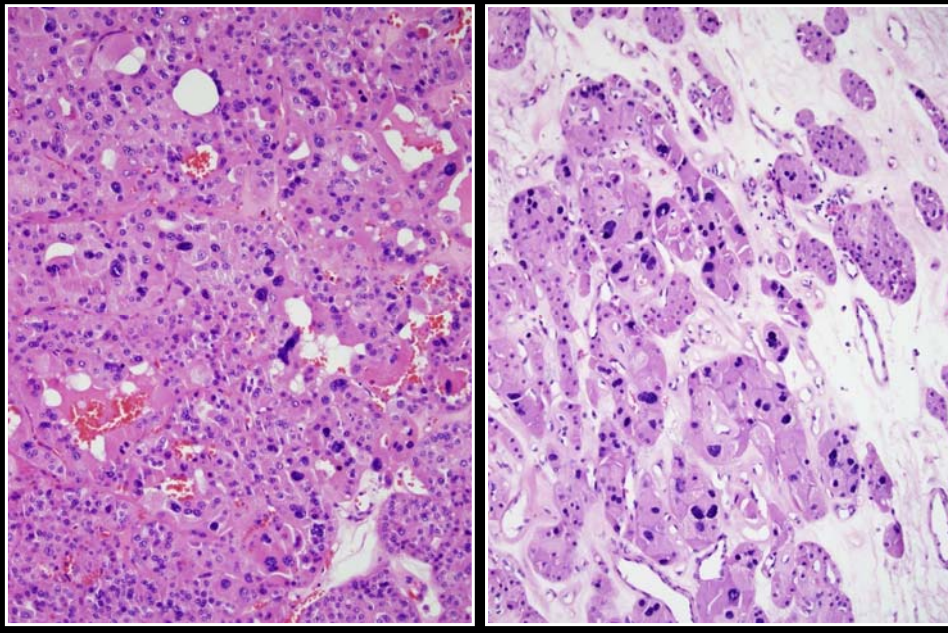
CYSTIC CHANGE



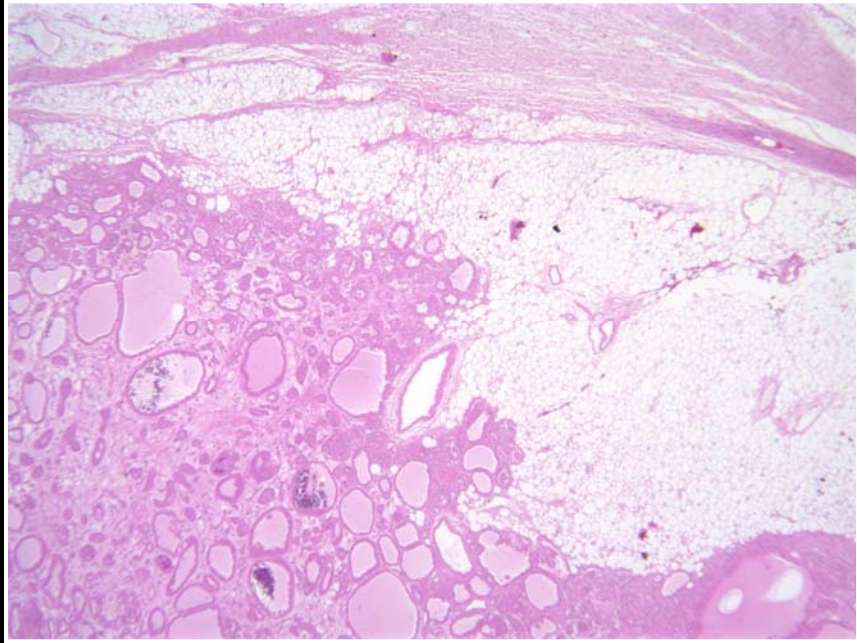
PAPILLARY ARCHITECTURE



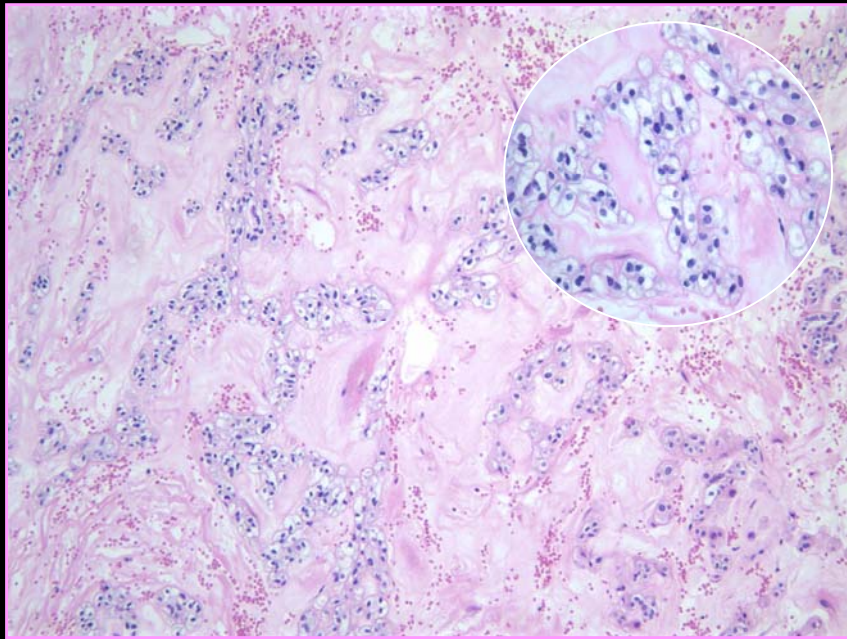
NUCLEAR PLEOMORPHISM



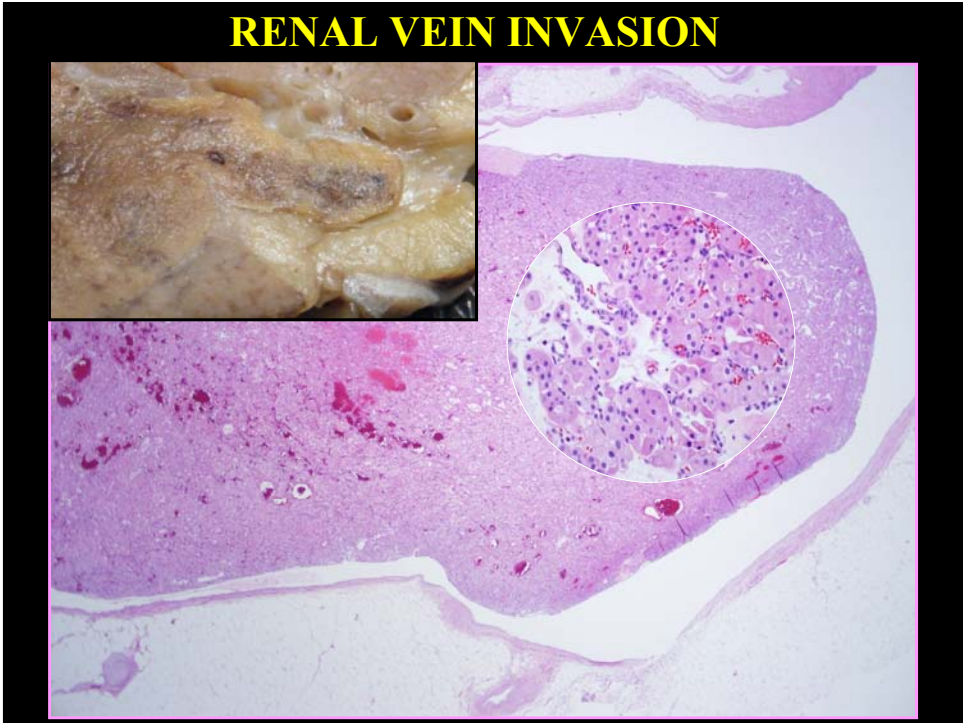
PERINEPHRIC FAT INVASION



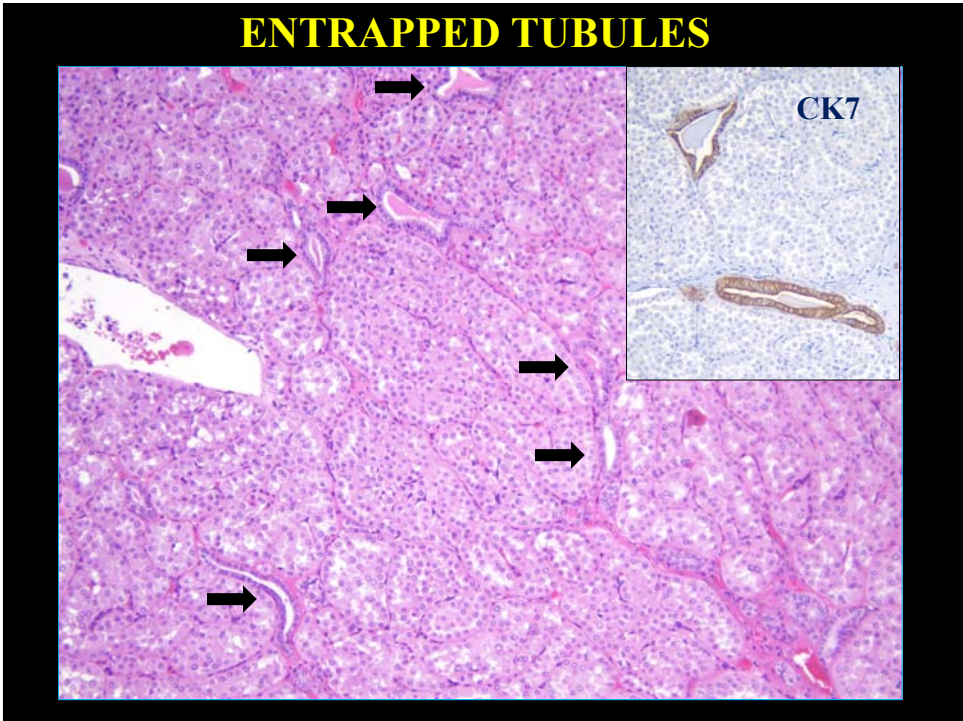
CLEAR CELL CHANGE



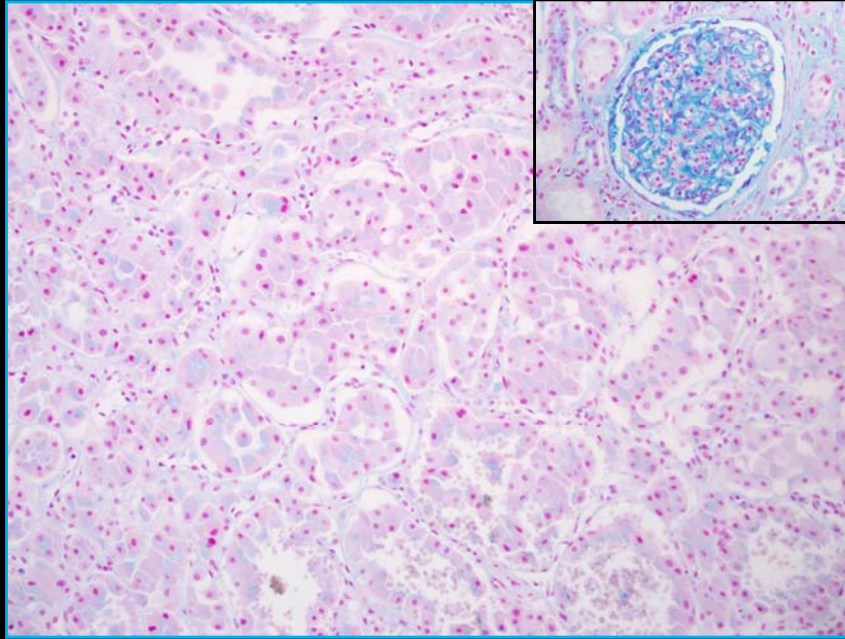
RENAL VEIN INVASION



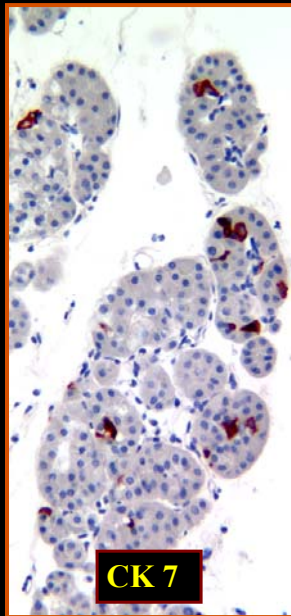
ENTRAPPED TUBULES



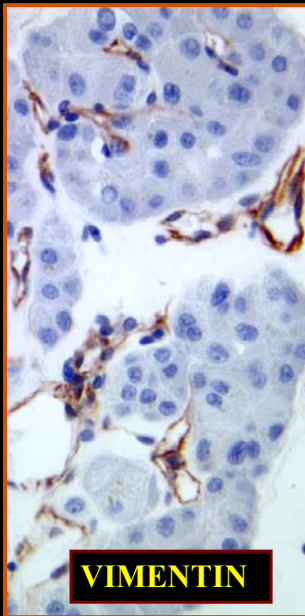
HALE'S COLLOIDAL IRON



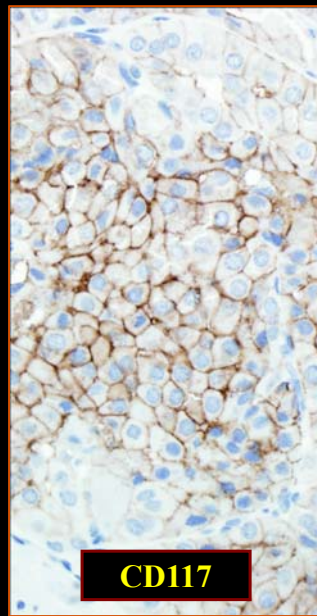
ONCOCYTOMA - IMMUNO



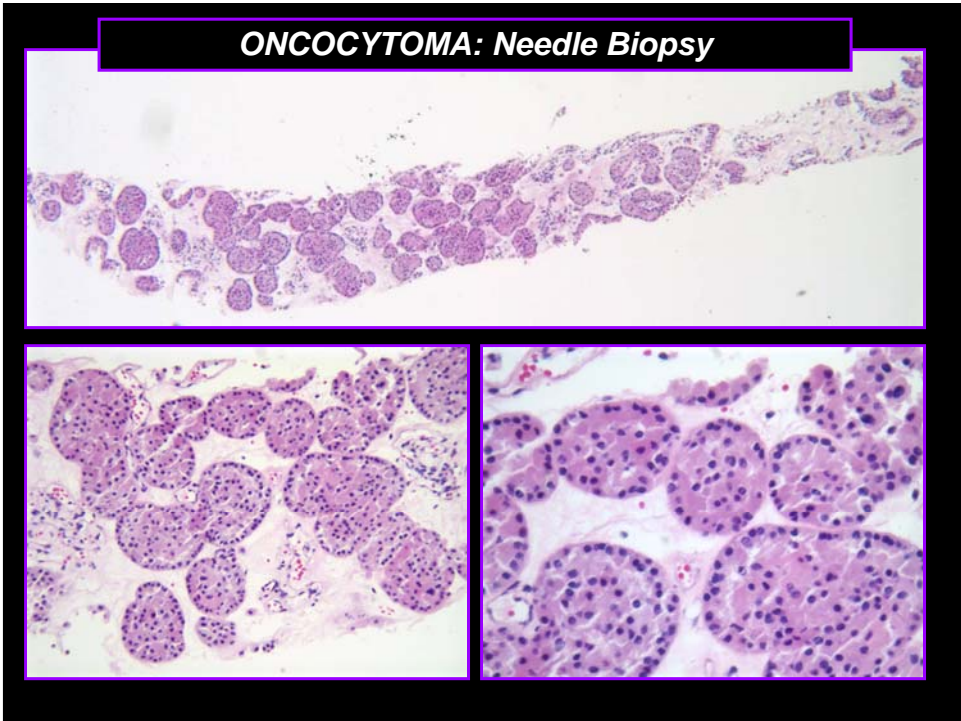
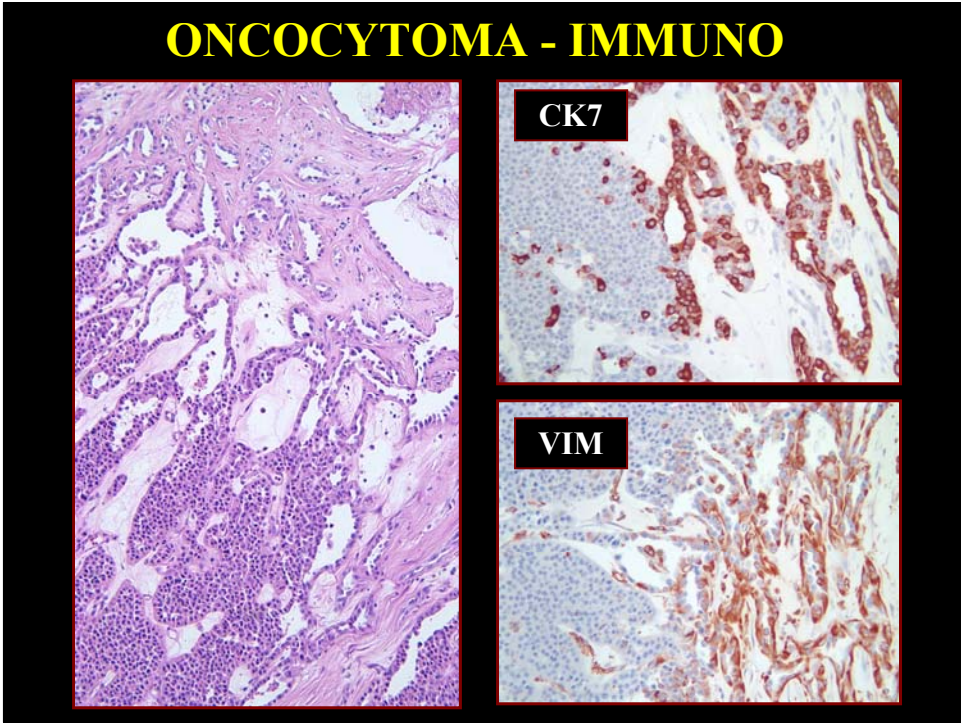
CK 7



VIMENTIN

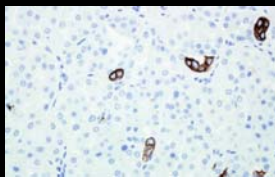
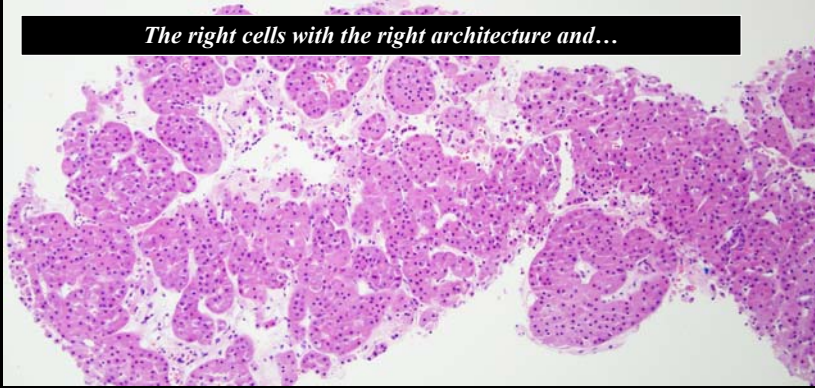


CD117

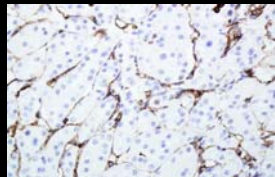


ONCOCYTOMA – NEEDLE BIOPSY: OUR CRITERIA

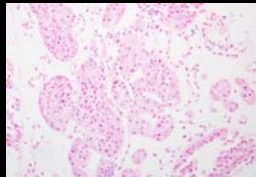
The right cells with the right architecture and...



Cytokeratin 7



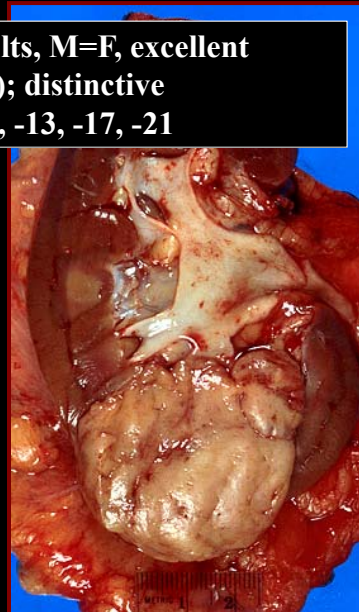
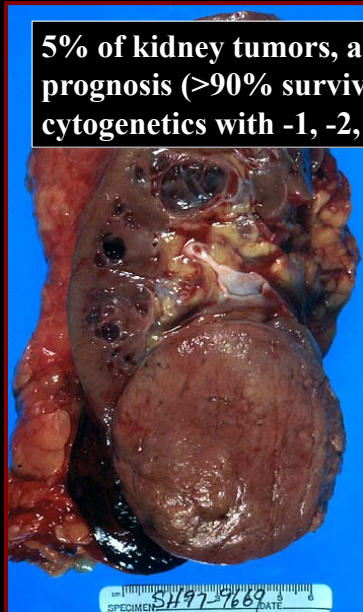
Vimentin

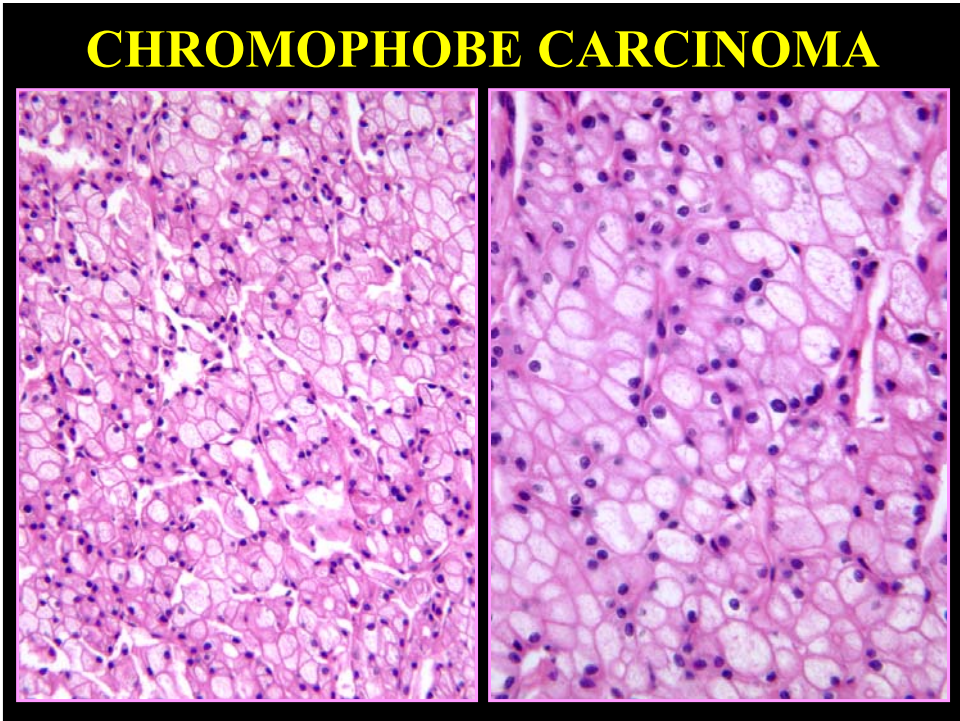
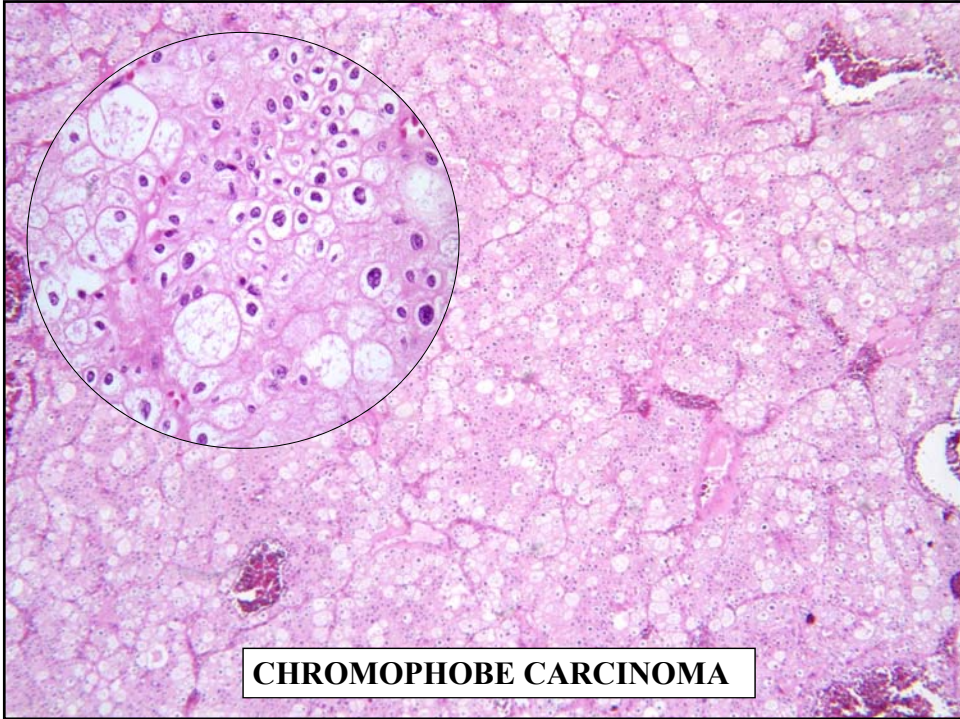


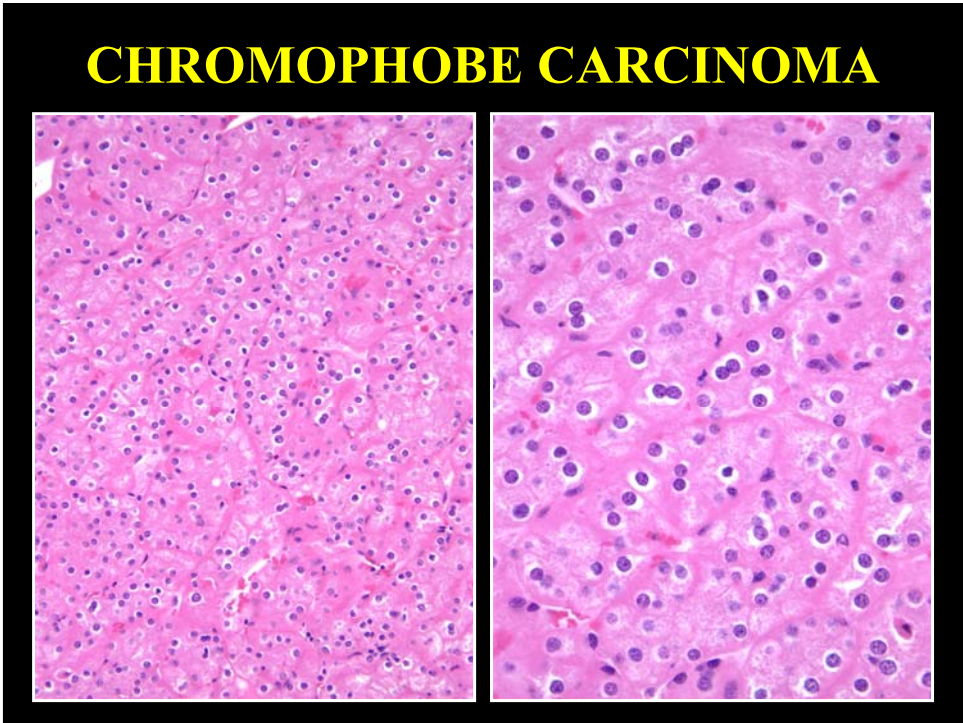
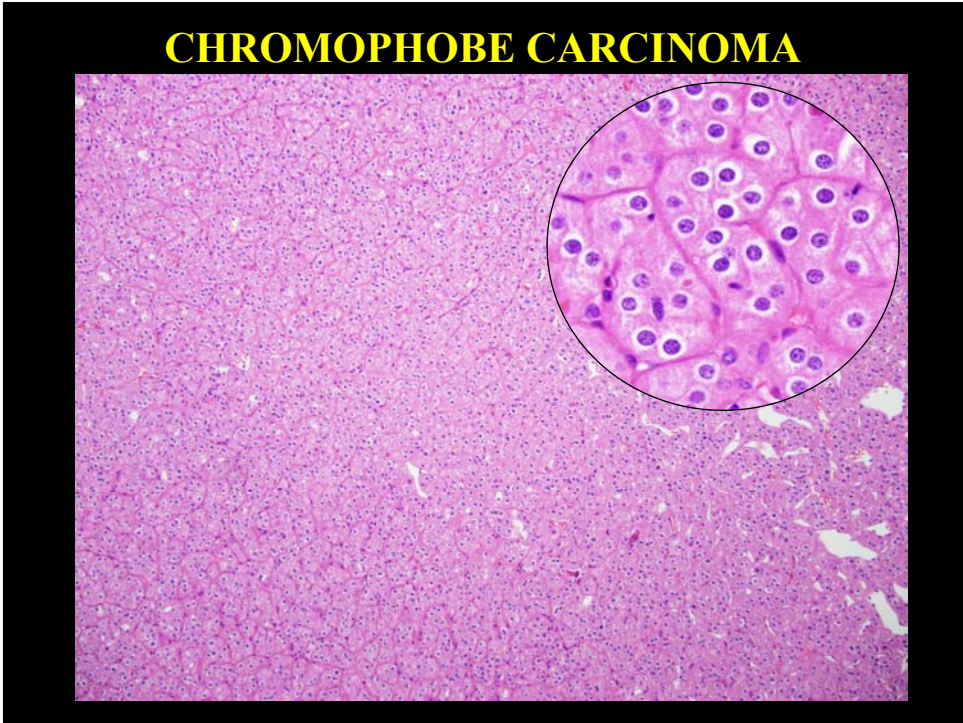
Hale's colloidal iron

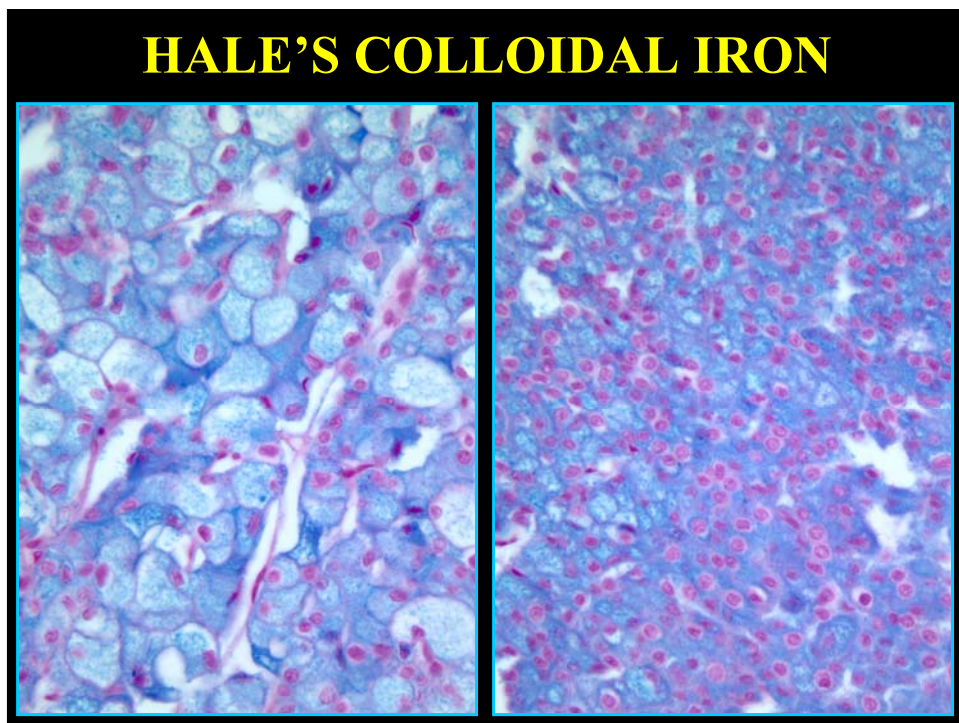
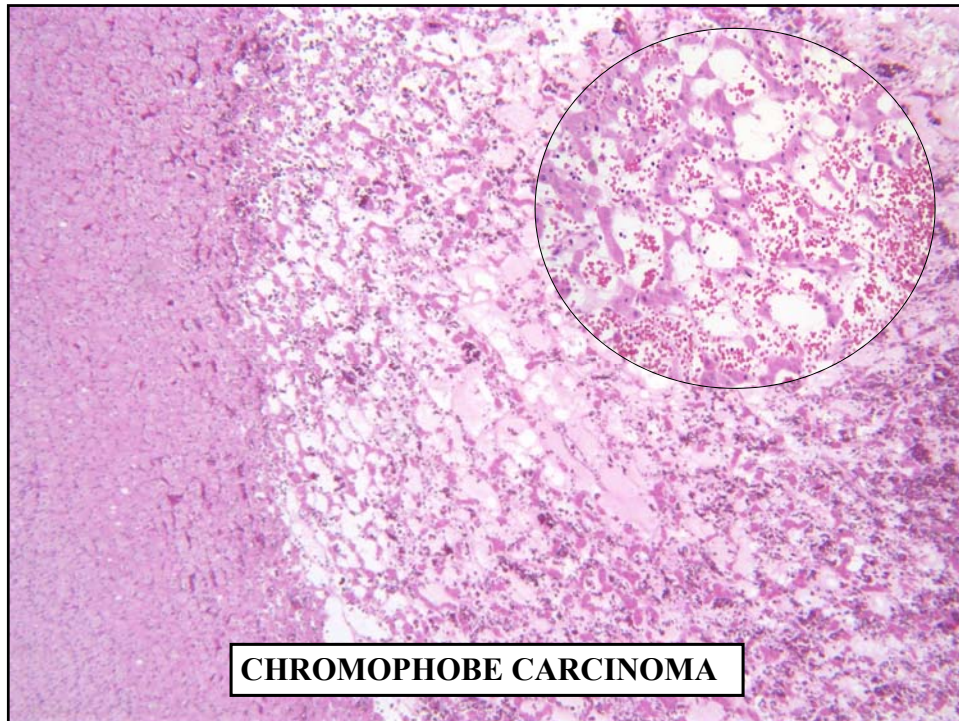
CHROMOPHOBE CARCINOMA

5% of kidney tumors, adults, M=F, excellent prognosis (>90% survival); distinctive cytogenetics with -1, -2, -6, -13, -17, -21

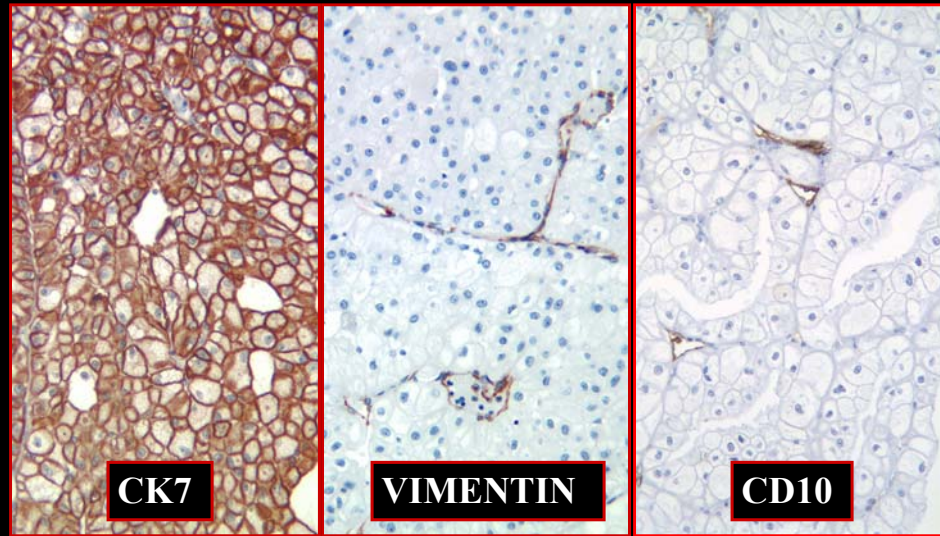








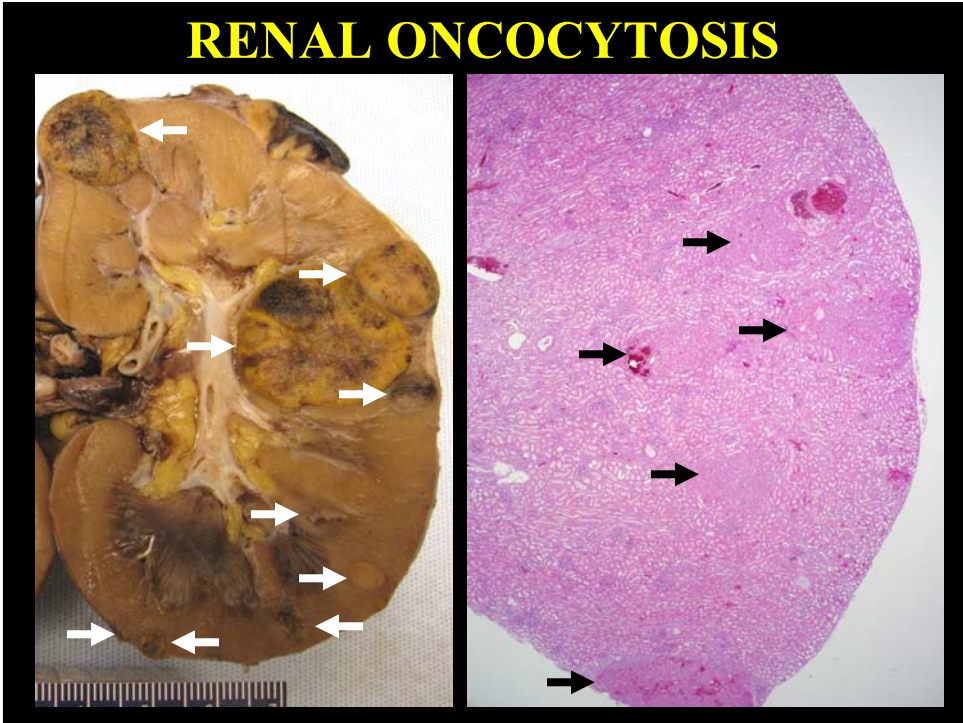
CHROMOPHOBE CARCINOMA IMMUNOHISTOCHEMISTRY



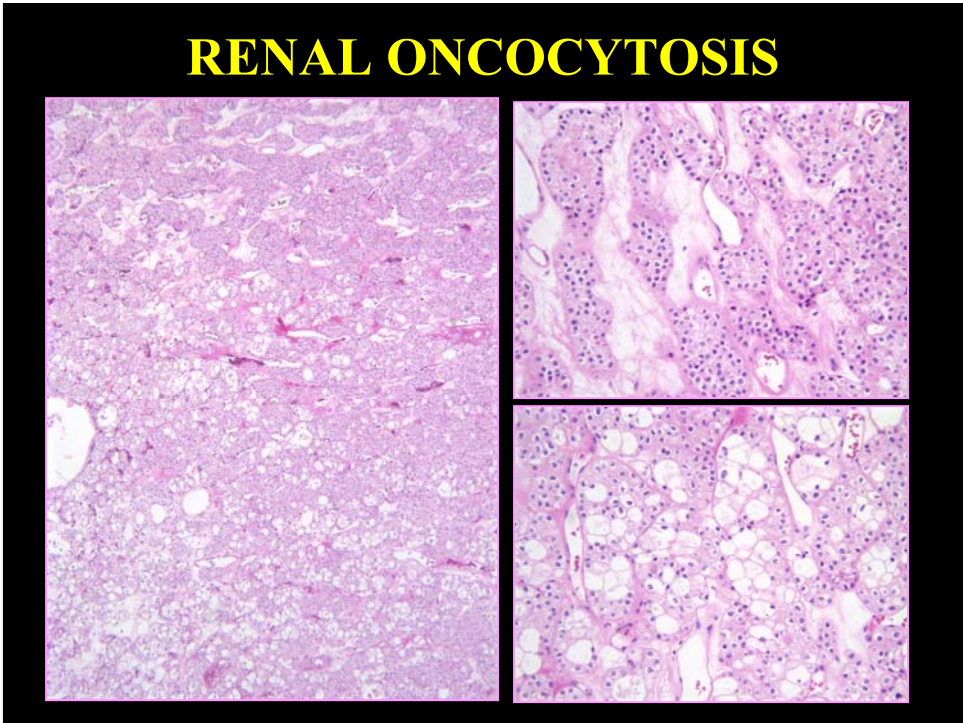
“HYBRID” TUMORS

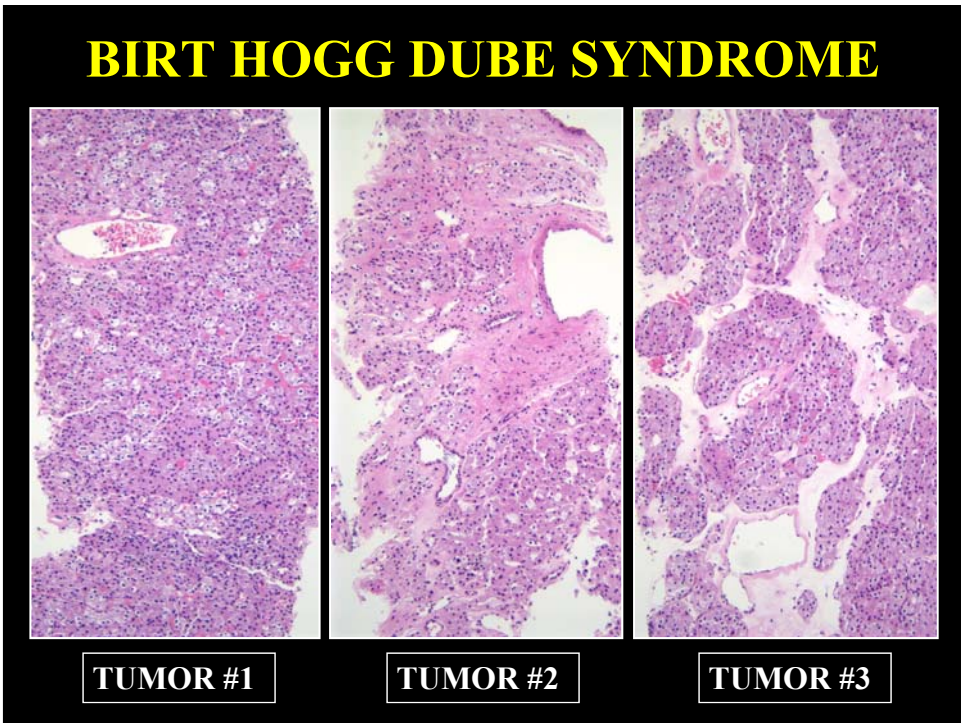
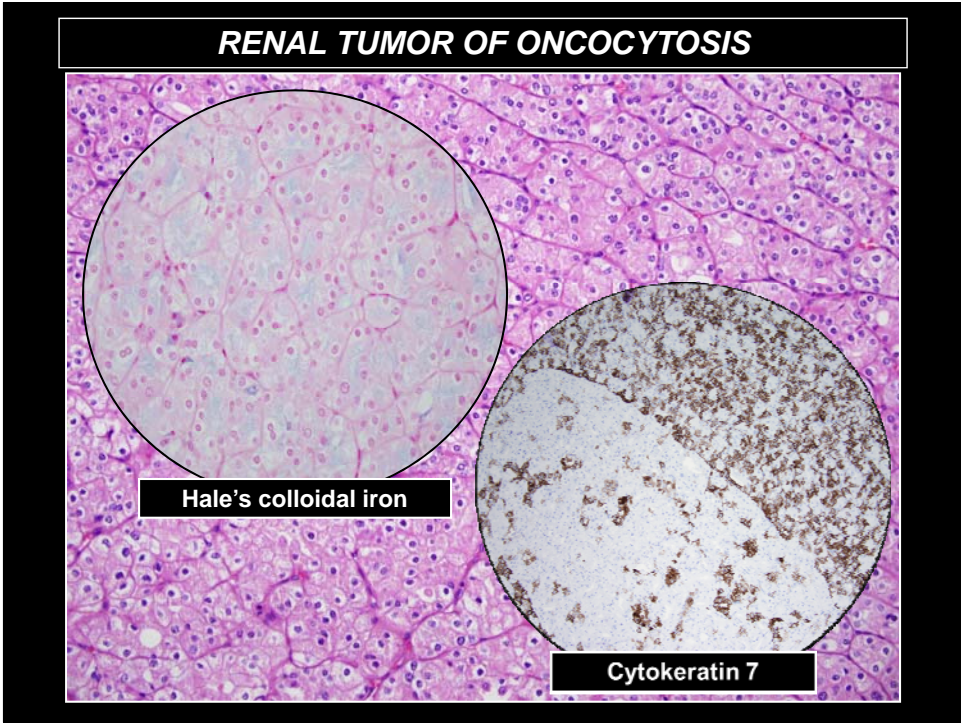
- **RENAL ONCOCYTOSIS**
 - Bilateral, multiple tumors
 - Oncocytoma, chromophobe RCC and hybrid tumors
- **BIRT HOGG DUBE SYNDROME**
 - Skin tumors (trichofolliculomas, achrochordons), multiple renal tumors and pneumothoraces
 - Oncocytoma, chromophobe and clear cell RCC, and hybrid tumors
 - Autosomal dominant, 17p11.2 (folliculin)
- **DE NOVO**
 - 4/425 cases in recent series

RENAL ONCOCYTOSIS

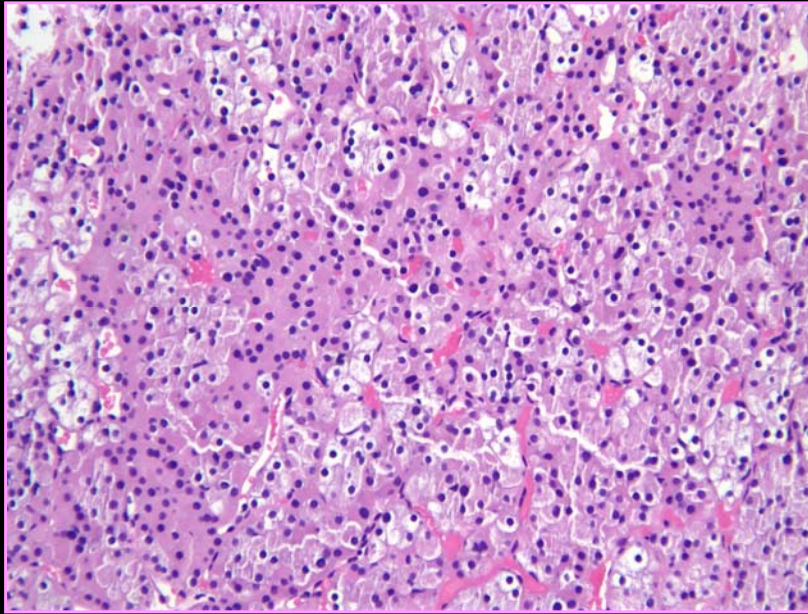


RENAL ONCOCYTOSIS





BIRT HOGG DUBE SYNDROME



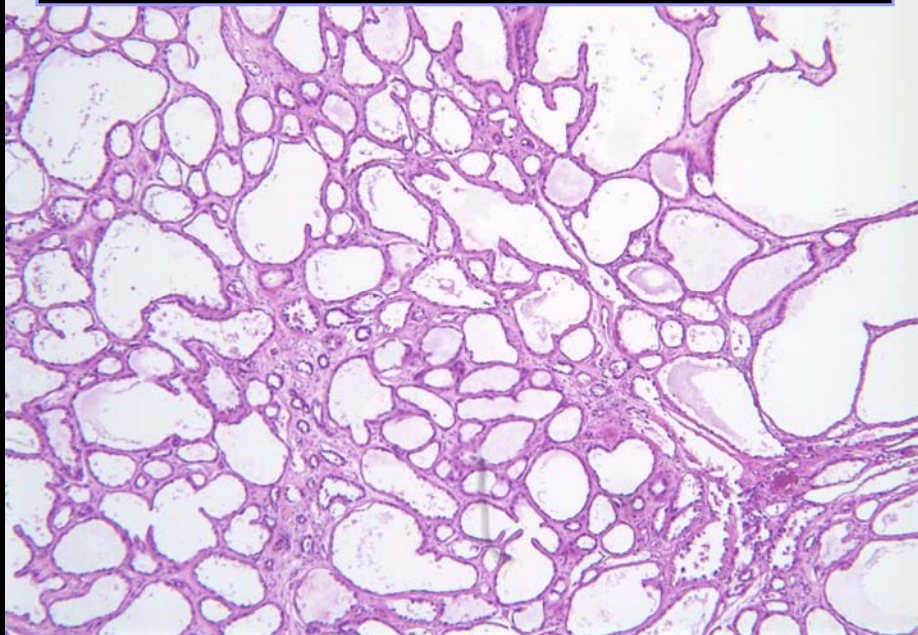
TUBULOCYSTIC CARCINOMA

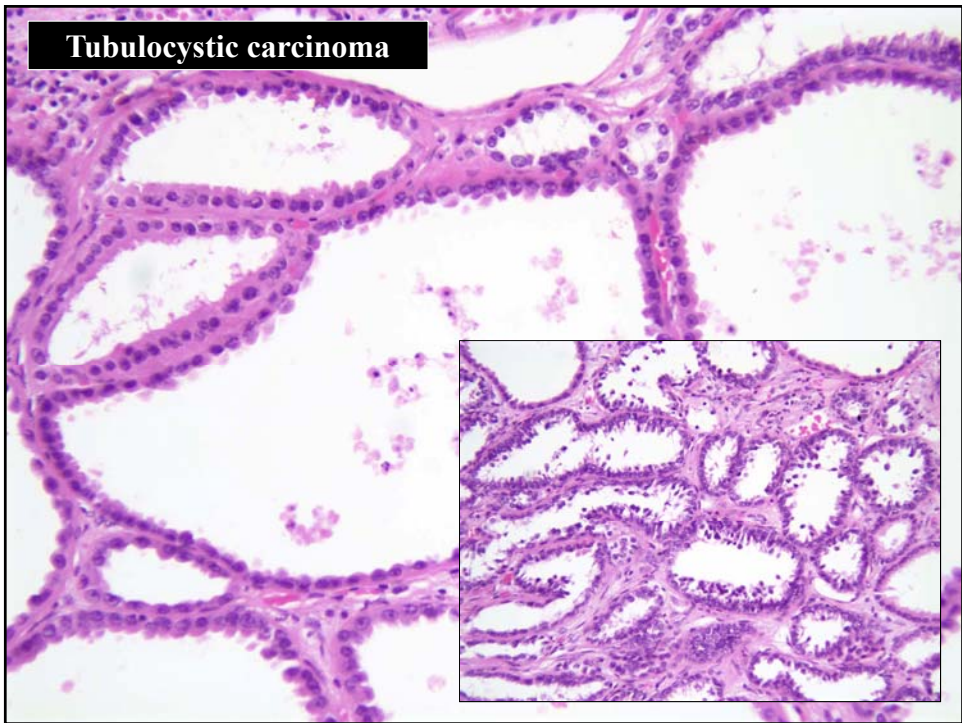
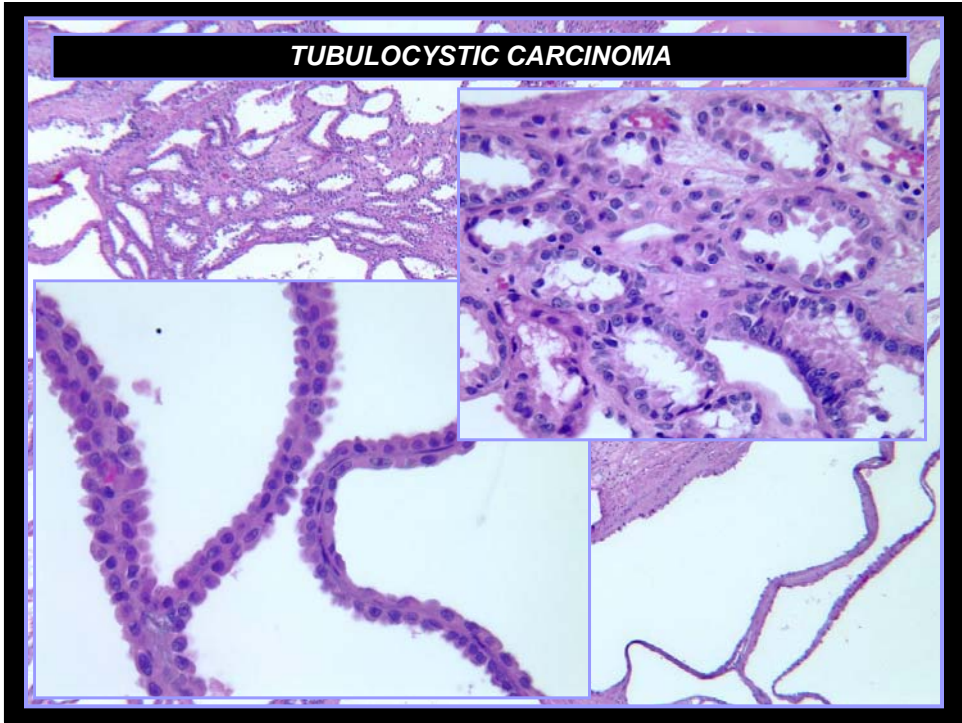
- **Wide age range (34 – 74 yrs; mean 54)**
- **Male predominance (7:1)**
- **Majority localized at diagnosis (pT1-2)**
- **Metastases in 5% - 10%**
- **High grade variants now described**
- **Cytogenetic profile by CGH similar to but not identical to papillary RCC**
- **Overlapping trisomies with papillary RCC by FISH**

TUBULOCYSTIC CARCINOMA

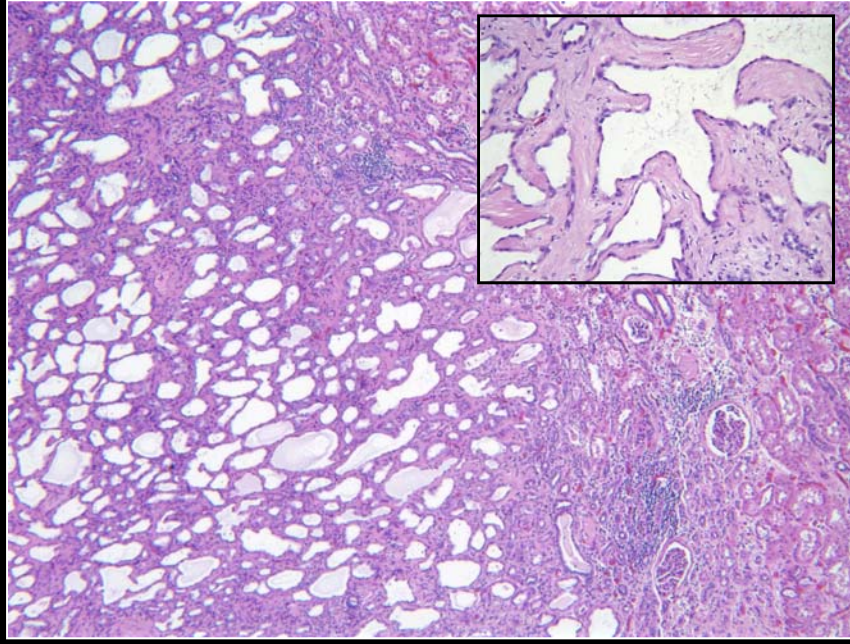


TUBULOCYSTIC CARCINOMA

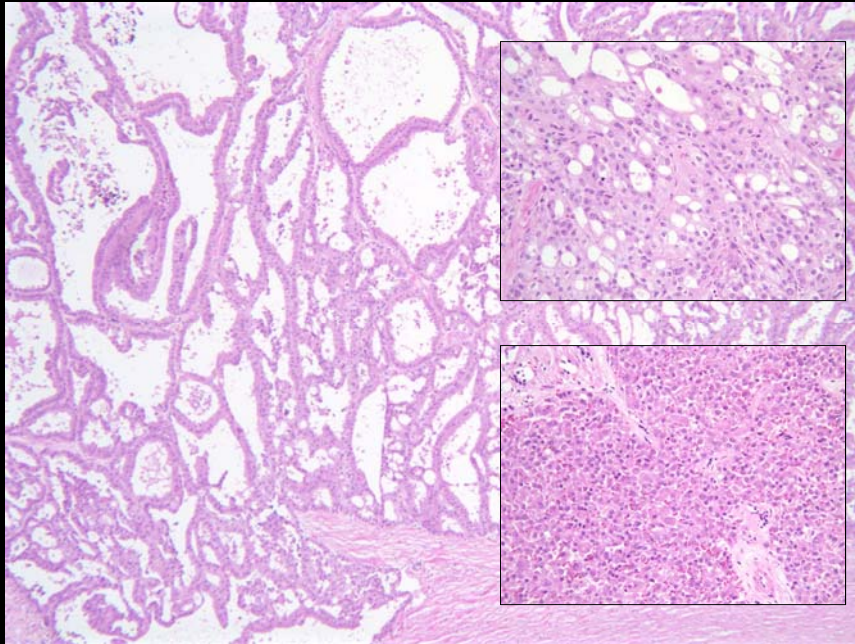




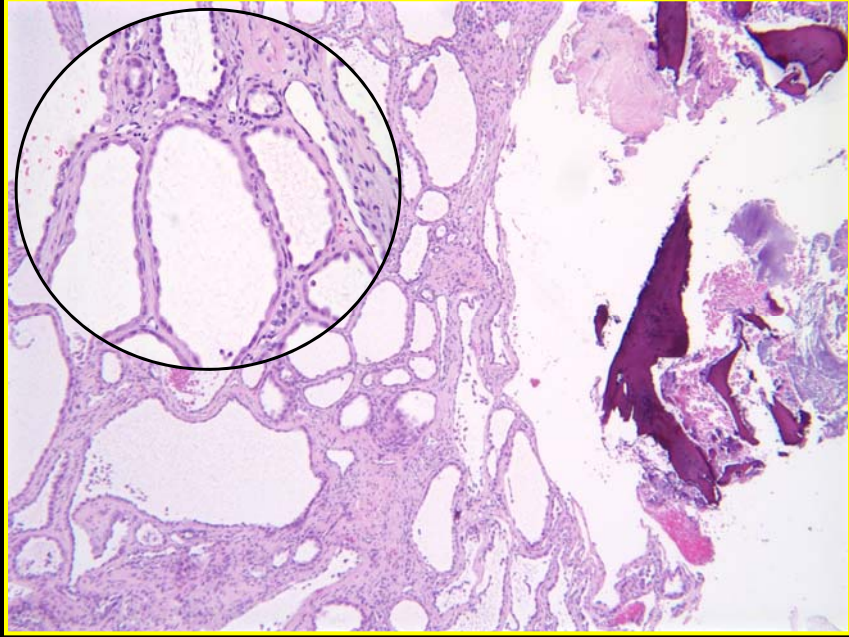
TUBULOCYSTIC CARCINOMA



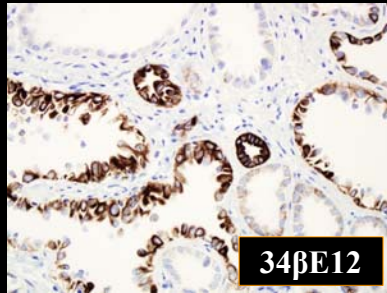
TUBULOCYSTIC CARCINOMA



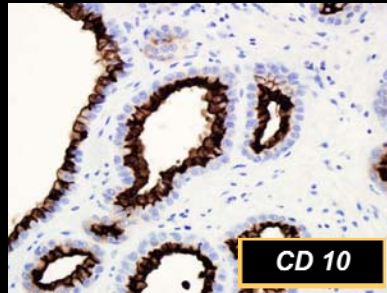
TUBULOCYSTIC CARCINOMA



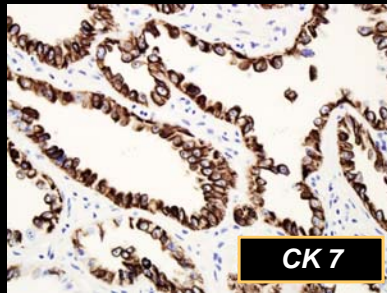
TUBULOCYSTIC CARCINOMA



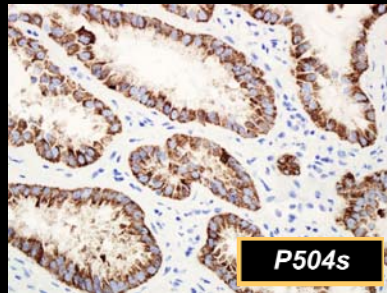
34βE12



CD 10



CK 7

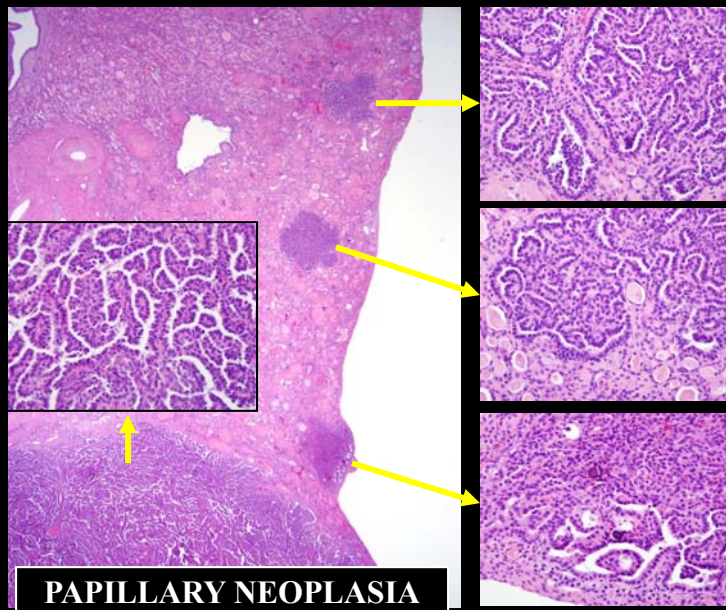


P504s

ACQUIRED CYSTIC KIDNEY DISEASE

- Patients with renal failure +/- dialysis
- Incidence increases with time on dialysis
 - 3 years 10 – 20%
 - 5 years 40 – 60%
 - 10 years 90%
- About 25% of patients develop tumors
- 4% to 7% with tumors develop metastases
- Papillary neoplasia most common

ACQUIRED CYSTIC KIDNEY DISEASE



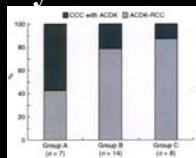
ACQUIRED CYSTIC KIDNEY DISEASE

- Examined 66 kidneys from 52 patients
- Identified a variety of tumor types:
 - ACD associated carcinoma 33%
 - Clear cell papillary carcinoma 21%
 - Papillary carcinoma 16%
 - Chromophobe carcinoma 16%
 - Clear cell carcinoma 14%
- Considered the first two potentially unique tumor types

Tickoo et al, Am J Surg Pathol 30:141, 2006

ACQUIRED CYSTIC DISEASE ASSOCIATED RENAL CELL CARCINOMA

- Increased frequency with increasing duration of dialysis

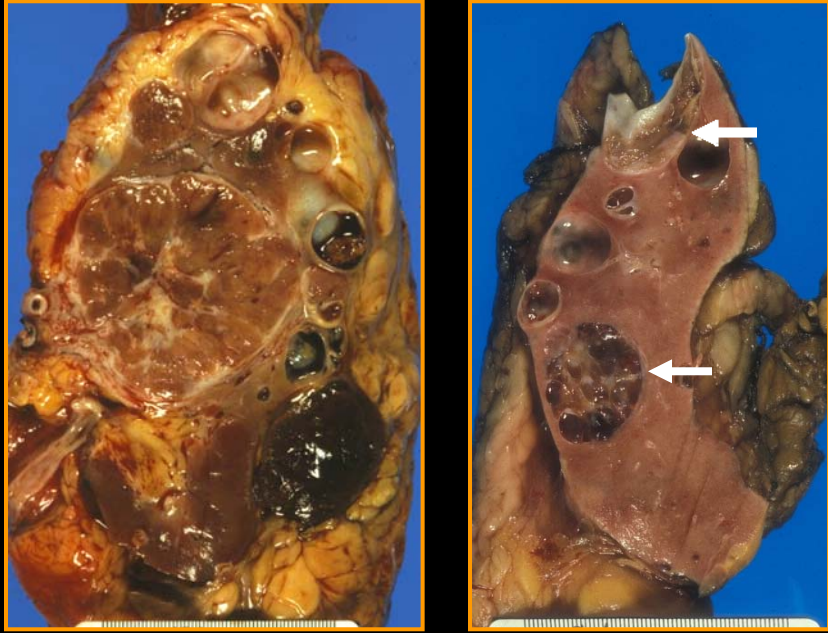


Mean dialysis time: A, 47 mos;
B, 177 mos; C, 317 mos

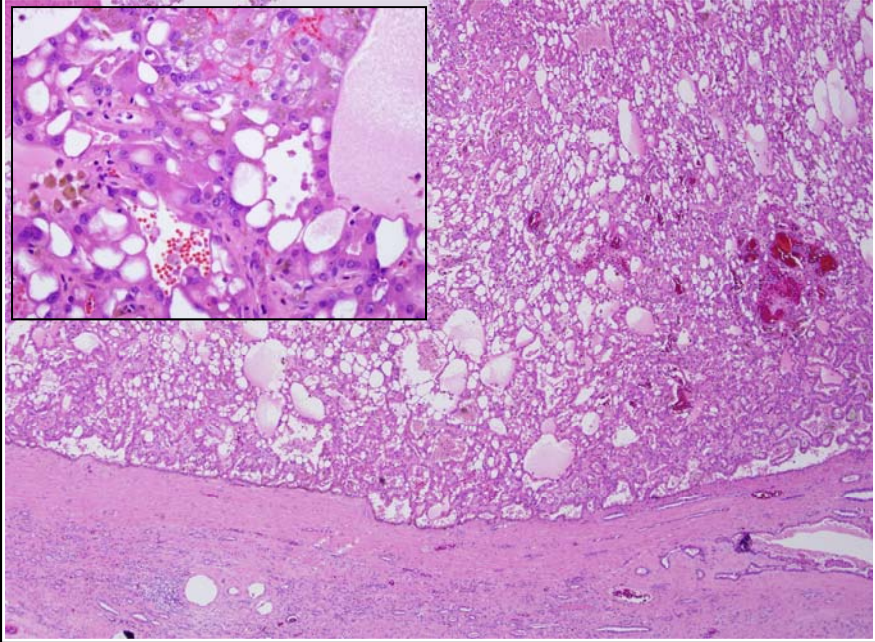
Enoki et al. Histopathol 56:384, 2010

- Dialysis <10 yrs: 1/15 (7%) vs >10 yrs: 7/12 (58%)
Nouh et al. BJU Int 105:620, 2009
- Genomic profiling study clustered these with clear cell papillary and papillary RCC (*Inoue et al. Cancer Science 2011*)
- 4/18 (22%) patients with mets/DOD (*Enoki et al, 2010*)
- 2/25 (8%) patients with mets (*Tickoo et al AJSP 30:141, 2006*)

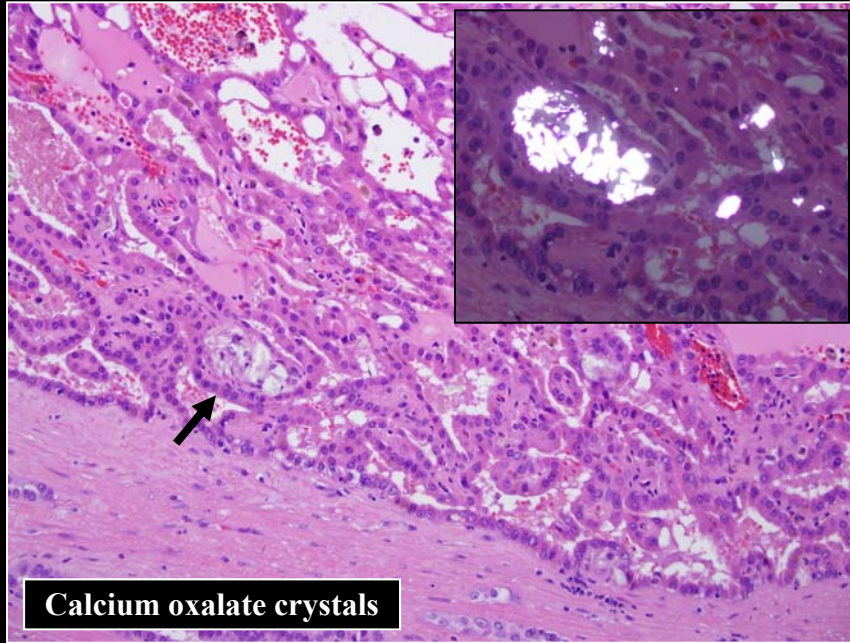
AcqCKD ASSOCIATED CARCINOMA



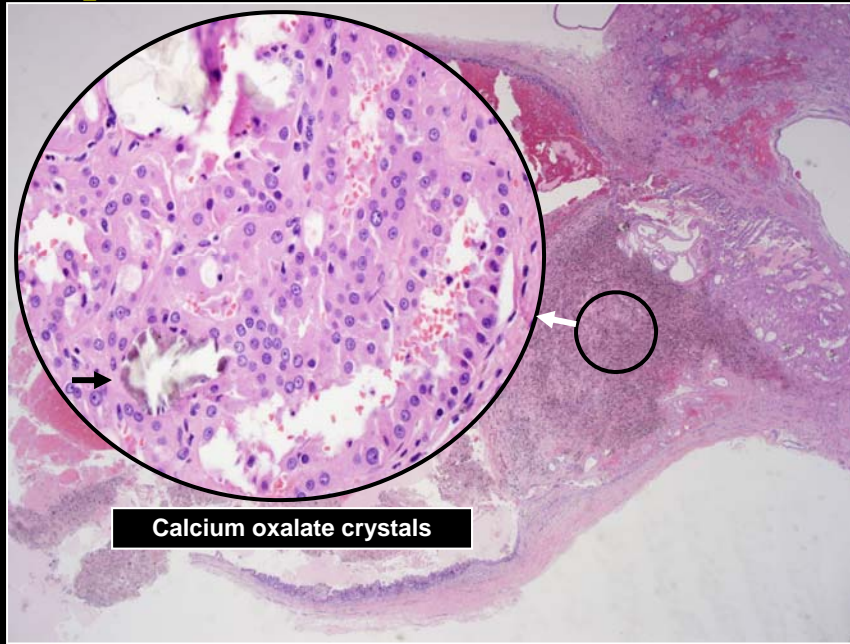
AcqCKD ASSOCIATED CARCINOMA



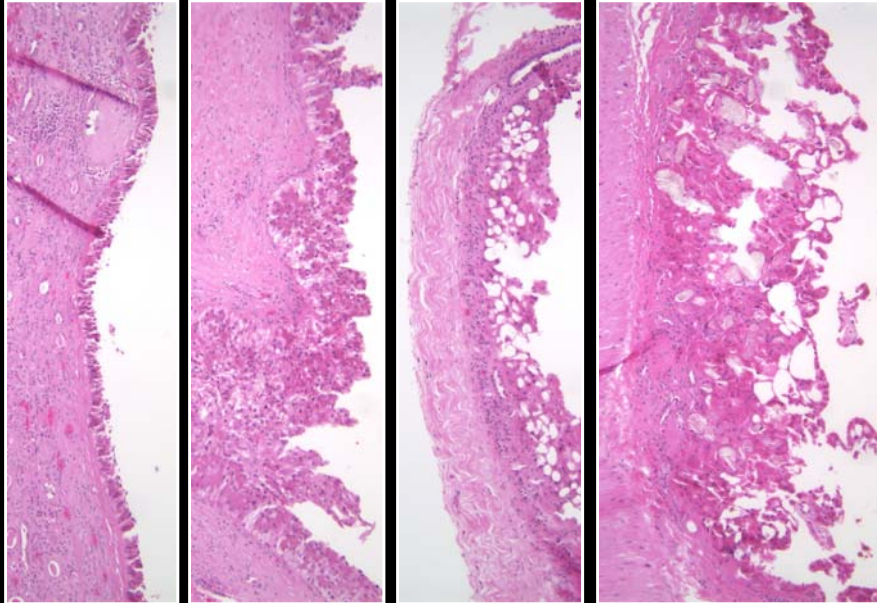
AcqCKD ASSOCIATED CARCINOMA



AcqCKD ASSOCIATED CARCINOMA



AcqCKD ASSOCIATED CARCINOMA



CLEAR CELL PAPILLARY RCC

- 55 tumors in 34 patients
- 2002-2004: 14/469 (3%)
 - 10 reported as clear cell; 4 as papillary
- M:F = 19:15; Age 33 – 87 years (mean 61)
- 8 (24%) patients with ESRD
- Stage: pT1a-53 (96%), pT1b-1, pT2-1
- Multiple tumors in 9 patients (26%)
- No cases with metastases

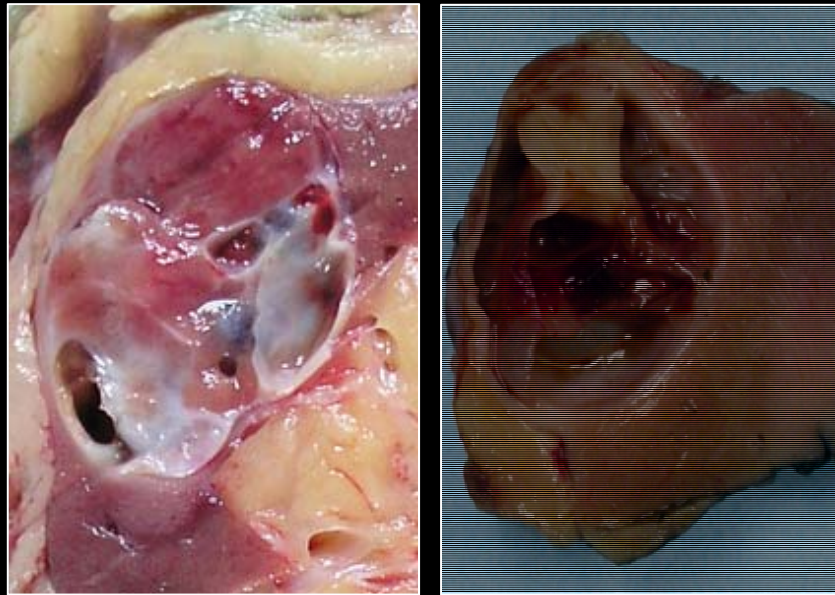
Williamson et al. Modern Pathol 26:697-708, 2013

CLEAR CELL PAPILLARY RCC: A DISTINCT ENTITY

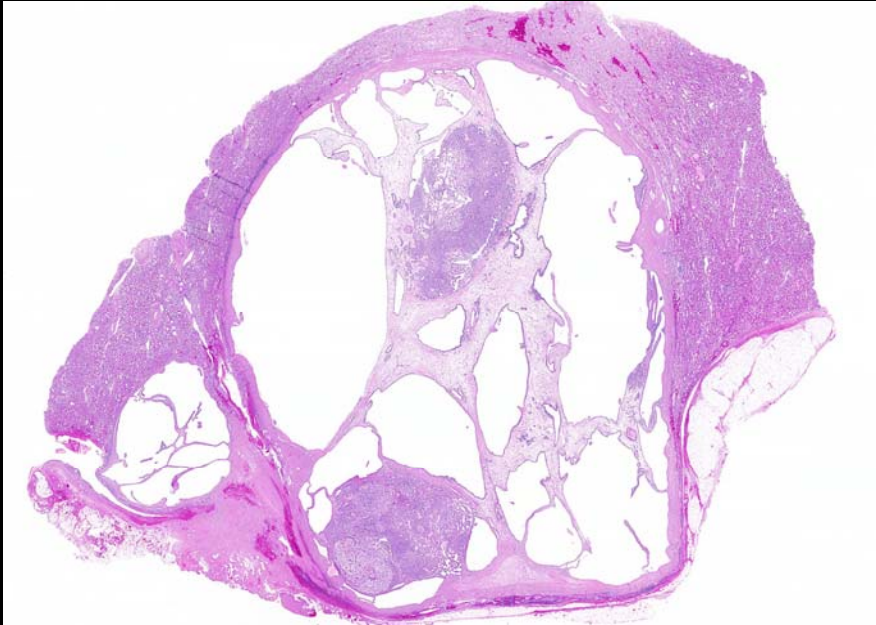
- **Immunohistochemical profile:**
 - Cytokeratin 7 +, CD10 -: Not clear cell
 - AMACR -, CD 10 -, CAIX +: Not papillary
- **Fluorescence in situ hybridization:**
 - Majority show no trisomy 7 or 17: Not papillary
 - No loss of 3p: Not clear cell
- **DNA sequencing**
 - No 3p mutations: Not clear cell

Mai et al, 2008; Gobbo et al, 2008; Michal et al, 2009; Aydin et al, 2010

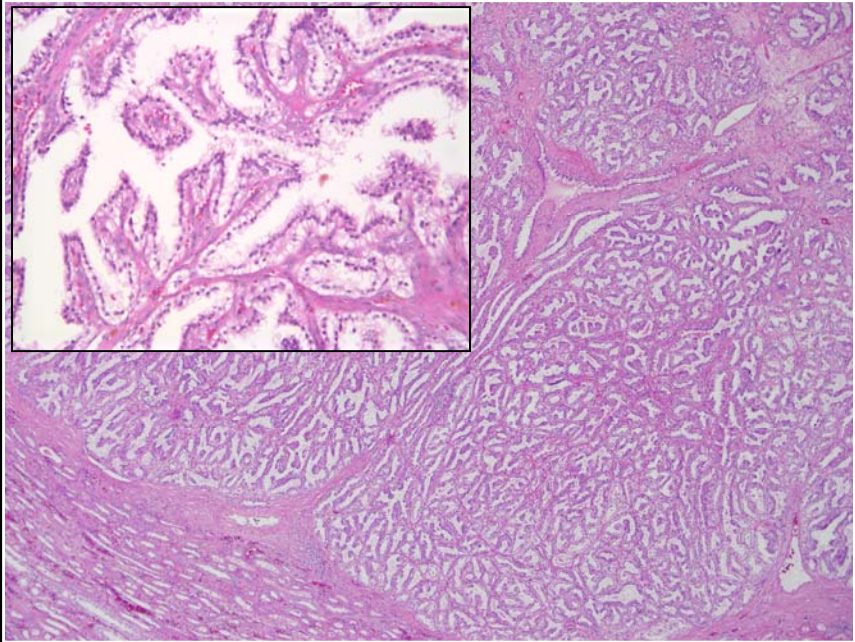
CLEAR CELL PAPILLARY RCC

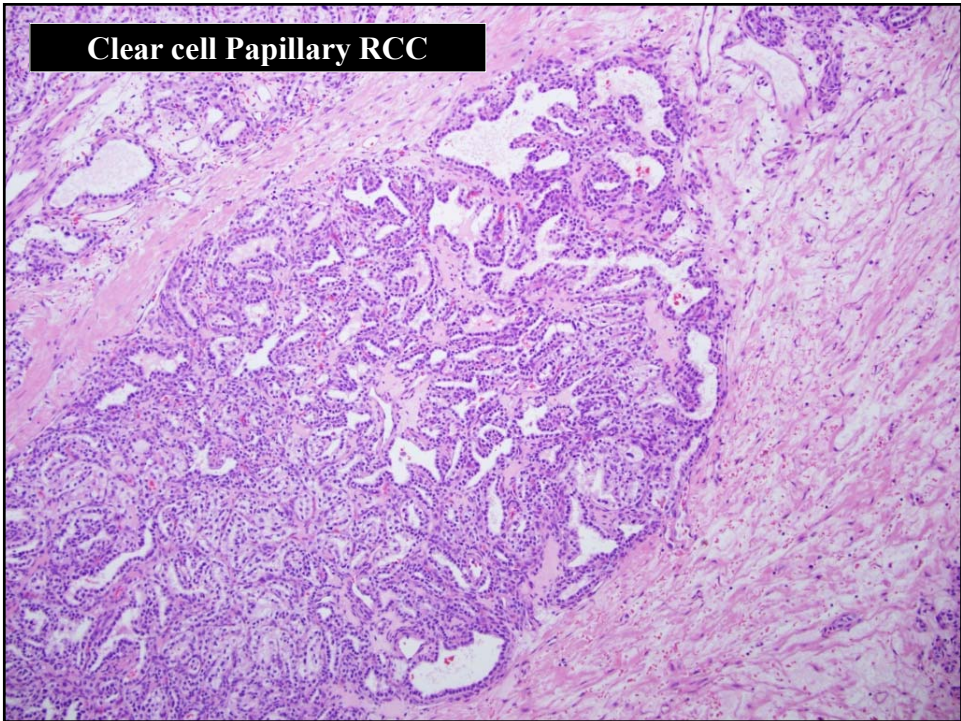
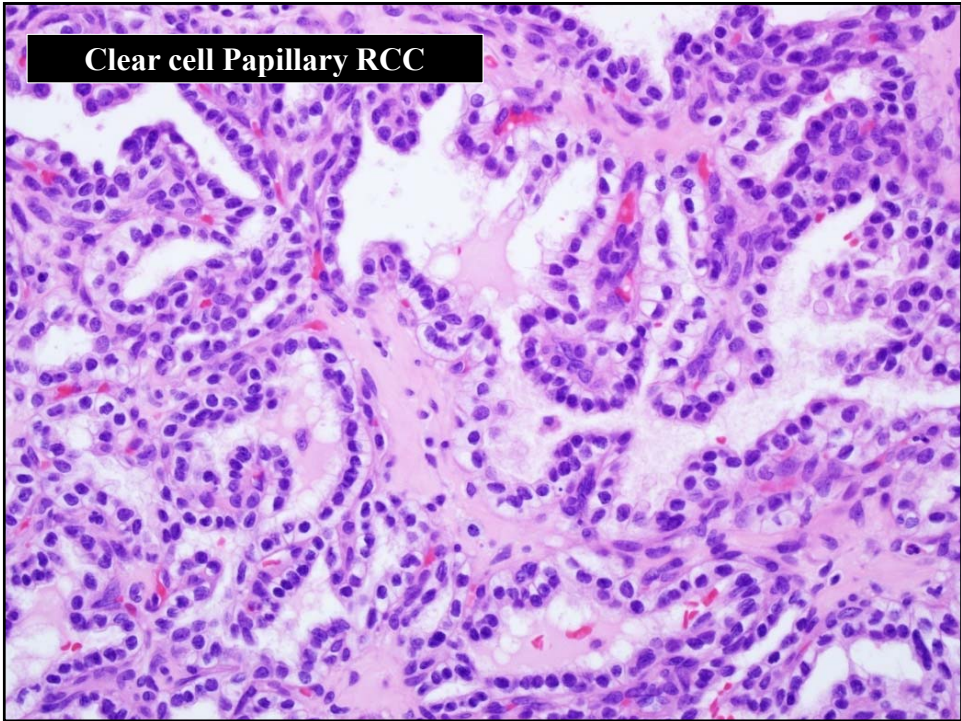


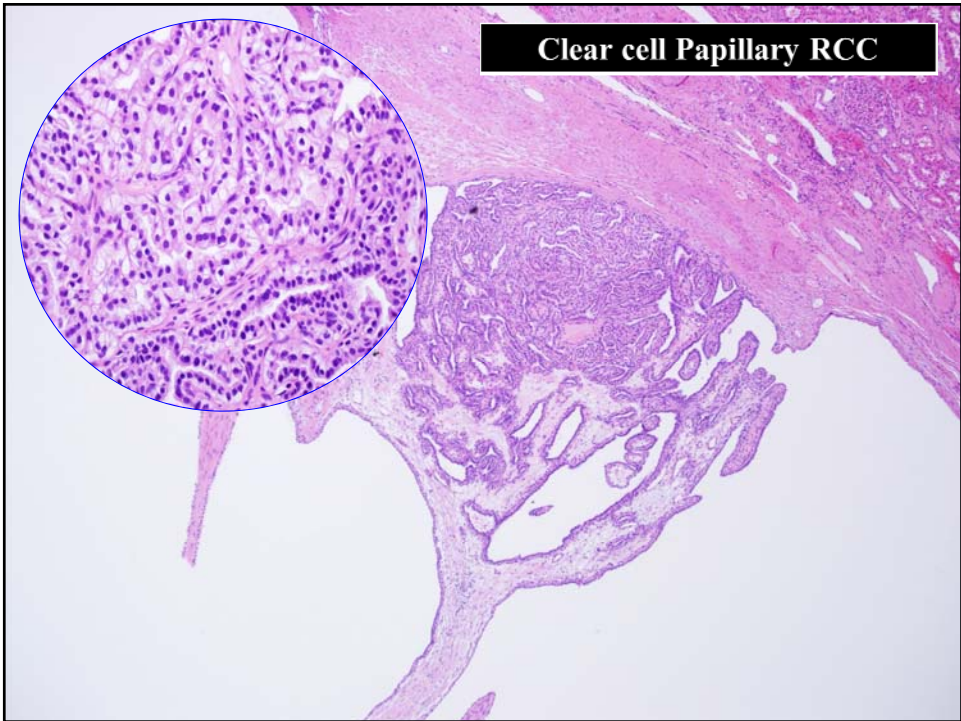
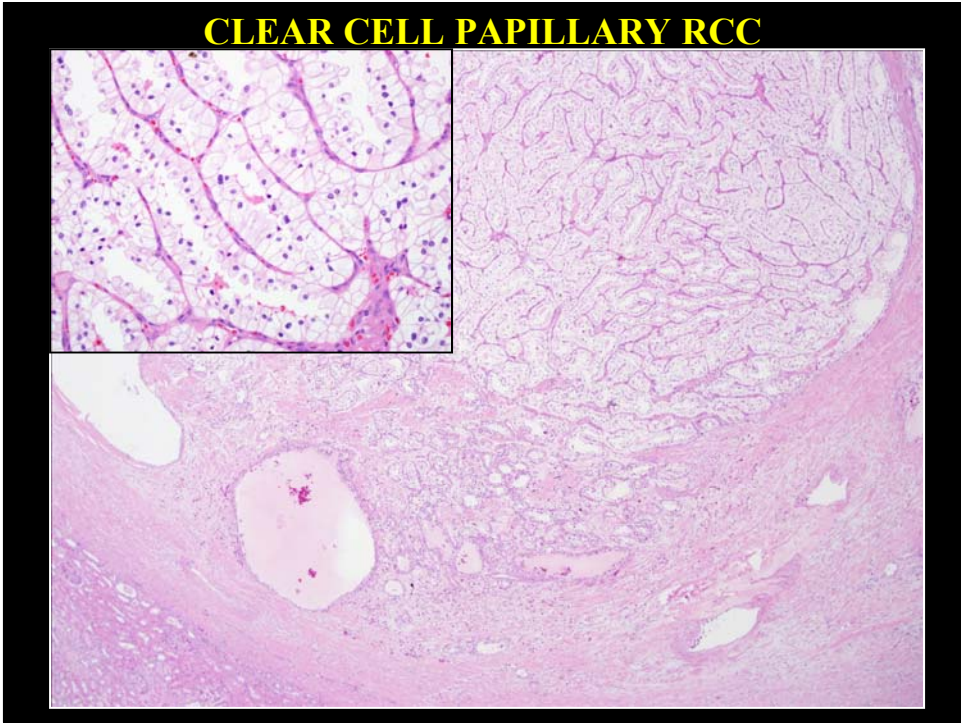
CLEAR CELL PAPILLARY RCC



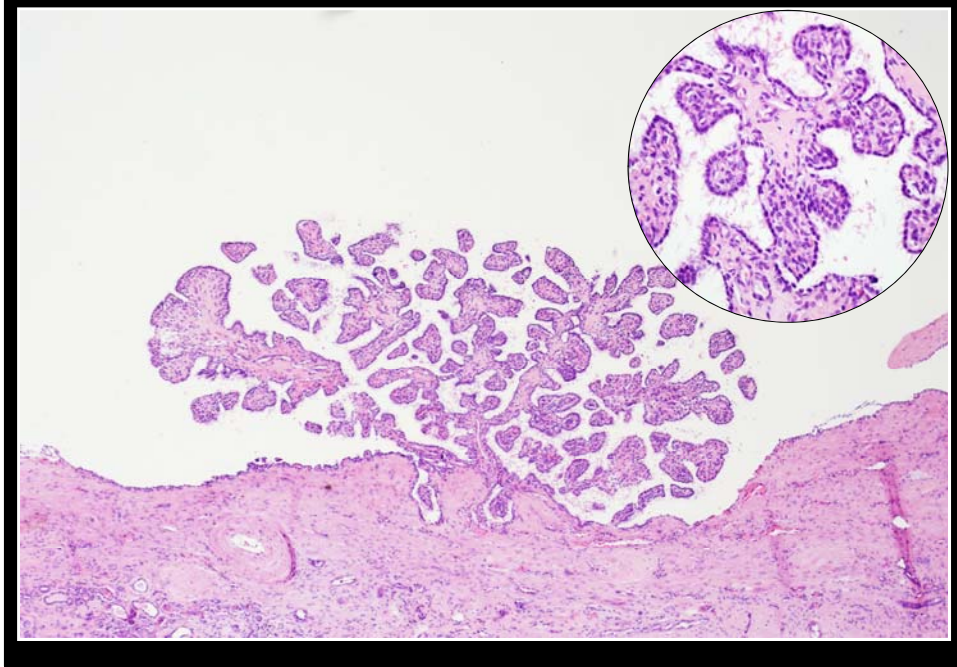
CLEAR CELL PAPILLARY RCC



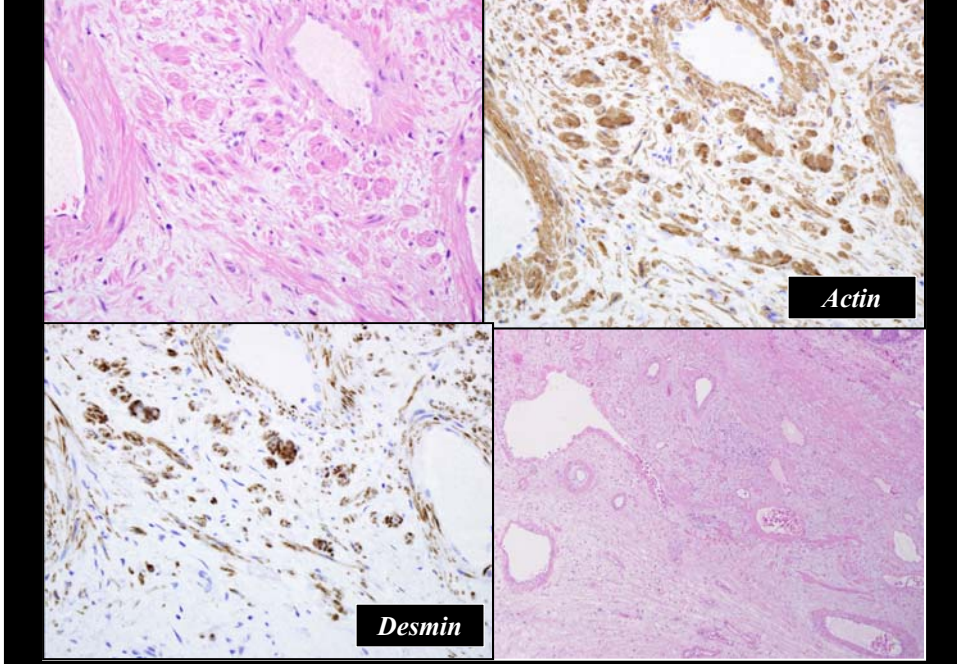


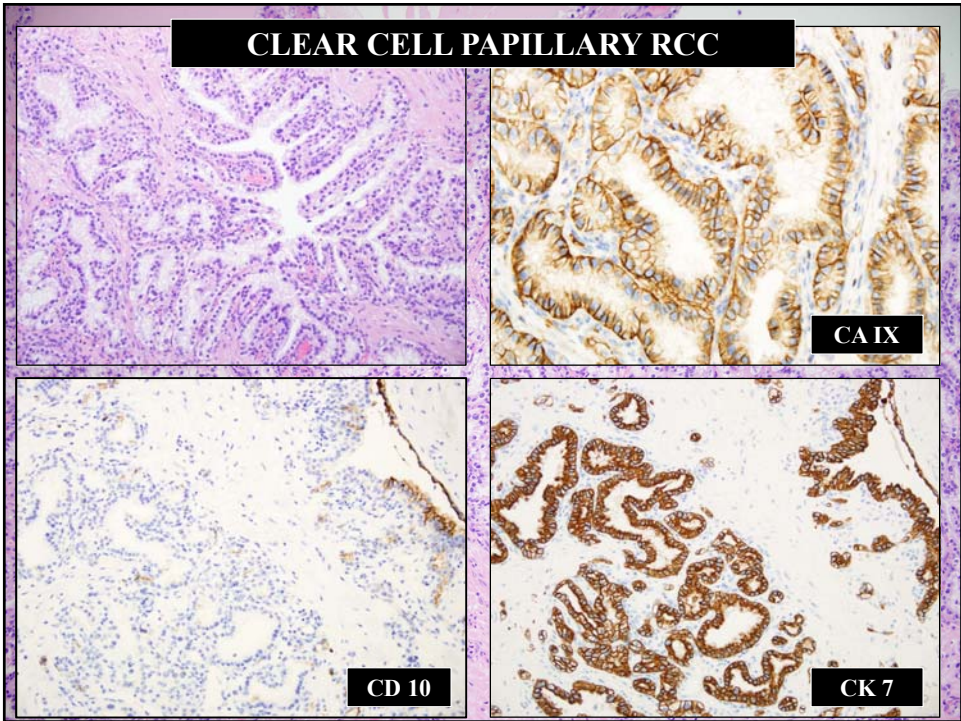
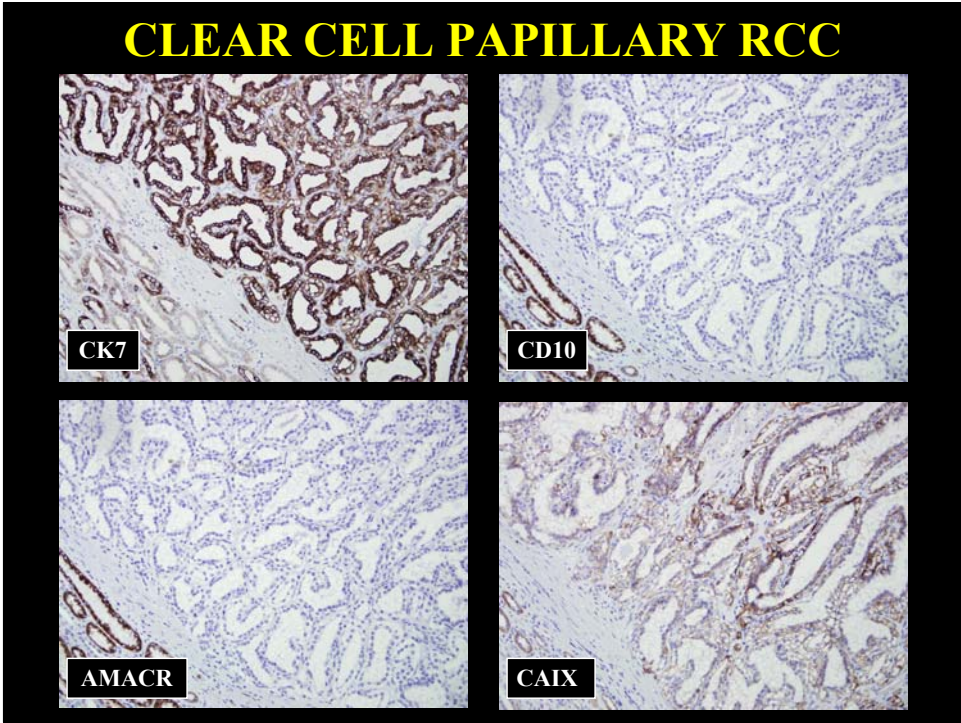


CLEAR CELL PAPILLARY RCC



CLEAR CELL PAPILLARY RCC



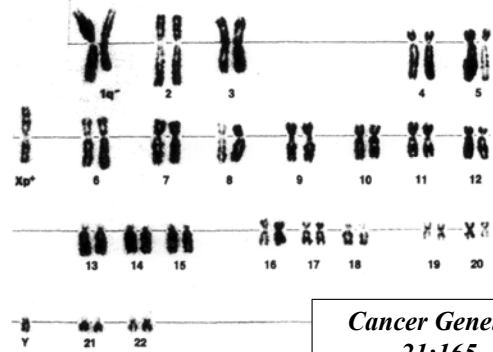


TRANSLOCATION ASSOCIATED RCC

Cytogenetics of a Renal Adenocarcinoma in a 2-Year-Old Child

Bauke de Jong, Ineke M. Molenaar, J. Albertus Leeuw, Vera J. S. Idenberg, and J. Wolter Oosterhuis

Figure 2 The 46,XY, t(X;1)(p11;q21) karyotype of the tumor cells.



Cancer Genet Cytogen
21:165, 1986

TRANSLOCATION ASSOCIATED RCC

© 1996 Oxford University Press

Human Molecular Genetics, 1996, Vol. 5, No. 9 1333-1338

The t(X;1)(p11.2;q21.2) translocation in papillary renal cell carcinoma fuses a novel gene *PRCC* to the *TFE3* transcription factor gene

Sanjiv K. Sidhar^{1,*}, Jeremy Clark^{1,*}, Sandra Gill¹, Rifat Hamoudi², A. Jayne Crew^{1,6}, Rhian Gwilliam⁴, Mark Ross⁴, W. Marston Linehan⁵, Sandra Birdsall³, Janet Shipley³ and Colin S. Cooper^{1,3,*}

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Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 15294-15298, December 1996
Genetics

Fusion of the transcription factor *TFE3* gene to a novel gene, *PRCC*, in t(X;1)(p11;q21)-positive papillary renal cell carcinomas

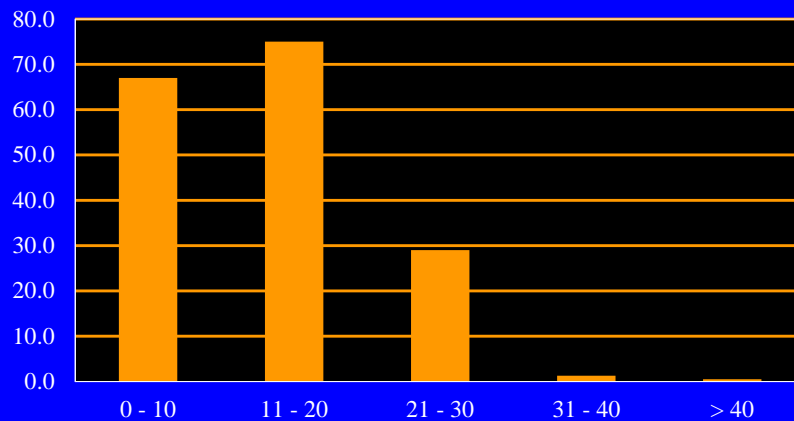
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X-ASSOCIATED CARCINOMAS

TRANSLOCATION	AGE	FUSION
T(X;1)(p11.2;q21)	2 - 70	<i>PRCC-TFE3</i>
t(X;17)(p11.2;q25)	2 - 68	<i>ASPL-TFE3</i>
der(17)(X;17)(p11.2;q25)	5 - 40	<i>ASPL-TFE3</i>
t(X;1)(p11.2;p34)	3 - 68	<i>PSF-TFE3</i>
inv(X)(p11.2;q12)	39	<i>NonO-TFE3</i>
t(X;17)(11.2q23)	14	<i>CLTC-TFE3</i>

X:1 TRANSLOCATION ASSOCIATED RCC: FREQUENCY BY AGE

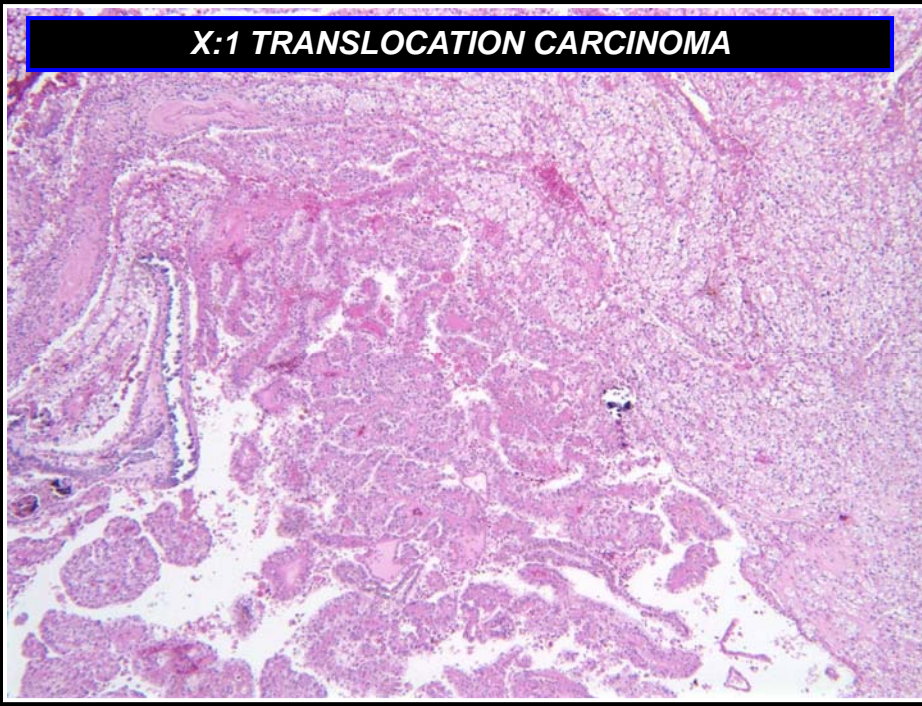


Klatte et al. Am J Clin Pathol 137:761, 2012

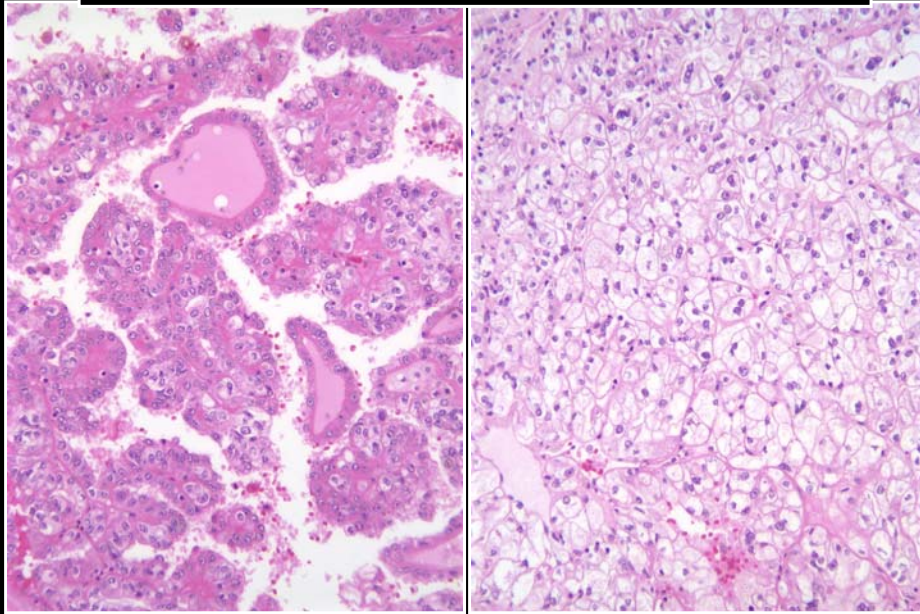
TRANSLOCATION ASSOCIATED CARCINOMA



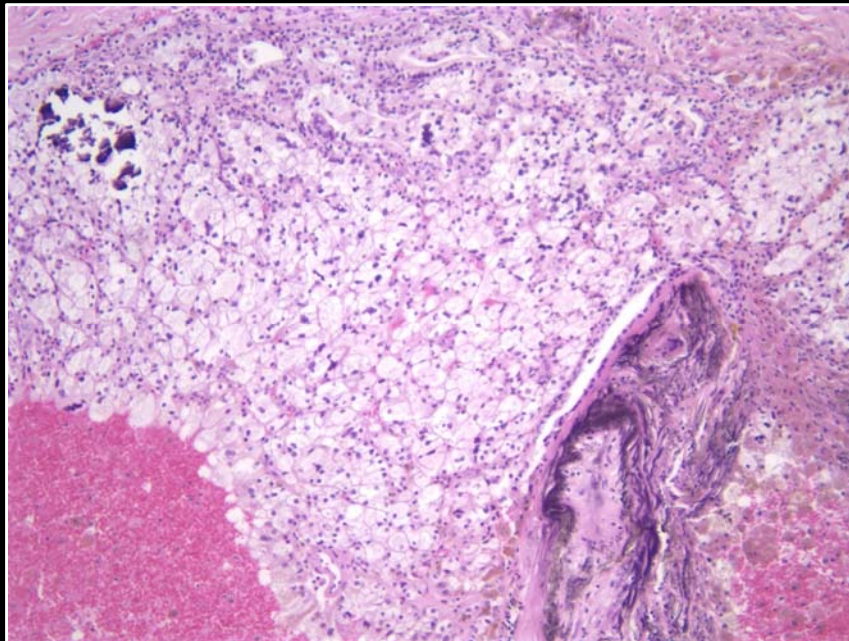
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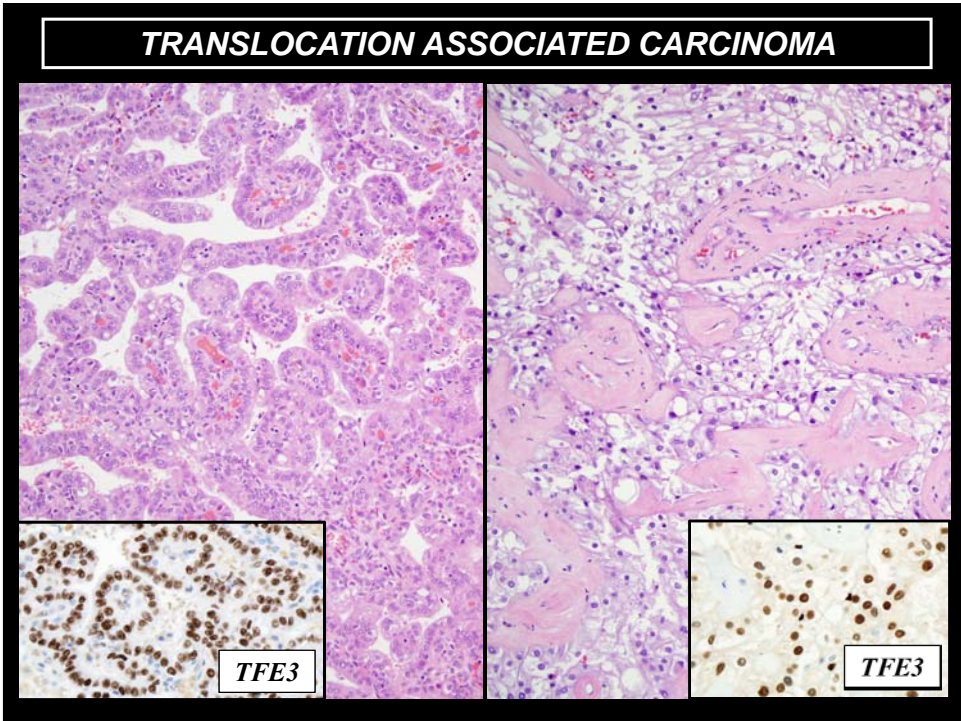
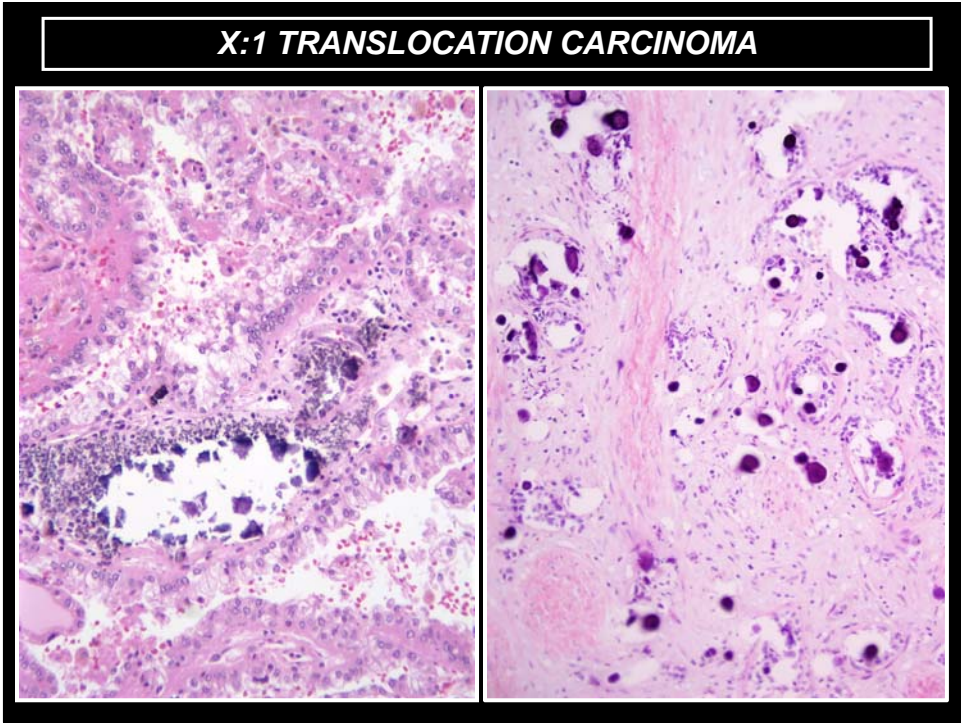


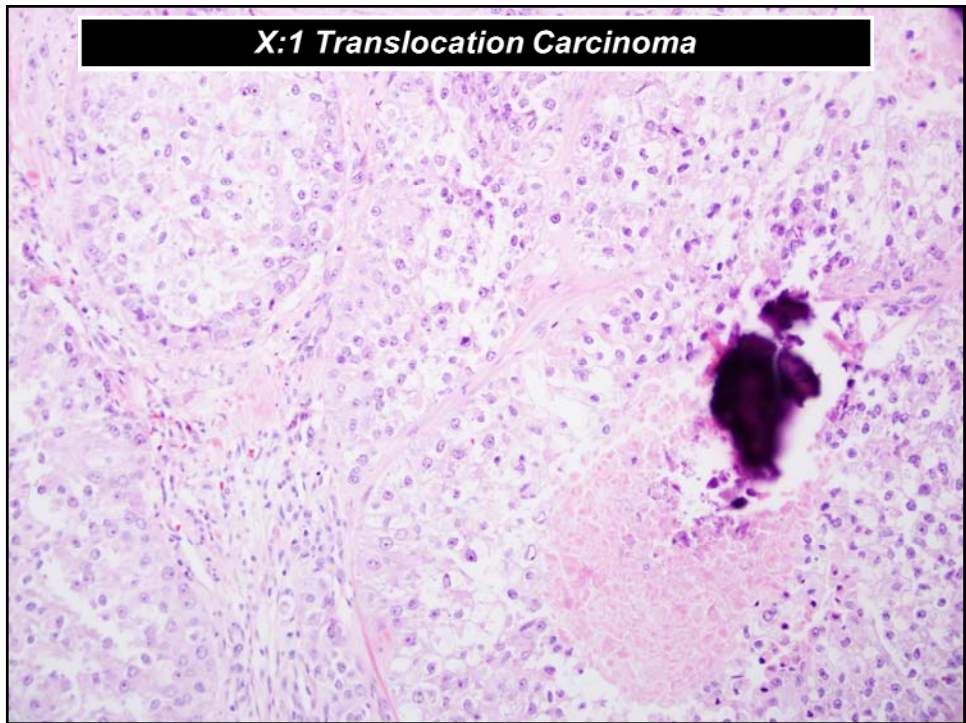
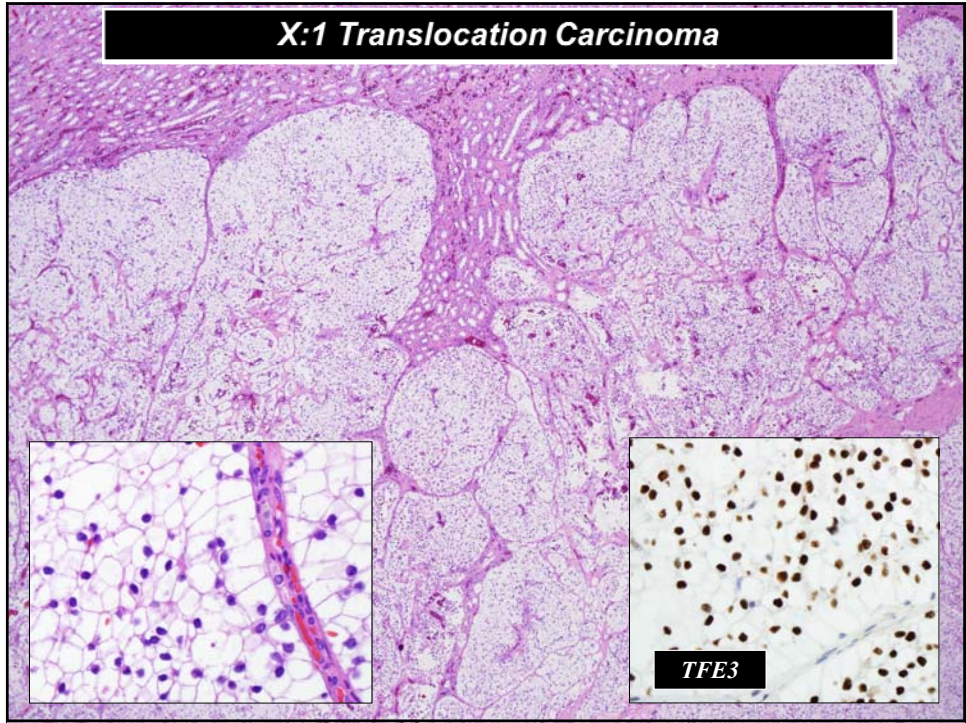
X:1 Translocation Carcinoma

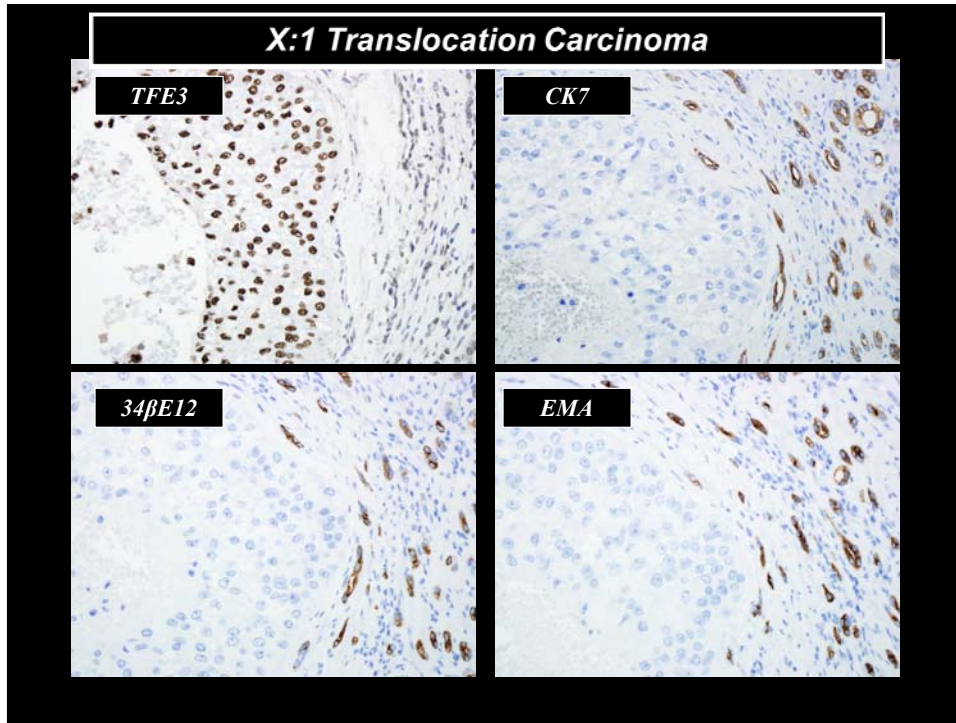


X:1 TRANSLOCATION ASSOCIATED CARCINOMAS



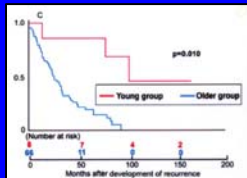






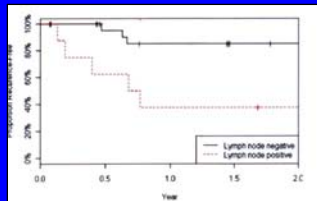
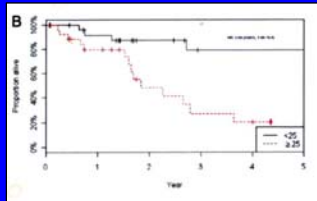
Xp11TRANSLOCATION ASSOCIATED CARCINOMAS

- Because of limited number of published cases prognostic features are unclear



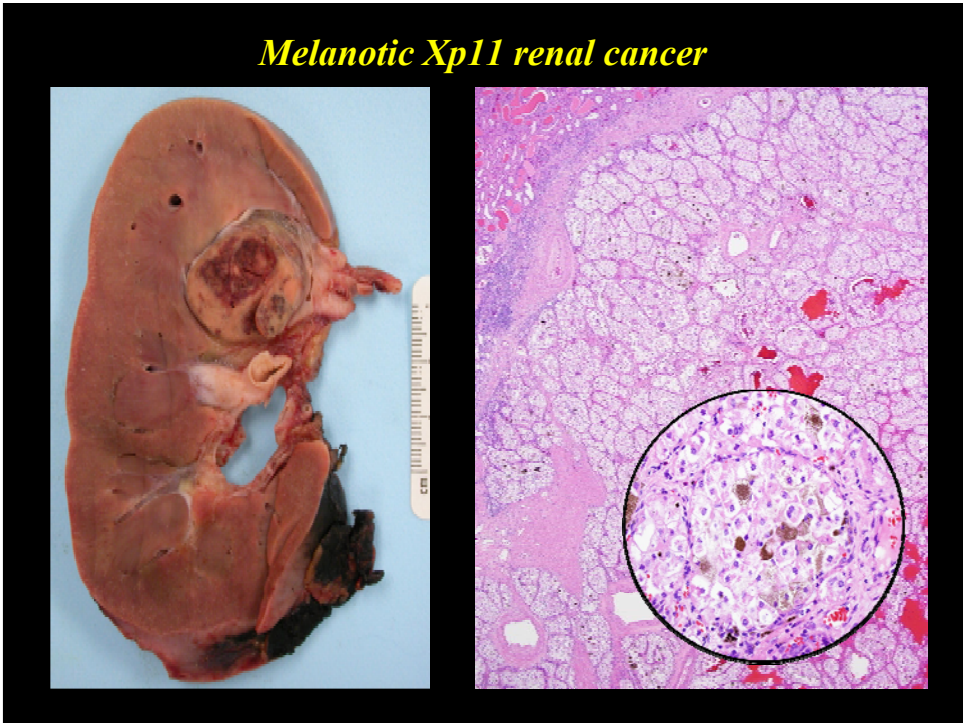
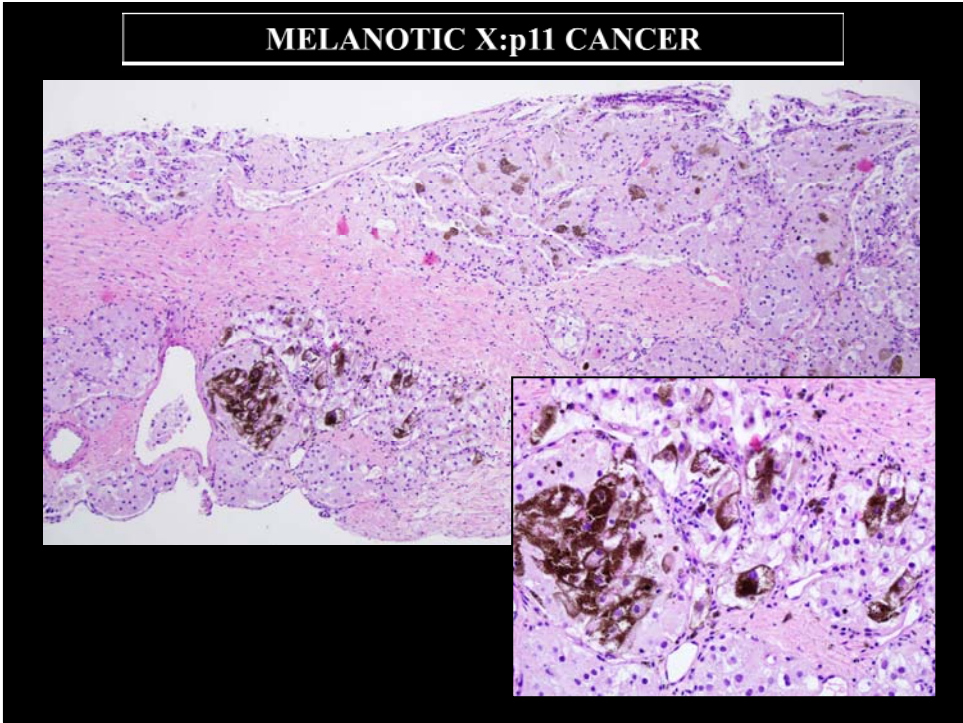
Prolonged survival in young patients with recurrence/metastases (4/8 with Xp11 translocation RCC)

Komai et al, Urology 77:842, 2011

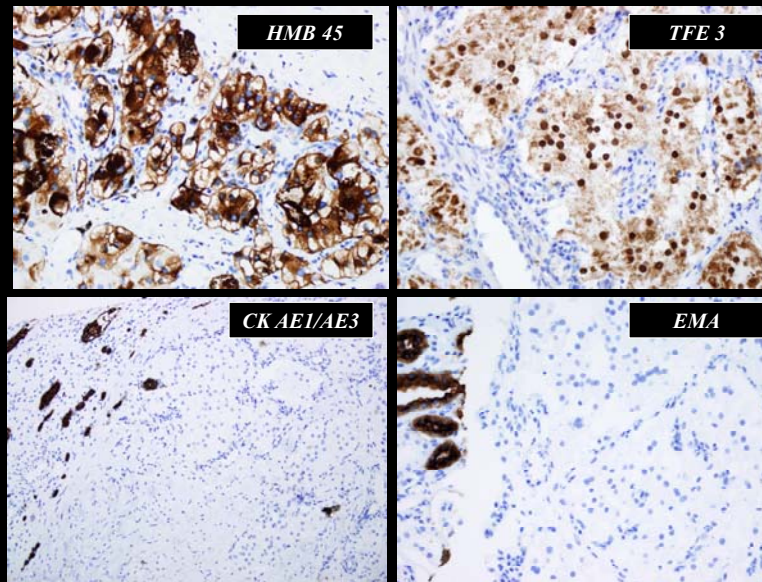


**54 cases
median age 36
50 *TFE3*
4 *TFEB***

Malouf et al, J Urol 185:24, 2011



Melanotic Xp11 renal cell carcinoma

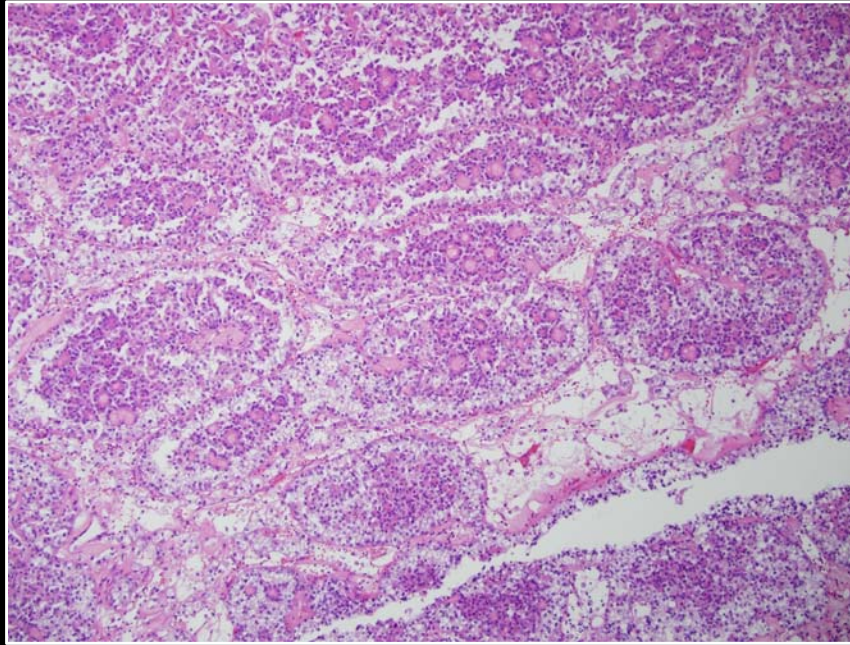


MELANOTIC Xp11 RENAL CANCER

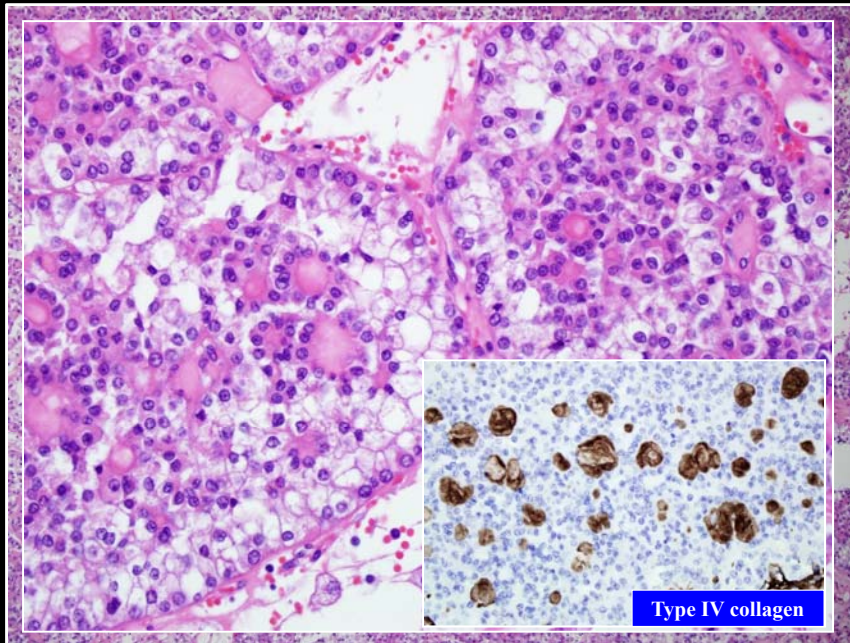
- Rare tumors with 4 published proven cases
- Melanin production reported in primary renal melanoma, renal cell carcinoma, renal PEComa and most recently in translocation carcinoma
- Cases with documented translocations have been in children or young adults
- Aggressive tumor with widespread metastases and death from tumor in 3 published cases; 4th case with short FU

Agaram P, et al. Am J Surg Pathol 33:609-619, 2009
 Chang I-W, et al. Am J Surg Pathol 33:1894-1901, 2009
 Varinot J, et al. Int J Surg pathol 19:285-289, 2011

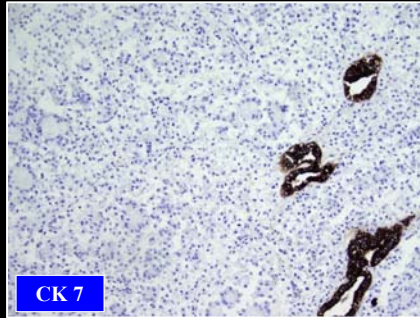
6:11 TRANSLOCATION CARCINOMA



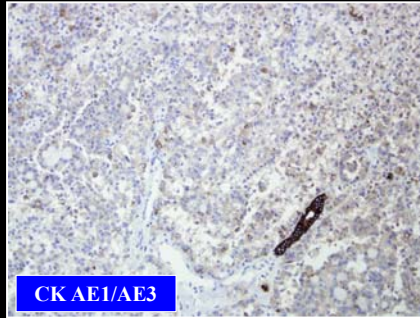
6:11 TRANSLOCATION CARCINOMA



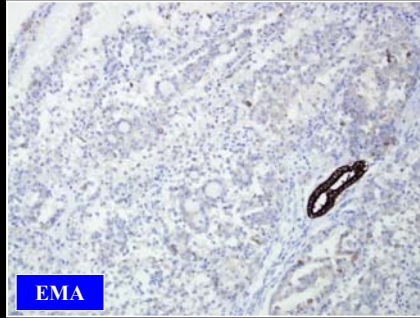
6:11 TRANSLOCATION CARCINOMA



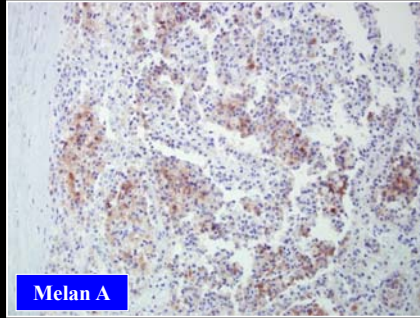
CK 7



CK AE1/AE3

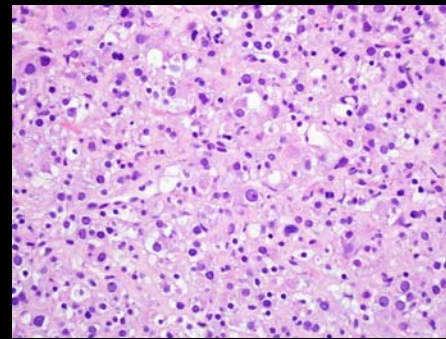
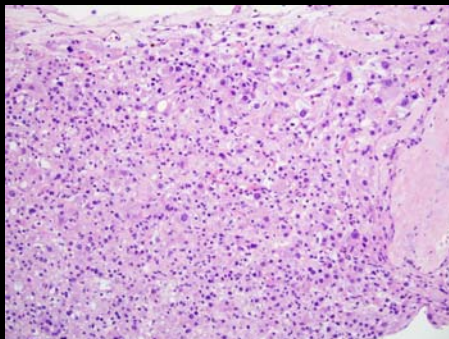
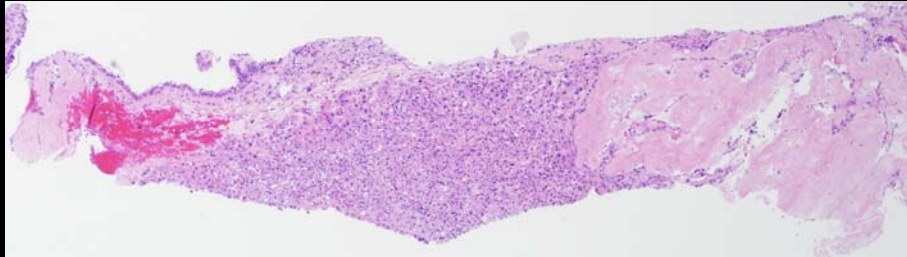


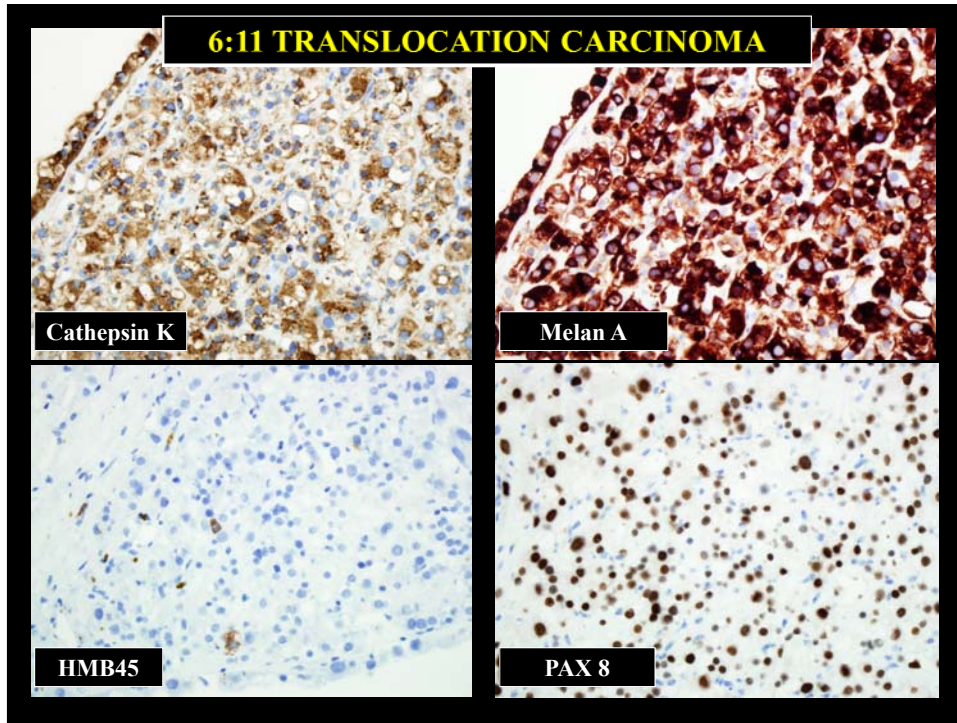
EMA



Melan A

6:11 TRANSLOCATION CARCINOMA





Translocation associated renal cell carcinoma is in the differential diagnosis of ALL unclassifiable renal cell carcinomas

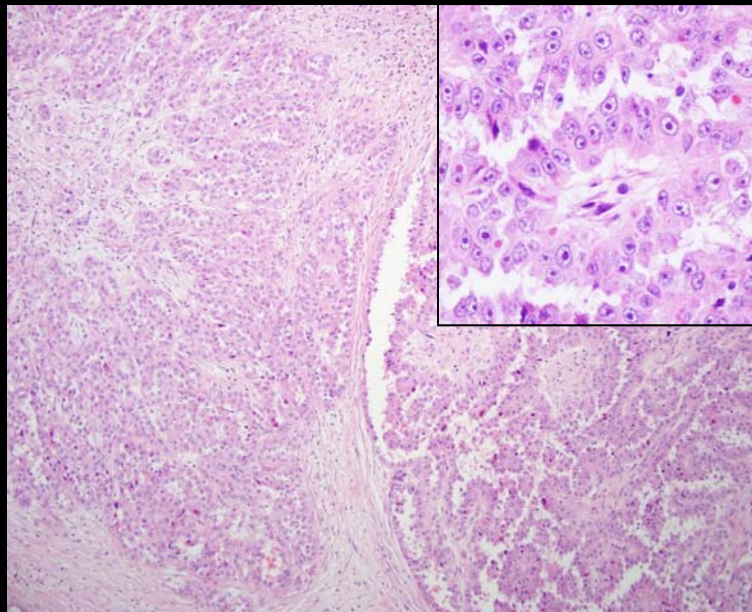
HLRCC SYNDROME

- Patients with mutation of *fumarate hydratase* gene (1q42.3-q43)
- Cutaneous and uterine leiomyomas
- Wide age range (17 – 87 years)
- More common in females
- Complex solid and papillary histology with macro orangophilic nucleoli and perinucleolar halo
- Aggressive tumors with up to 50% with metastasis at diagnosis

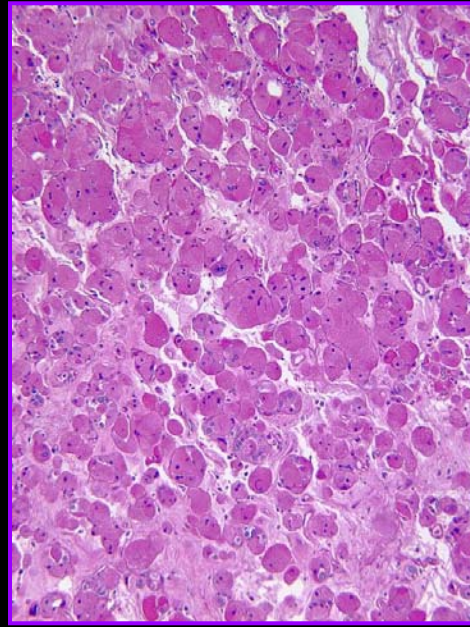
Merino et al. Am J Surg Pathol 31:1578, 2007

Grubb et al. J Urol 177:2074, 2007

HEREDITARY LEIOMYOMATOSIS

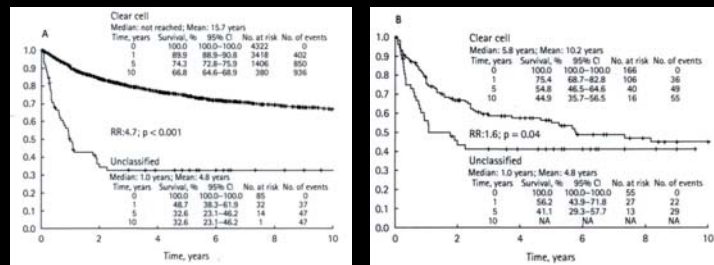


UNCLASSIFIED RENAL CELL CARCINOMA

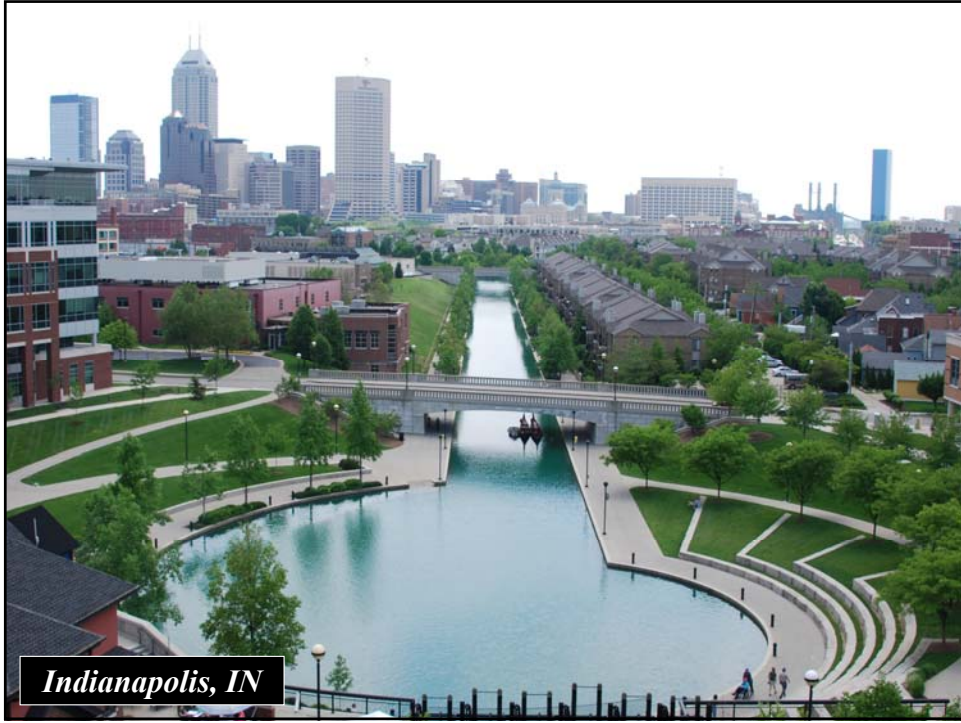


UNCLASSIFIED RCC

- Multi-institutional (12) study of 84 unclassified RCC
- Represented 1.3% of all RCC
- Matched with 166 clear cell RCC using Fuhrman grade and AJCC Stage



(Karakiewicz et al, BJU Int 100:802, 2007)



Indianapolis, IN