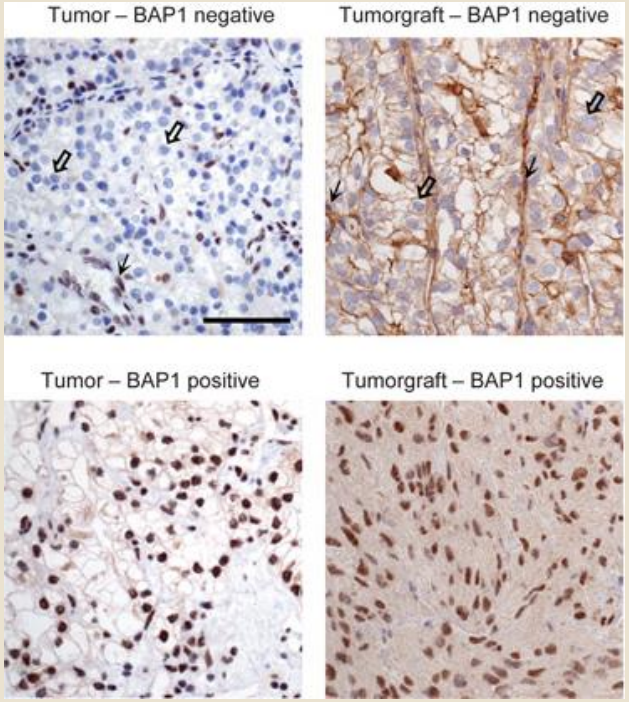
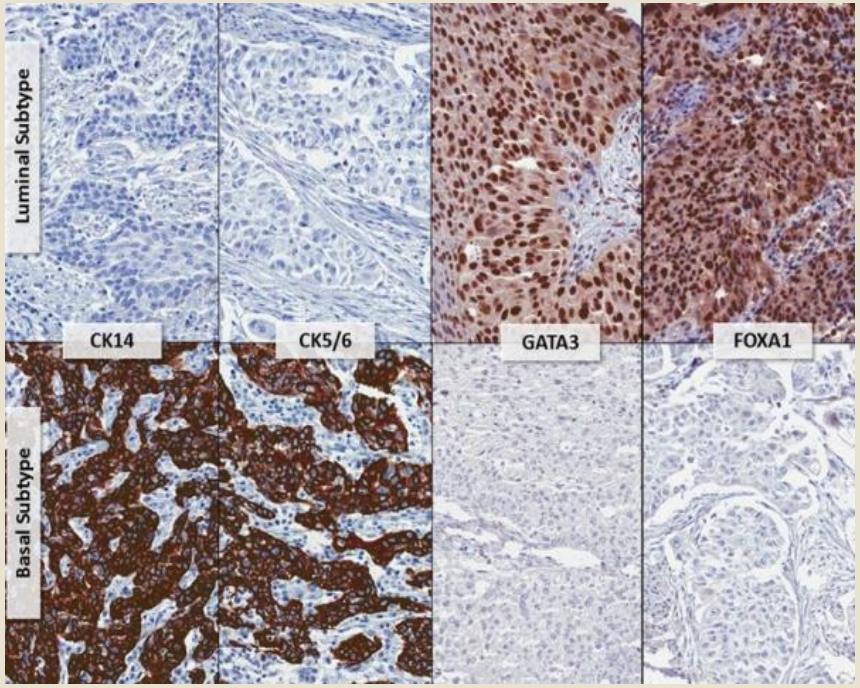
Renal and Bladder tumors What's new in 2016 ?





Dr Ph Camparo
Centre de Pathologie
Amiens
France

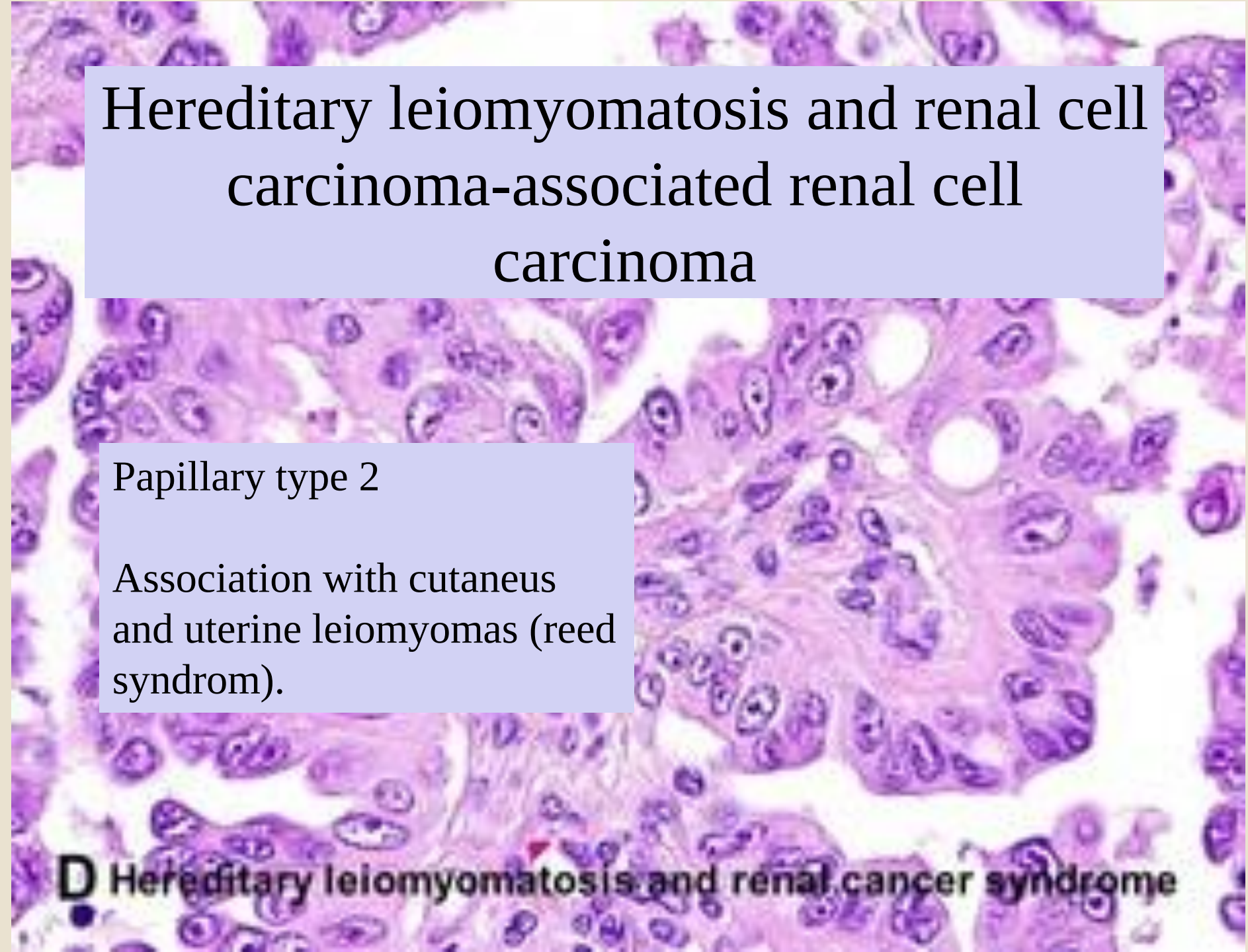
Renal Tumors
NEW ENTITES

Renal cell tumours	
Clear cell renal cell carcinoma	8310/3
Multilocular cystic renal neoplasm of low malignant potential	8316/1
Papillary renal cell carcinoma	8255/1
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated renal cell carcinoma	8311/3*
Chromophobe renal cell carcinoma	8317/3
Collecting duct carcinoma	8319/3
Renal medullary carcinoma	8510/3
MiT Family translocation carcinomas	8311/3
Succinate dehydrogenase (SDH)-deficient renal carcinoma	8312/3
Mucinous tubular and spindle cell carcinoma	8480/3
Tubulocystic renal cell carcinoma	8316/3
Acquired cystic disease associated renal cell carcinoma	8316/3
Clear cell papillary renal cell carcinoma	8323/1
Renal cell carcinoma, unclassified	8312/3
Papillary adenoma	8260/0
Oncocytoma	8290/0

Hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma

Papillary type 2

Association with cutaneus and uterine leiomyomas (reed syndrom).

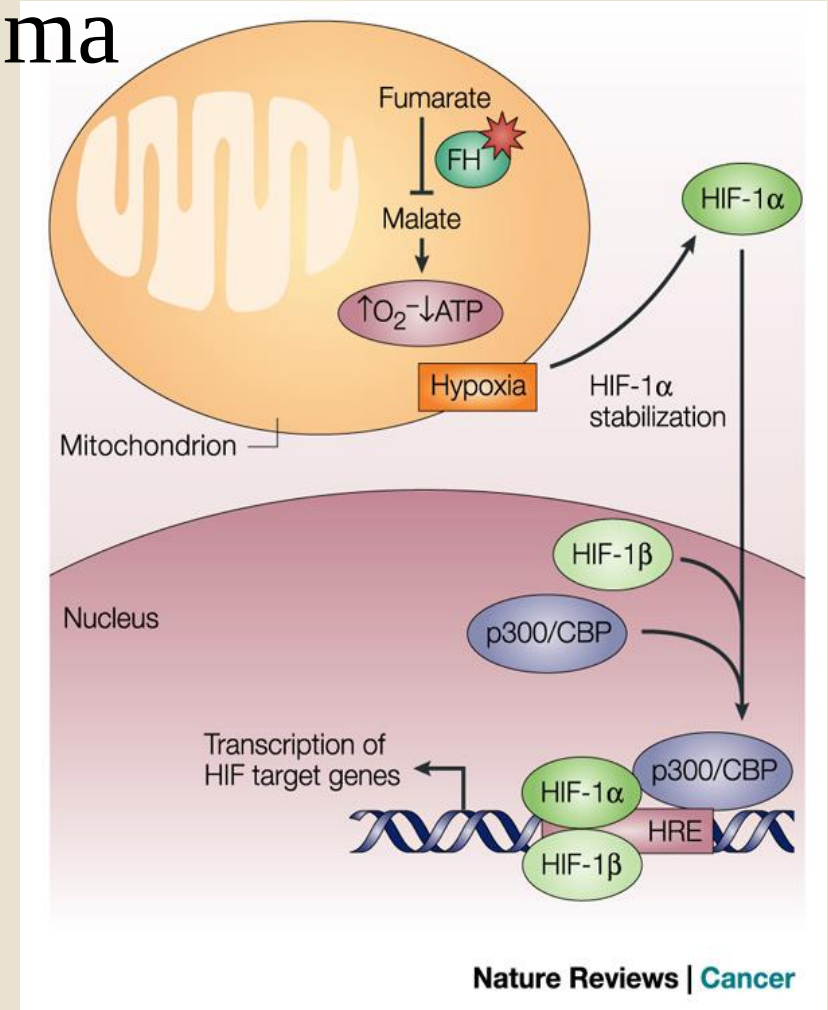


Hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma

Dominant Autosomic :
Chr 1q42.3-43 (fumarate hydratase gene) (HIF/VHL metabiolic pathway)

IHC : loss of FH expression

Poor prognosis

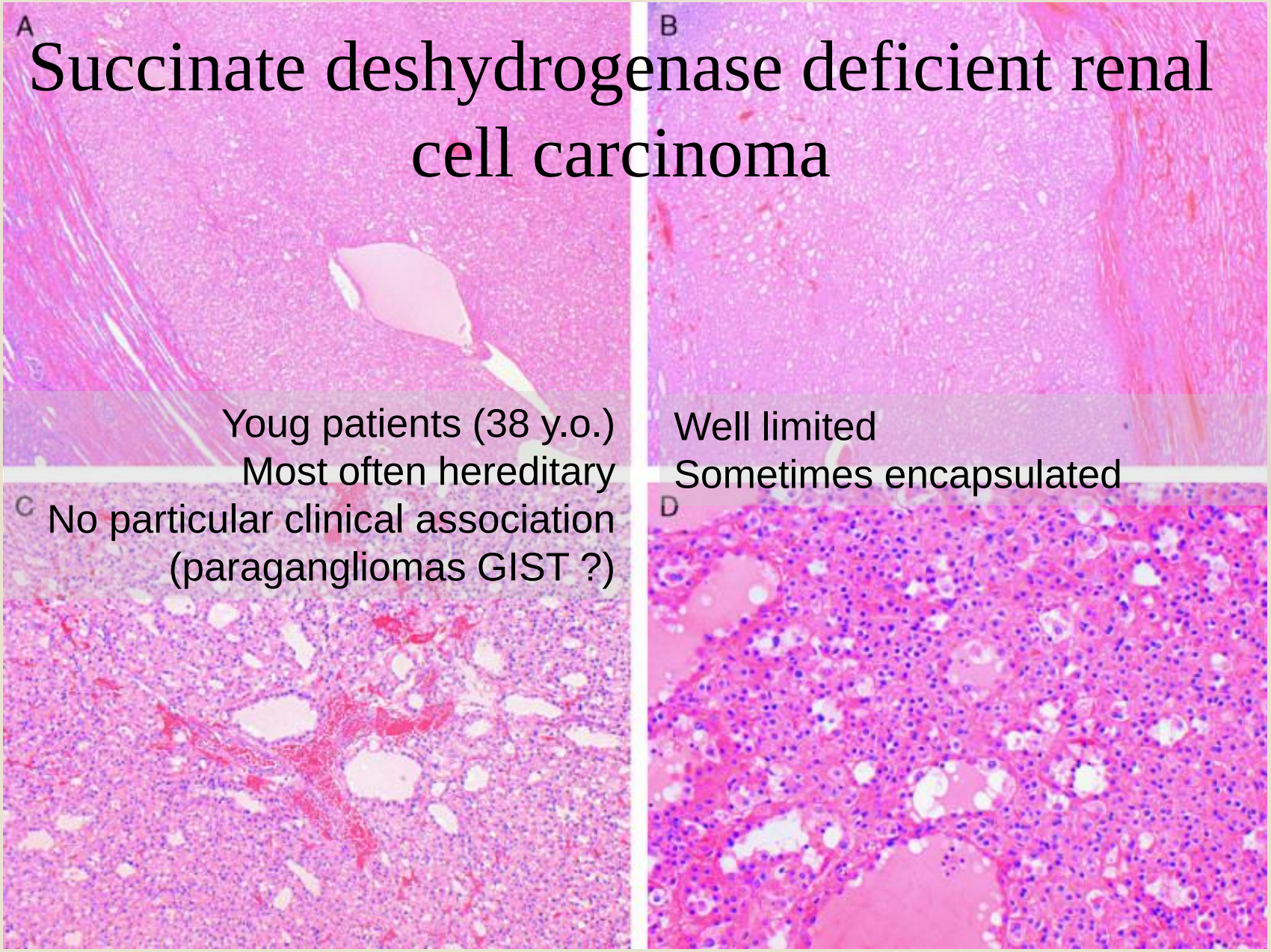


Major inherited syndromes involving kidney

Syndrome	Gene	Chromosome	Kidney	Other
VHL	VHL	3p25	Multiple, bilateral CCRCC, renal cysts	Retinal and CNS haemangioblastomas, phaeochromocytoma, pancreas cysts and neuroendocrine tumours, endolymphatic sac tumors of the inner ear, epididymal and broad ligament cystadenomas
Hereditary PRCC	C-MET	7q31	Multiple, bilateral PRCC Type 1	
Hereditary leimyomatosis and RCC	FH	1q42	PRCC non type 1	Uterine leiomymoas and leiomyosarcomas
Birt-Hogg-Dubé	BHD	17p11	Multiple ChRCC, CCRCC, hybrid Onco, PRCC oncocytic tumors	Lung cysts, spontaneaous pneumothorax, facial fibrofolliculomas
Tuberous sclerosing complex (Bourneville syndrom)	TSC1 TSC2	9q34 16p13	Multiple, bilateral angiomyolipomas, lymphangioleomyoma tosis	Cardiac rhabdomymoas, adenomatous popypd f duodenum and small intestine, lung and kidney cysts, coritacla tubers and subependymal giant cell tumors

Renal cell tumours	
Clear cell renal cell carcinoma	8310/3
Multilocular cystic renal neoplasm of low malignant potential	8316/1
Papillary renal cell carcinoma	8255/1
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated renal cell carcinoma	8311/3*
Chromophobe renal cell carcinoma	8317/3
Collecting duct carcinoma	8319/3
Renal medullary carcinoma	8510/3
MiT Family translocation carcinomas	8311/3
Succinate dehydrogenase (SDH)-deficient renal carcinoma	8312/3
Mucinous tubular and spindle cell carcinoma	8480/3
Tubulocystic renal cell carcinoma	8316/3
Acquired cystic disease associated renal cell carcinoma	8316/3
Clear cell papillary renal cell carcinoma	8323/1
Renal cell carcinoma, unclassified	8312/3
Papillary adenoma	8260/0
Oncocytoma	8290/0

Succinate deshydrogenase deficient renal cell carcinoma



Youg patients (38 y.o.)
Most often hereditary
No particular clinical association
(paragangliomas GIST ?)

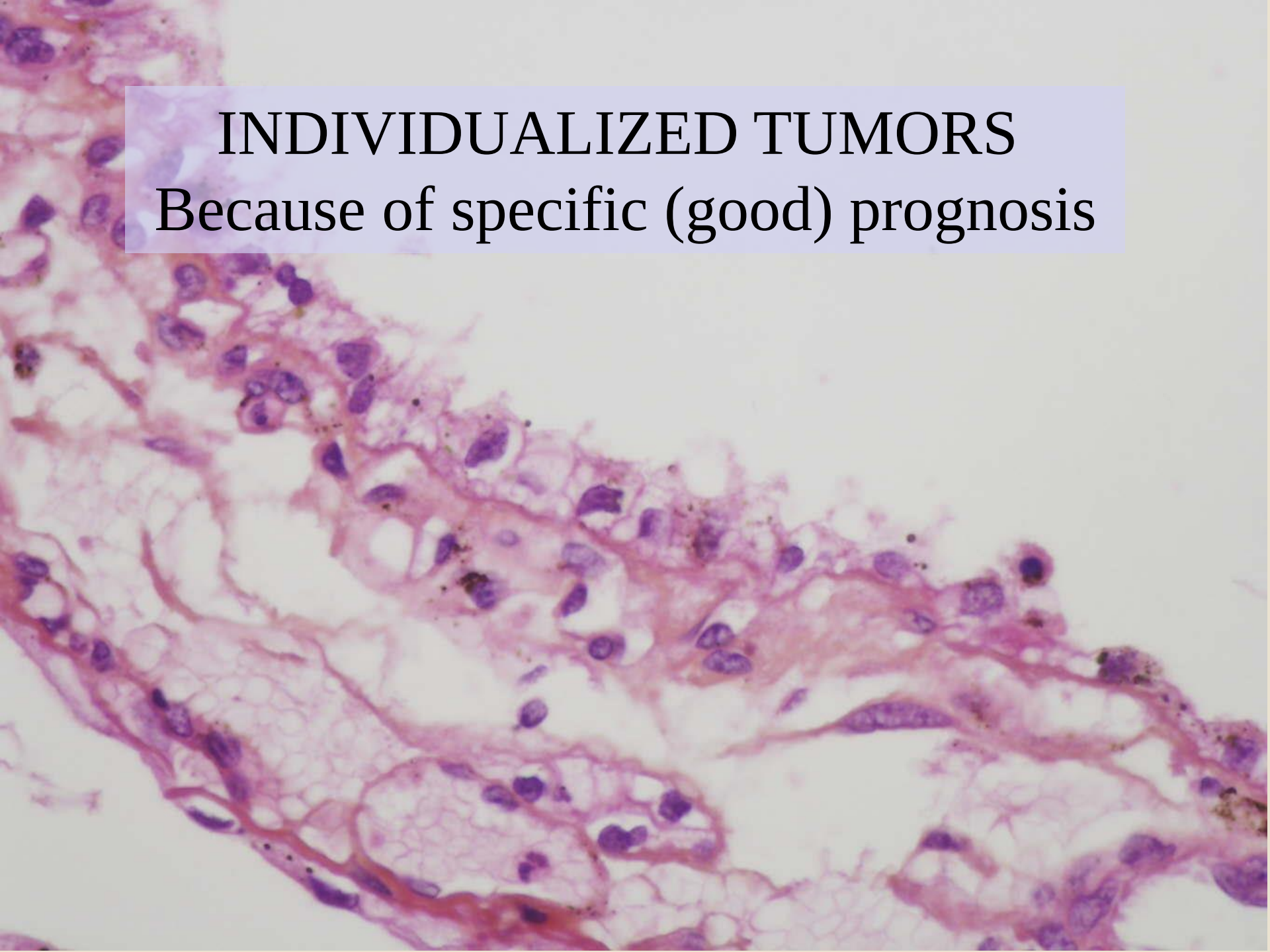
Well limited
Sometimes encapsulated

Succinate deshydrogenase deficient renal cell carcinoma

Germ cell mutations of SDH-B (most often)

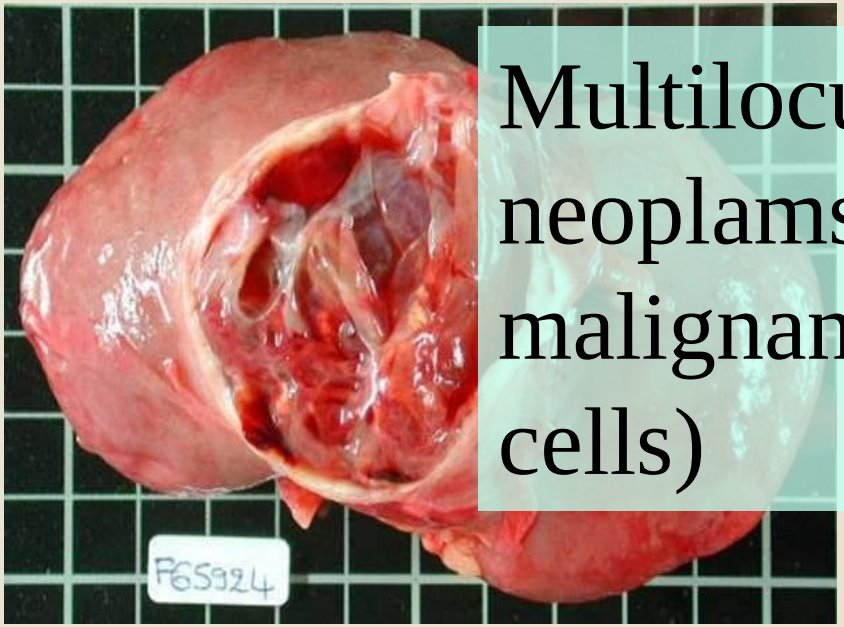
IHC :
SDH-B - (but SDH-A and C +)
CK7 –
c-kit +/- (focally)
Pax8 and E-Cadh « always » +
Differencial diagnosis : oncocytomas

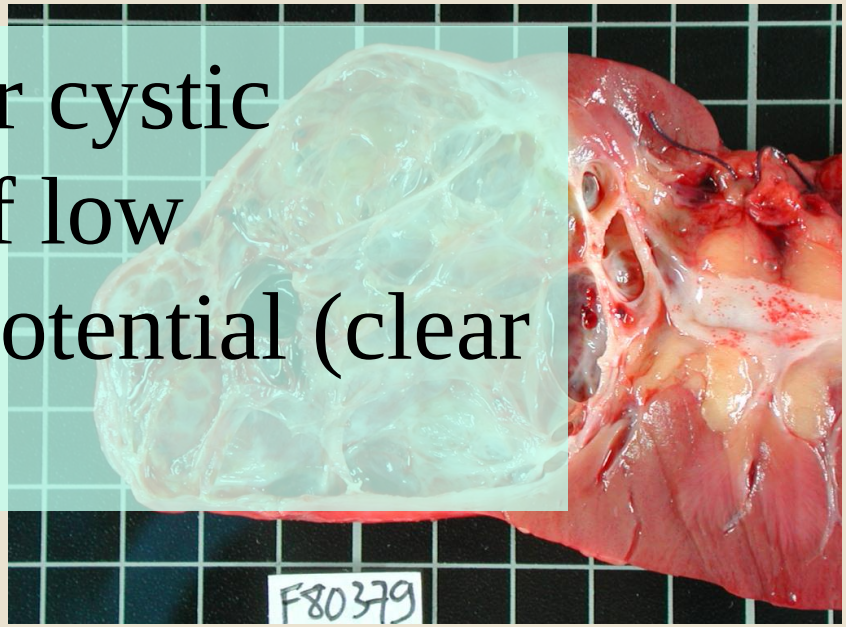
Am J Surg Pathol. 2014 Dec;38(12):1588-602



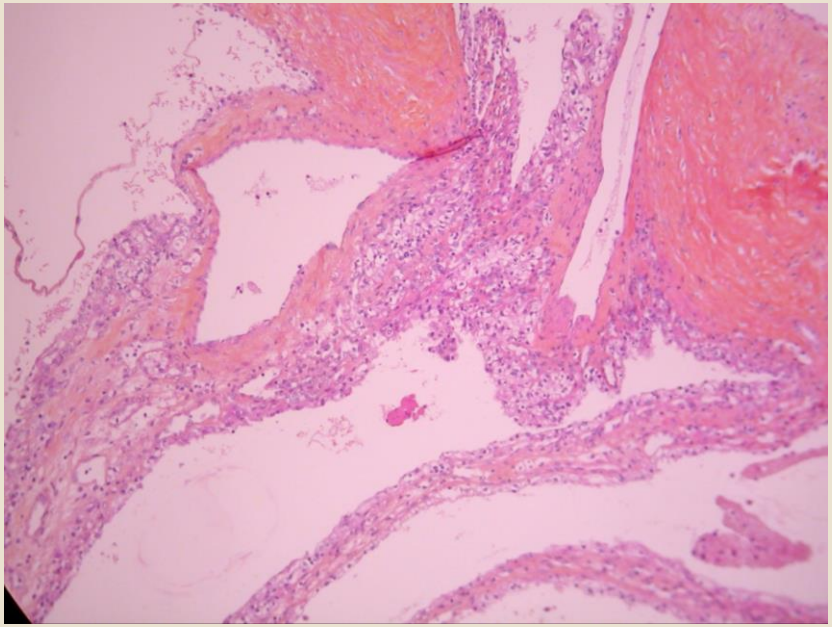
INDIVIDUALIZED TUMORS
Because of specific (good) prognosis

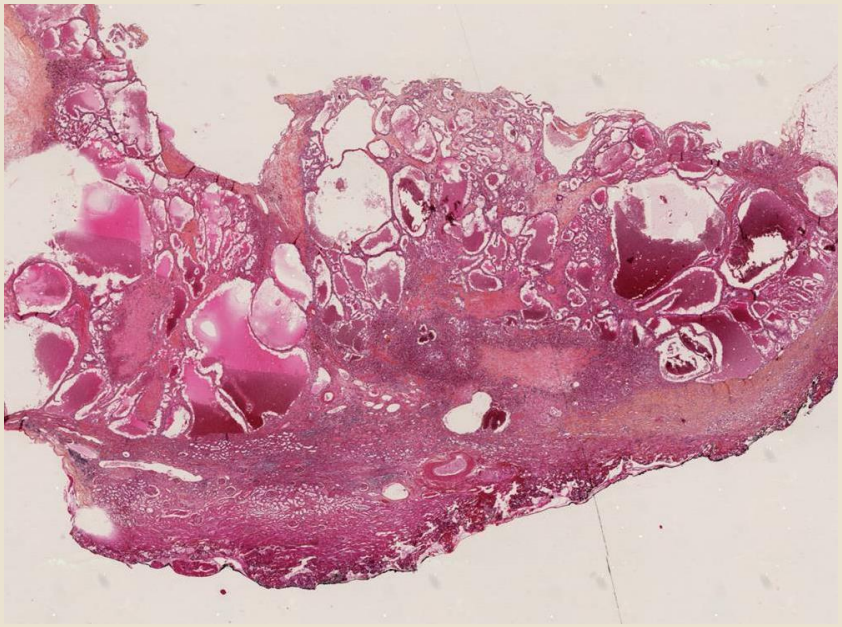
Multilocular cystic neoplams of low malignant potential (clear cells)



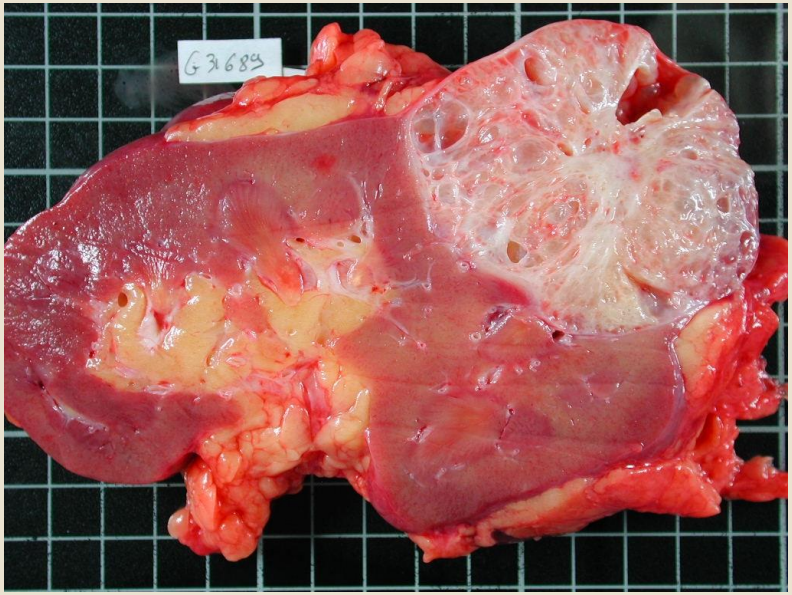


Cystic lesions Bosniak 3 or 4

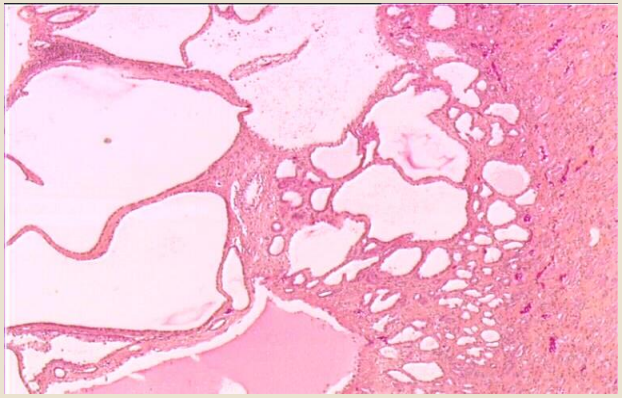


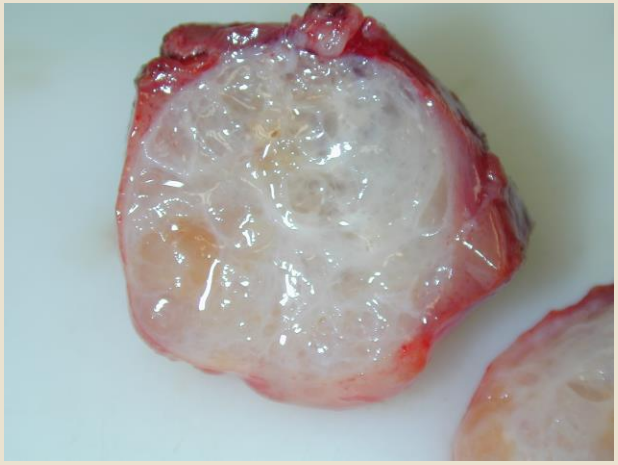


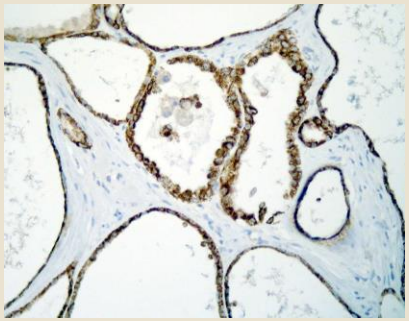
Tubulo-cystic carcinoma (low grade)

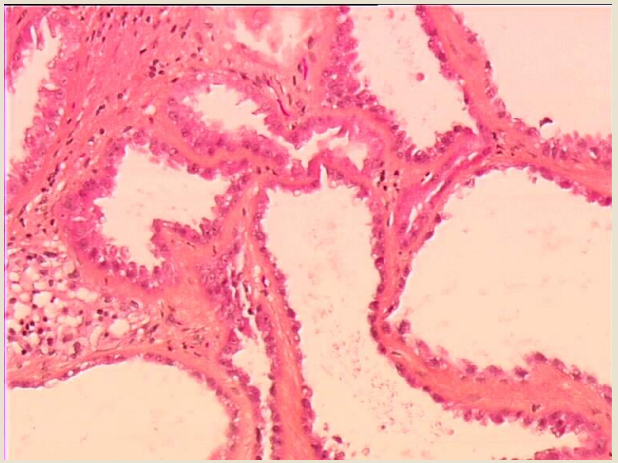


Small spongiform tumours









INDIVIDUALIZED TUMORS
Because of specific clinical conditions (end-stage renal disease)

Chromophobe renal cell carcinoma	8317/3
Collecting duct carcinoma	8319/3
Renal medullary carcinoma	8510/3
MiT Family translocation carcinomas	8311/3
Succinate dehydrogenase (SDH)-deficient renal carcinoma	8312/3
Mucinous tubular and spindle cell carcinoma	8480/3
Tubulocystic renal cell carcinoma	8316/3
Acquired cystic disease associated renal cell carcinoma	8316/3
Clear cell papillary renal cell carcinoma	8323/1
Renal cell carcinoma, unclassified	8312/3
Papillary adenoma	8260/0
Oncocytoma	8290/0

Acquired cystic disease associated renal cell carcinomas

Spectrum of Epithelial Neoplasms in End-Stage Renal Disease

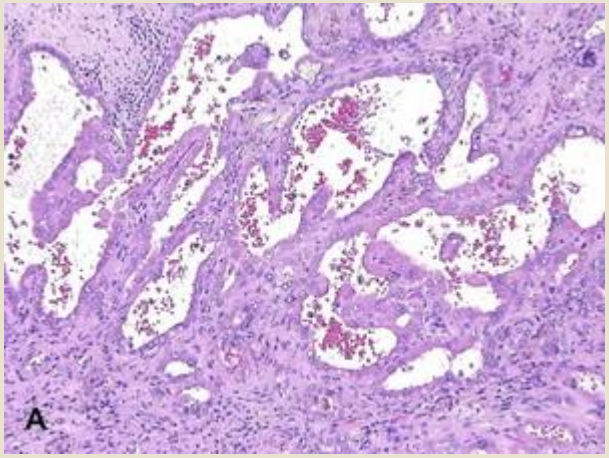
An Experience From 66 Tumor-Bearing Kidneys With Emphasis on Histologic Patterns Distinct From Those in Sporadic Adult Renal Neoplasia

Satish K. Tickoo, MD, Mariza N. dePeralta-Venturina, MD,†‡ Lara R. Harik, MD,* Heath D. Worcester, MD,§ Mohamed E. Salama, MD,‡ Andrew N. Young, MD,§ Holger Moch, MD,‖ and Mahul B. Amin, MD§*

>30% carcinomas in end-stage renal disease

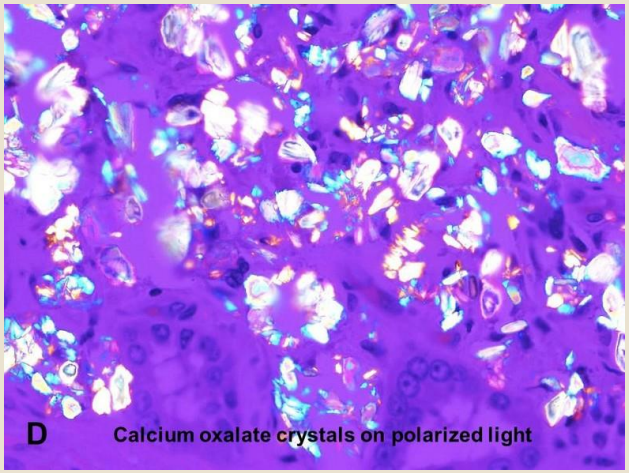
Multifocal

Bilateral 1/3



Calcium Oxalate crystals

Good prognosis



Clear Cell Papillary Renal cell carcinomas

Mean age : 58.1

Sex ratio : 2,3/1

Spectrum of Epithelial Neoplasms in End-Stage Renal Disease

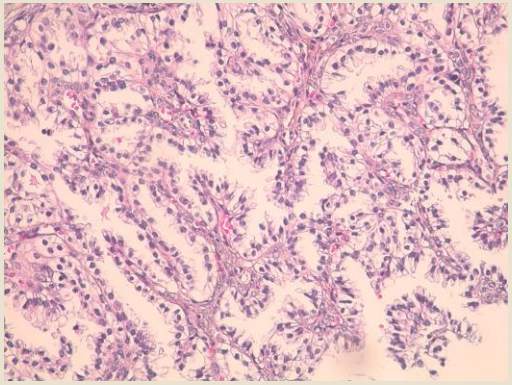
An Experience From 66 Tumor-Bearing Kidneys With Emphasis on Histologic Patterns Distinct From Those in Sporadic Adult Renal Neoplasia

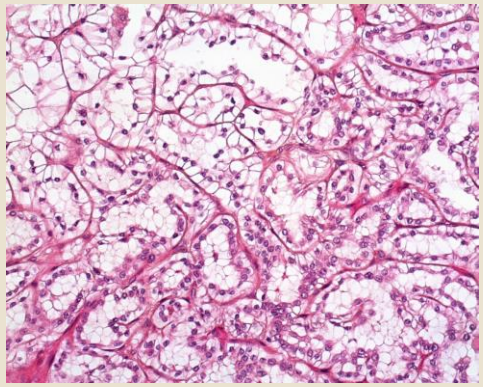
Satish K. Tickoo, MD, Mariza N. dePeralta-Venturina, MD,†‡ Lara R. Harik, MD,* Heath D. Worcester, MD,§ Mohamed E. Salama, MD,‡ Andrew N. Young, MD,§ Holger Moch, MD,‖ and Mahul B. Amin, MD§*

30% end-stage renal disease

60% : normal kidney

Tubular or papillary architecture, compact or cystic



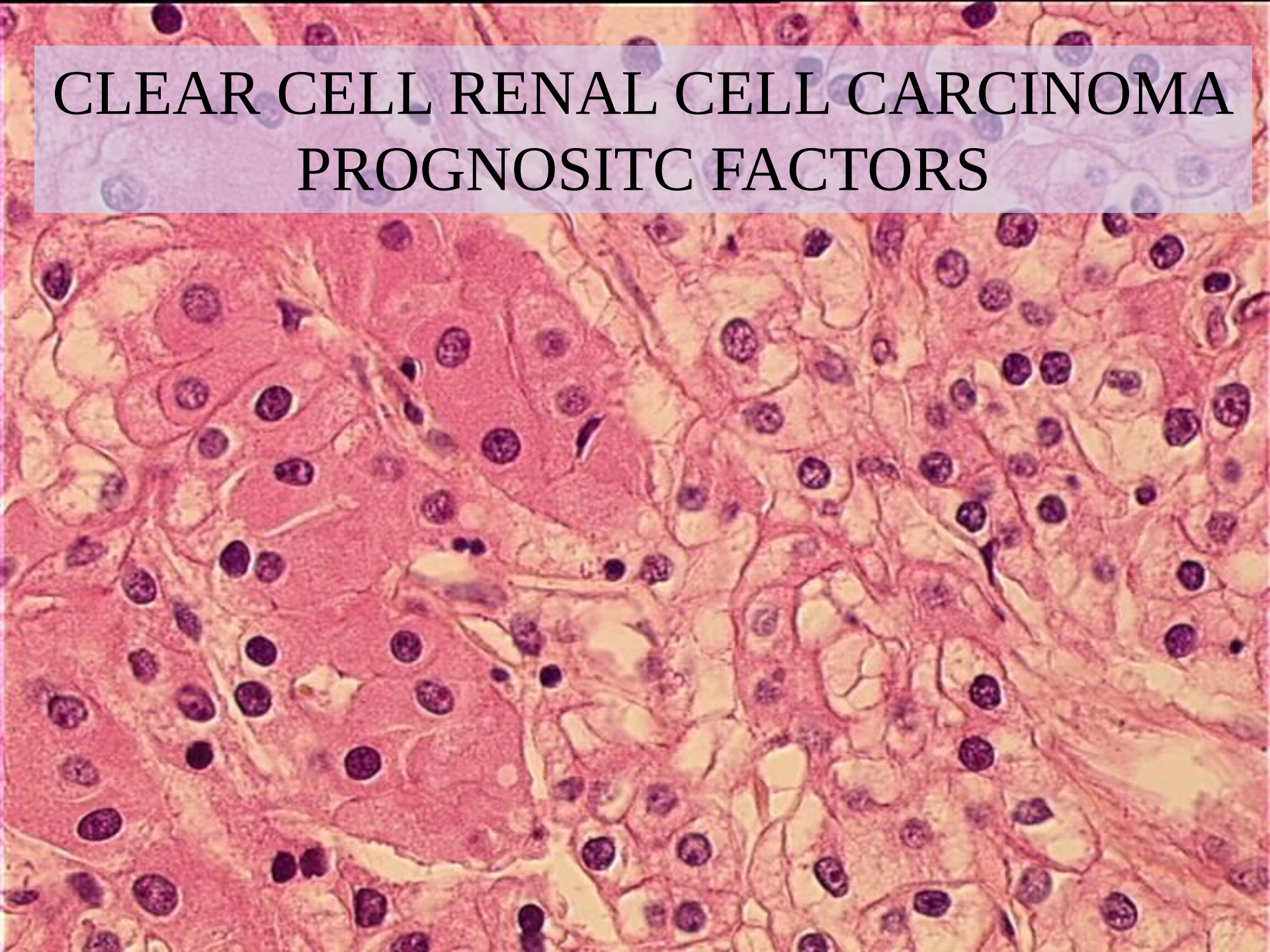


pT1

Low Fuhrman grade

No recurrence nor progression yet

CLEAR CELL RENAL CELL CARCINOMA PROGNOSITC FACTORS



Grade Fuhrman/ISUP

Table 1.03 WHO / International Society of Urological Pathology (ISUP) grading system for clear cell renal cell carcinoma and papillary renal cell carcinoma {677}.

Grade	Description
Grade 1	Nucleoli are absent or inconspicuous and basophilic at ×400 magnification.
Grade 2	Nucleoli are conspicuous and eosinophilic at ×400 magnification and visible but not prominent at ×100 magnification.
Grade 3	Nucleoli are conspicuous and eosinophilic at ×100 magnification.
Grade 4	There is extreme nuclear pleomorphism, multinucleate giant cells, and/or rhabdoid and/or sarcomatoid differentiation.

CLEAR CELL RENAL CELL CARCINOMA OTHER PROGNOSITC FACTORS

Sarcomatoid differenciation 1-8%, mainly CCRCC

- 15 à 20 % 5y OS

Rhabdoid differenciation : percentage. worse prognosis

Necrosis : percentage, focal diffuse

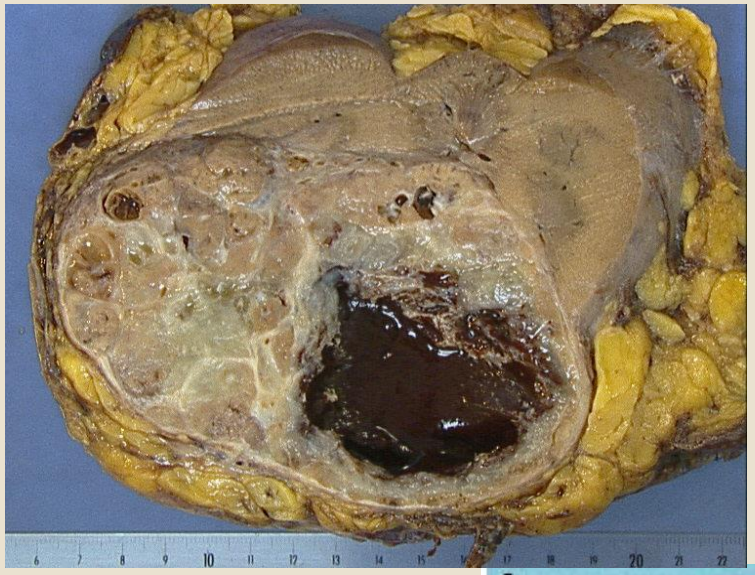
- Value +/- after antiangiogenic therapies

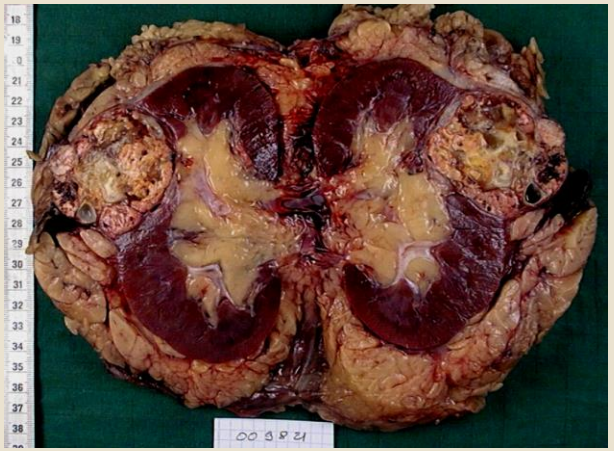
PT Stage is the major prognostic element

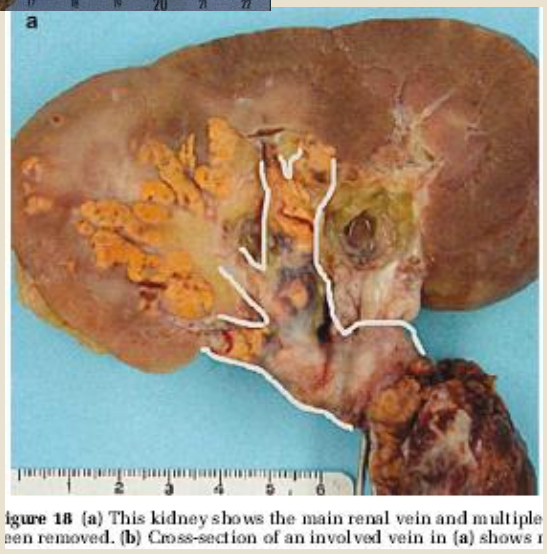
pT1 and pT2 are intra renal tumors (size 4, 7, 10 cm)

pT3 :
MACROSCOPICALLY

Adrenal gland involvement
Macroscopically +++
By contiguity (pT4)
If metastatic (pM1)

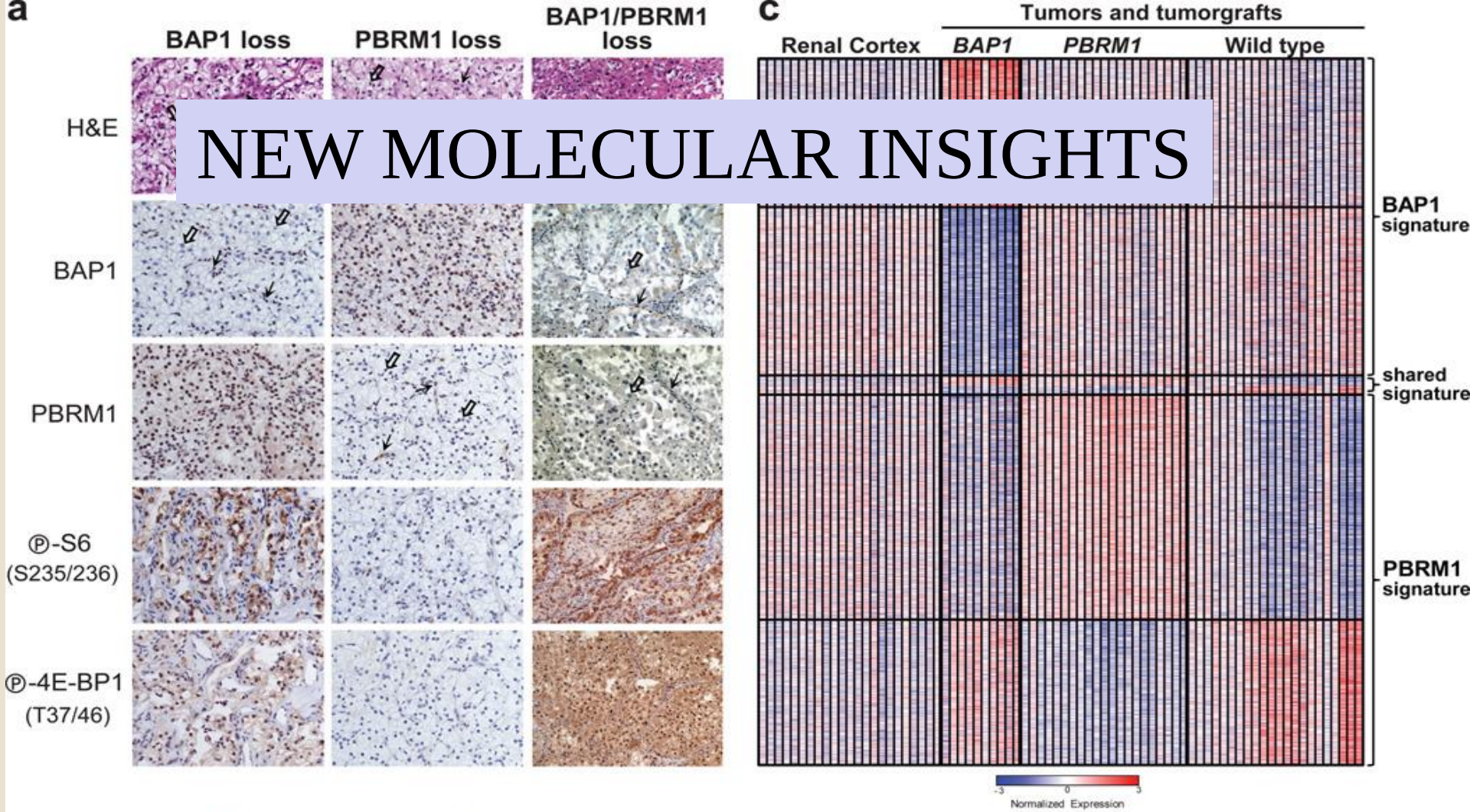


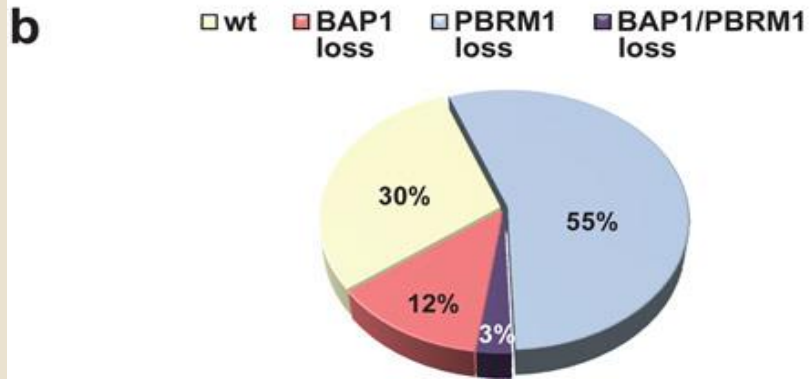


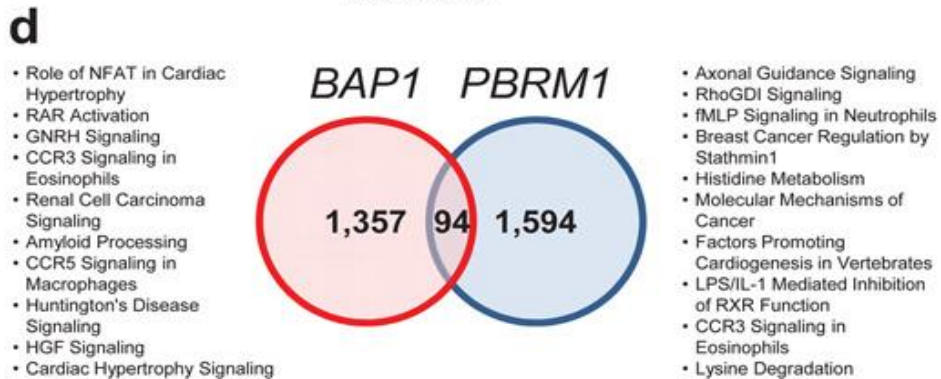


igure 18 (a) This kidney shows the main renal vein and multiple
een removed. (b) Cross-section of an involved vein in (a) shows

NEW MOLECULAR INSIGHTS







ARTICLE Nature 2013 49:43-49 OPEN
doi:10.1038/nature12222

Comprehensive molecular characterization of clear cell renal cell carcinoma

The Cancer Genome Atlas Research Network*

PBRM1 : Polybromo-1 Part of Switch/Sucrose NonFermentable (SWI/SNF) complex
DNA stabilisation and repair.
In CCRCC inactivating mutations of : 53%.

BAP 1 : BRCA1 associated protein-1
Cell proliferation
DNA stabilization and repair (BRCA1)
In CCRCC inactivating mutations of : 10-15%

Dalgliesh GL, et col. Nature. 2010 Jan 21; 463(7279): 360–363.
Peña-Llopis S et col. Nat Genet. 2012;44:751–759.

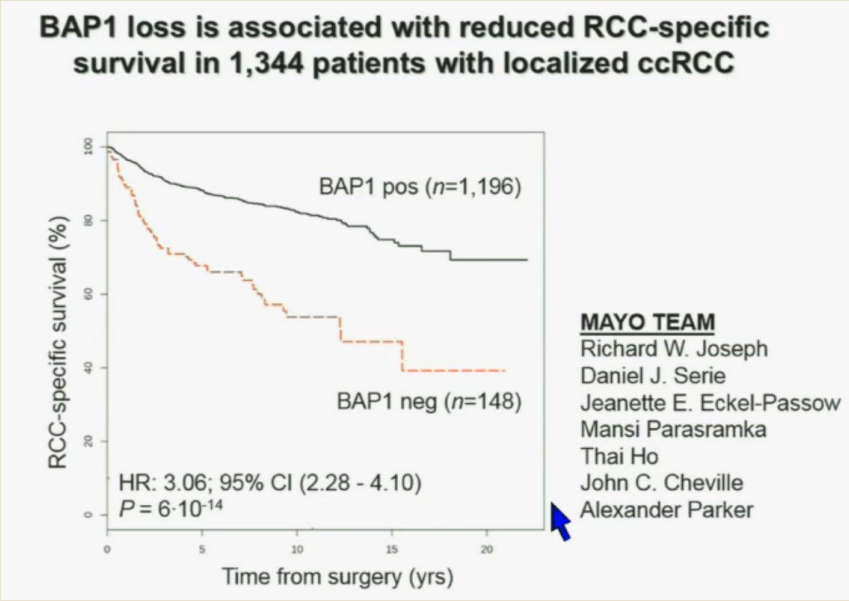
PBRM1 and BAP1 mutation are largely mutually exclusive and PBRM1 and BAP1 mutated CCRCC have distinct prognosis

Mutations of BAP1 associated with :

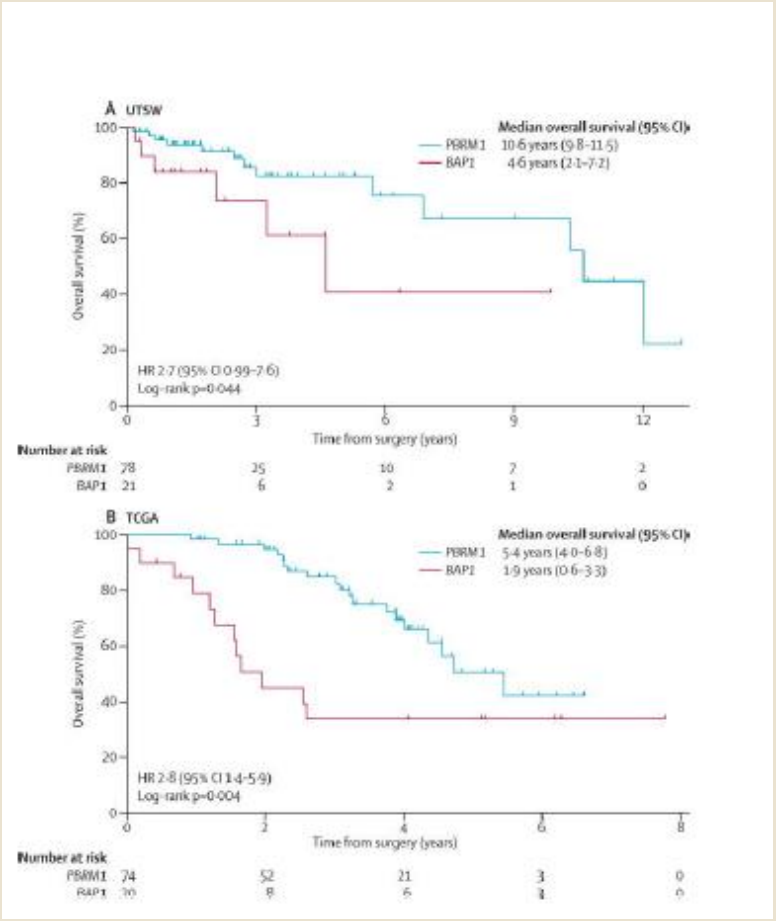
- hight risk tumors (grade/stage) (HR 7,71 95% CI 2,08-28,6 p=0002)

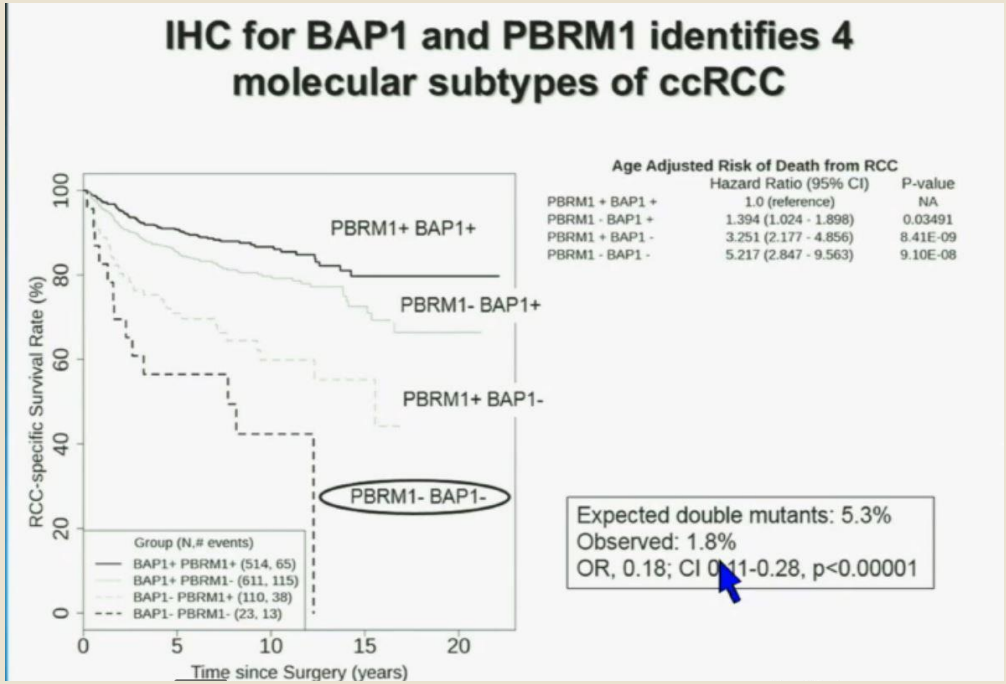
- shortened OS (4,6 y (95% CI 2,1-7,2) vs 10,6 y for PBRM1mutations (95% CI 9.8-11.5).

P Kapur et coll Lancet Oncology 2013;14:159-67



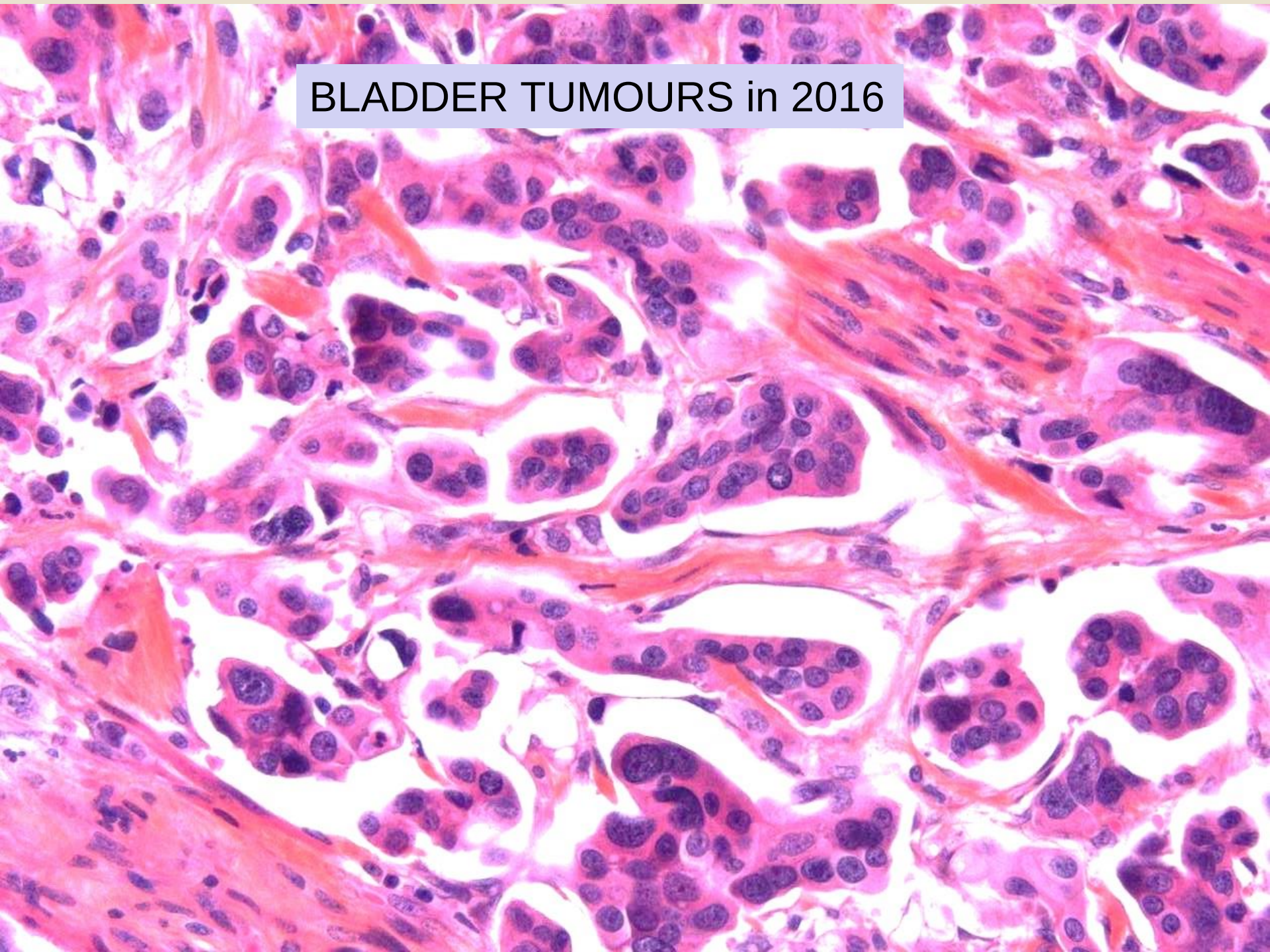
PBRM1 and BAP1 mutation are largely mutually exclusive and PBRM1 and BAP1 mutated CCRCC have distinct prognosis

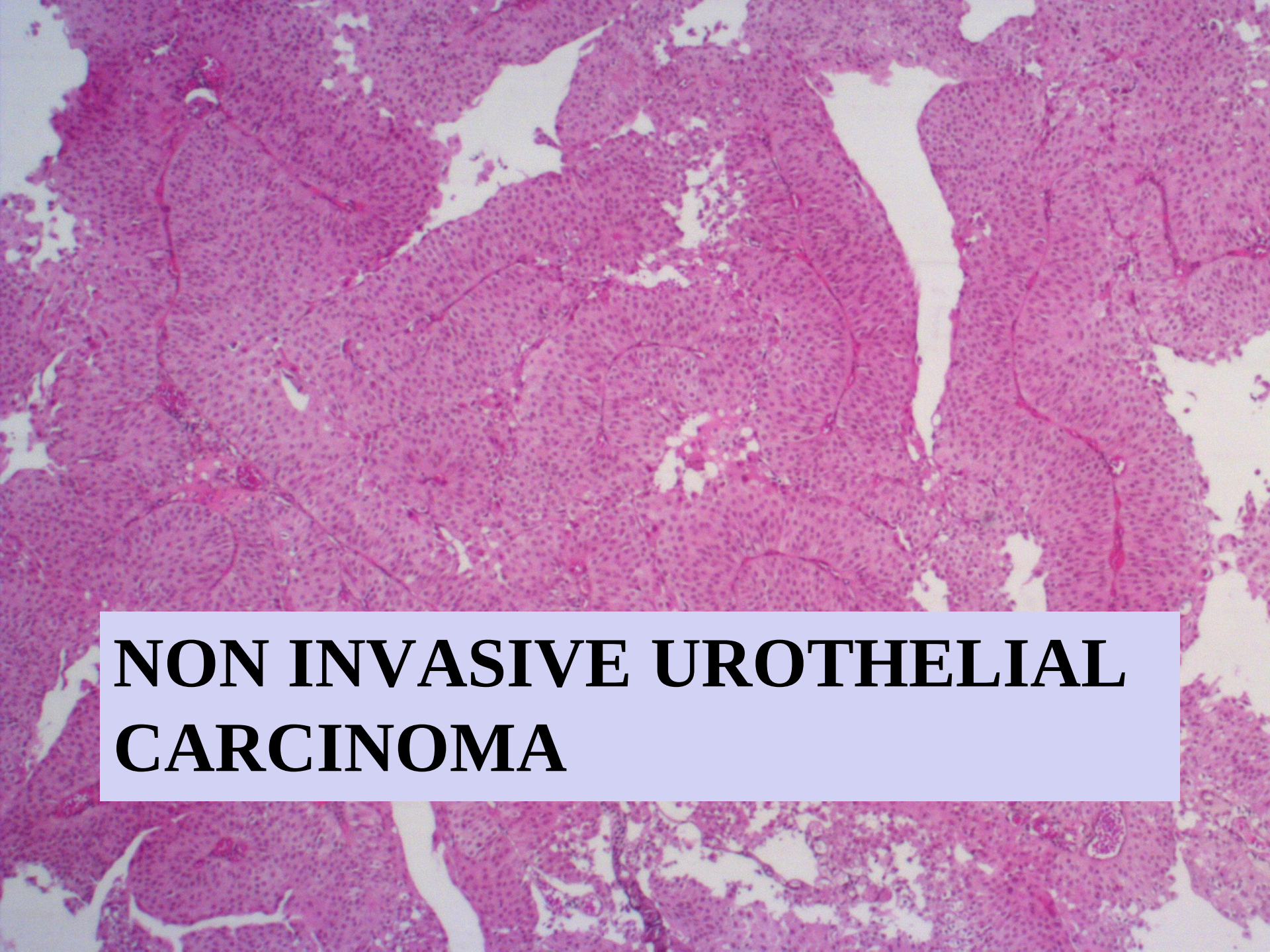




P Kapur et coll Lancet Oncology 2013;14:159-67

BLADDER TUMOURS in 2016





NON INVASIVE UROTHELIAL CARCINOMA

Maintining of PUNLMP, pTa LG-HG

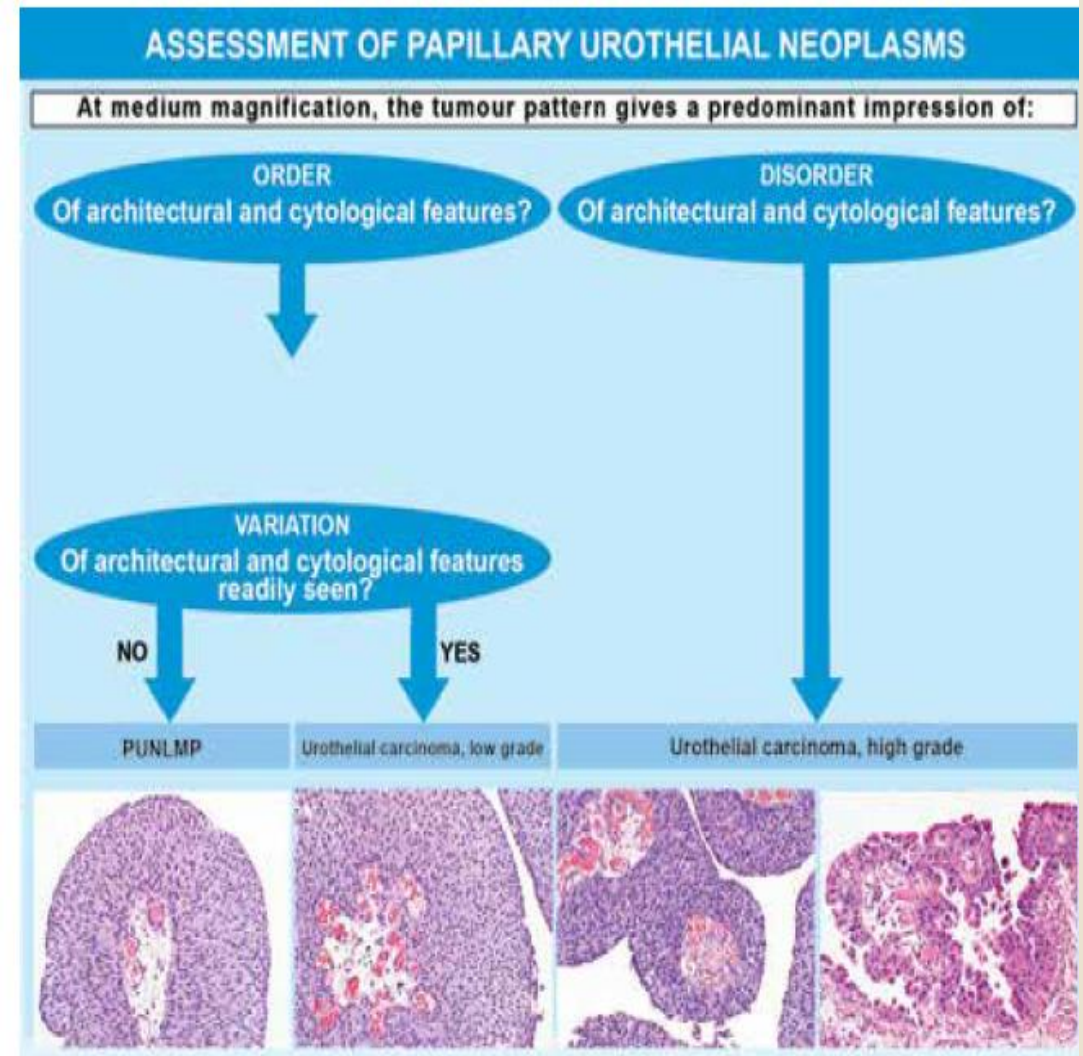
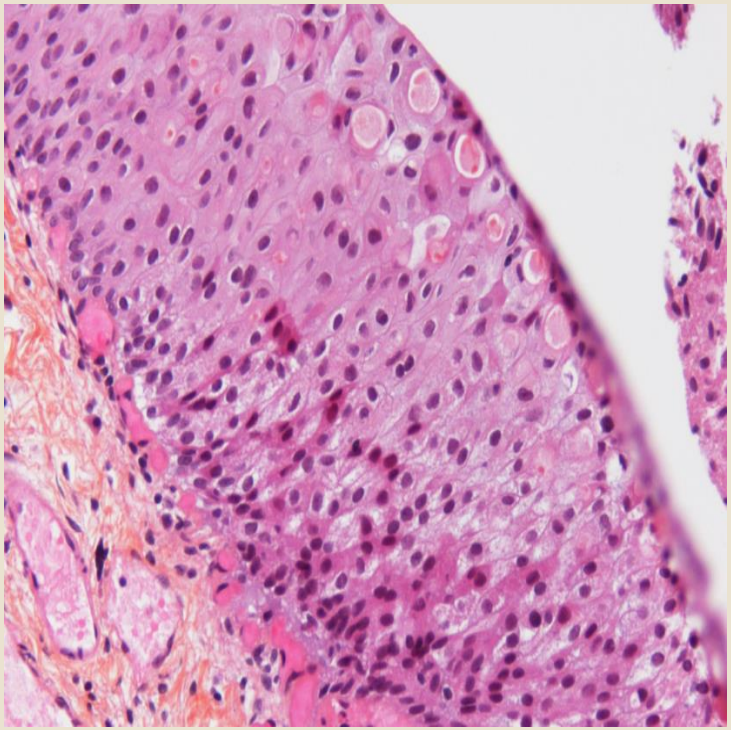


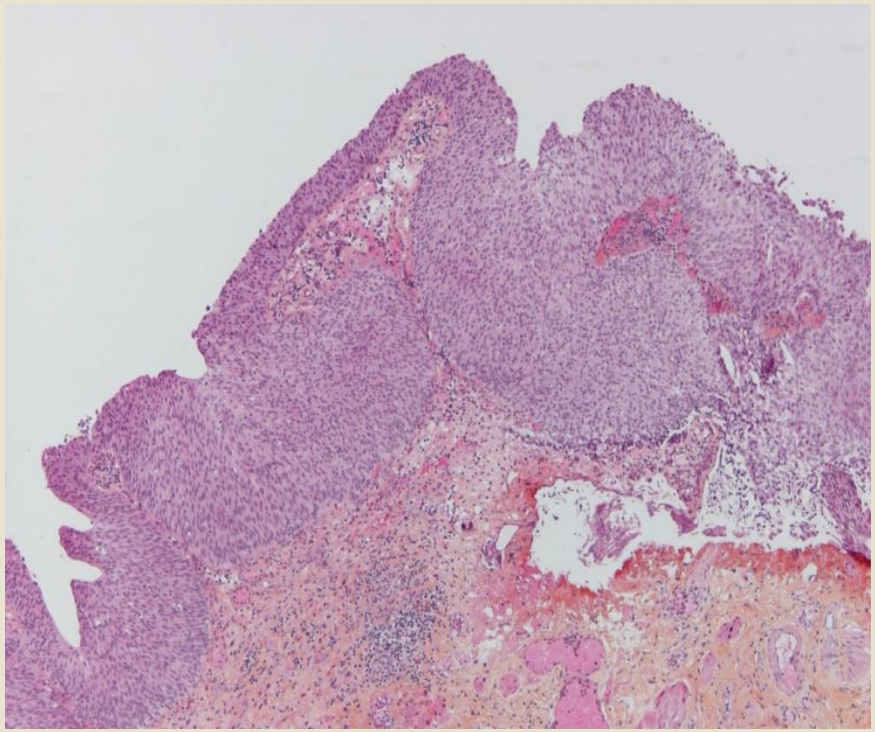
Fig. 2.29 Flow chart of the grading algorithm for papillary urothelial neoplasms.

WHO 2016

New terminology

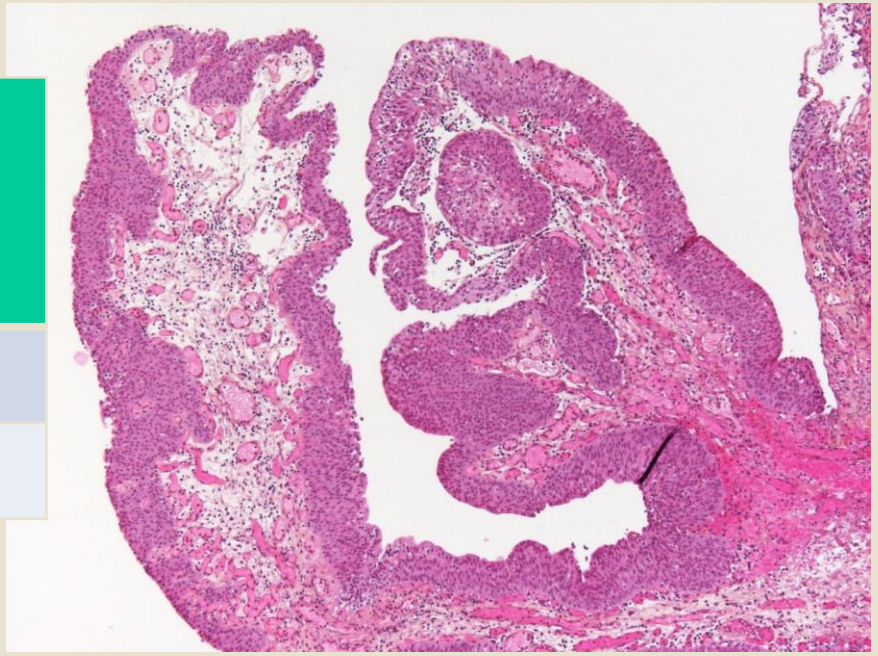
- Papillary and flat hyperplasia = urothelial proliferation of uncertain malignant potential





Papillary and flat hyperplasia = urothelial proliferation of uncertain malignant potential

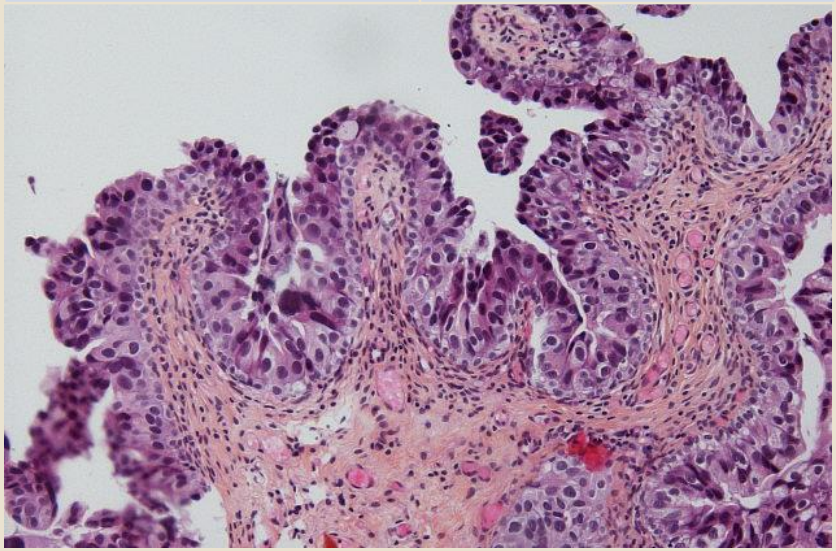
Papillary Hyperplasia Nb of cases	progression
16	4 pTa LG
	3 pTa HG



48% will developped urothelial carcinoma

PUPMI papillary with atypia

PUPMI with atypias	Follow-up 1 year
10	19 recurrences



Histology
1 papilloma
1 pTa low grade
10 pTa high grade
4 Cis
3 ≥pT1

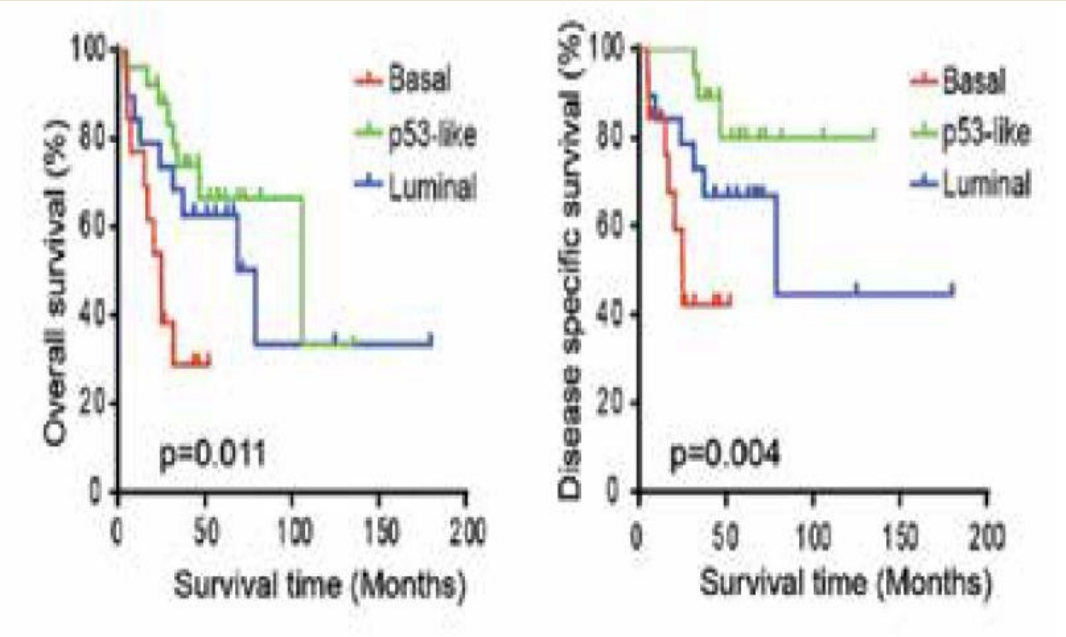
To be considered as CIS

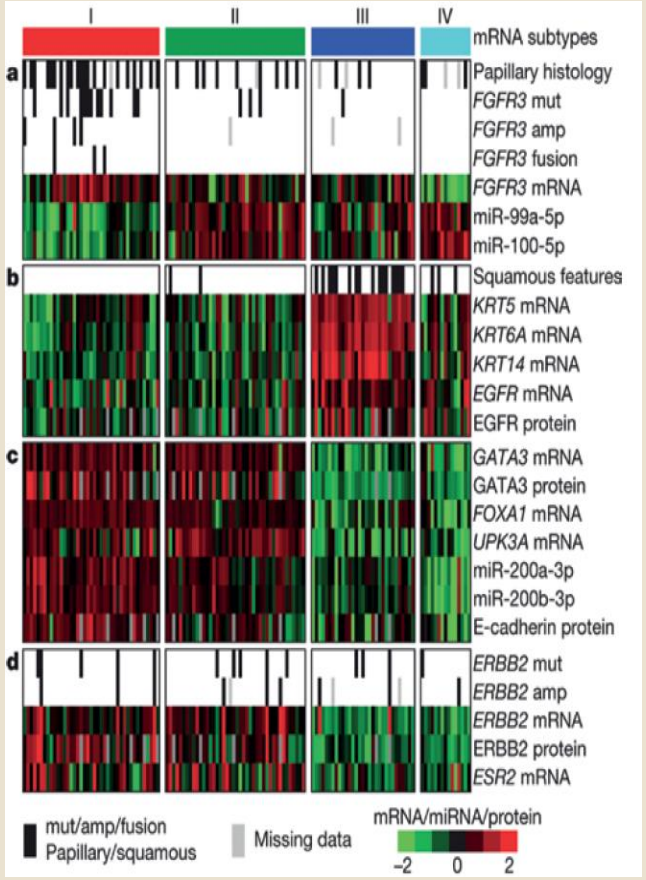
Hungerhuber, 2007, Urology
Obermann, 2003, J Pathol
Swierczynski Hum Path 2002

INVASIVE UROTHELIAL CARCINOMA

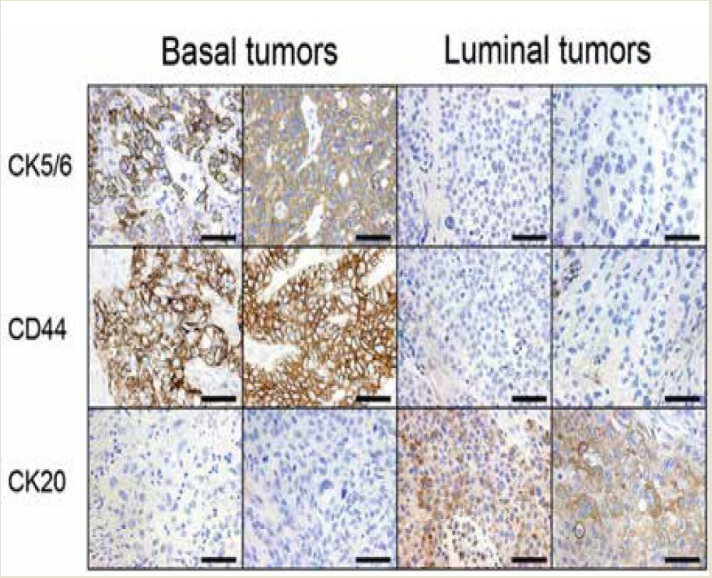
Molecular subtypes

- Gene sequencing studies
  - So-called luminal, p53-like and basal/squamous-like carcinomas





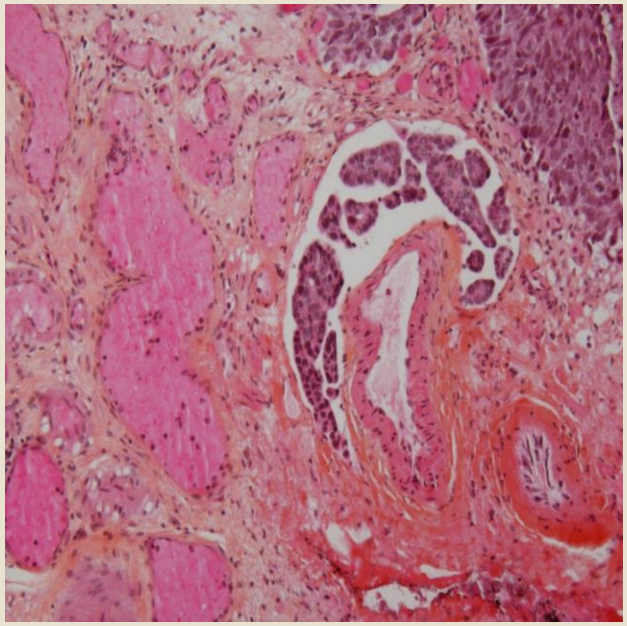
Molecular subtypes



- Luminal subtype
  - FGFR3↑
  - GATA-3+
  - Poor chemo sensitivity to neo adjuvant therapy
- p53-like luminal sub group of luminal subtype
  - Resistance to adjuvant MVAC
- Basal subtype has been linked to
  - Squamous or squamoïd morphology
  - Decreased cancer-specific survival
  - Neo adjuvant chemotherapy sensitive

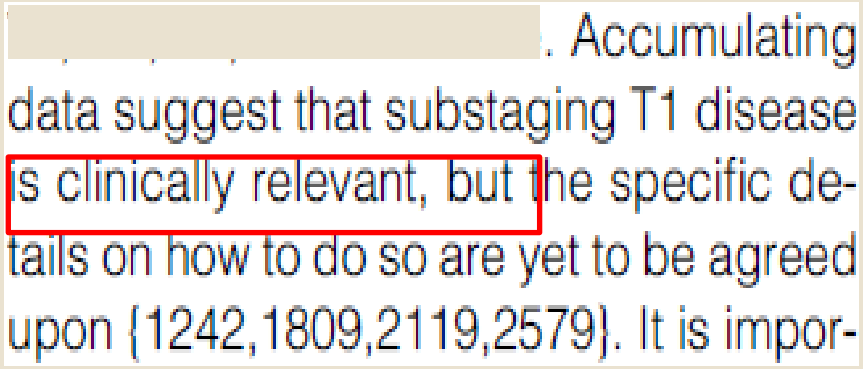
Morphologic factors of prognosis in MIBC

- Grade
- Stage
- Angiolymphatic invasion
- Cis +/-
- Subset of variant features

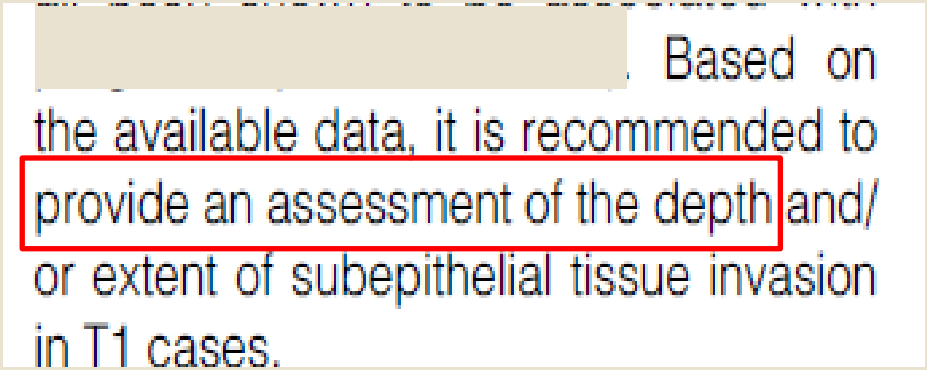


Sub-Staging

- Substaging pT1 tumors



. Accumulating data suggest that substaging T1 disease is clinically relevant, but the specific details on how to do so are yet to be agreed upon {1242,1809,2119,2579}. It is impor-



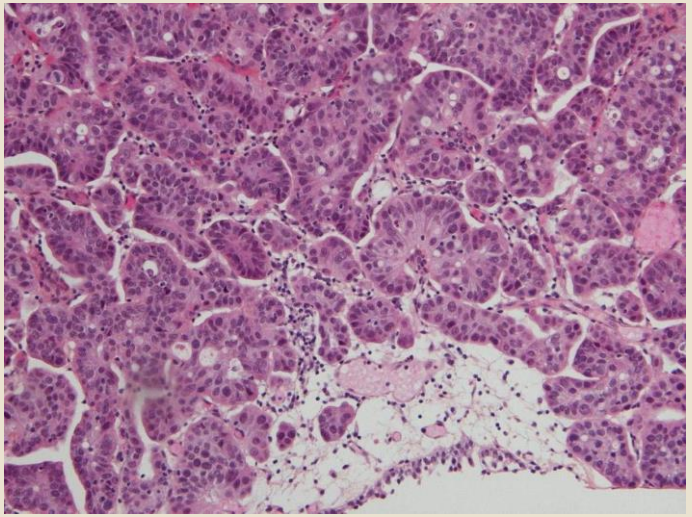
Based on the available data, it is recommended to provide an assessment of the depth and/or extent of subepithelial tissue invasion in T1 cases.

- ICCR (International Collaboration of Cancer Reporting)
  - mm invasion ?
  - or/and extent ?
  - and or pT1a/b ?

WHO 2016

Micropapillary Bladder Cancer (MBC)

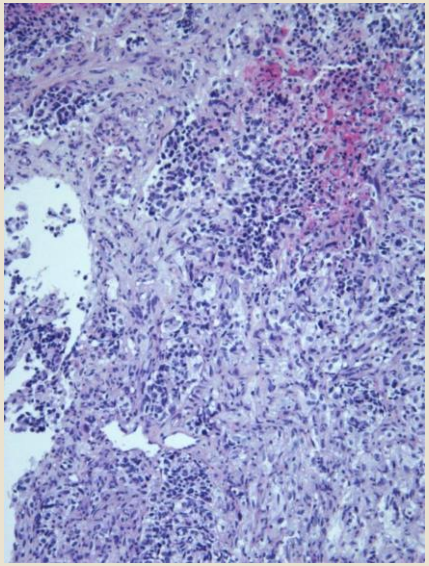
- Multiple pathways deregulations (cell proliferation and signal traduction).
- Almost exclusively luminal phenotype
- HER IHC expresion >70% : Herceptin ?
- PDL1-

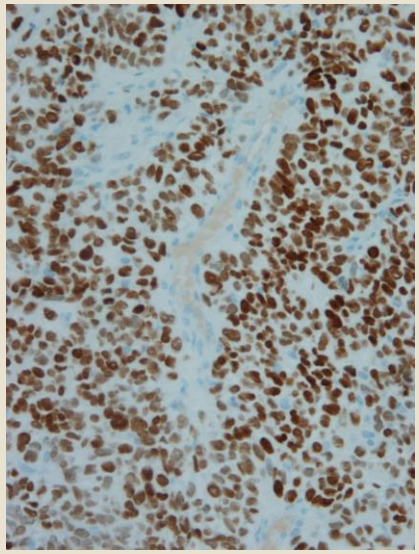


Charles C Guo, et al The University of Texas MD Anderson Cancer Center, Houston, TX, USA; Institute of Statistics, University of Warsaw, Warsaw, Pologne

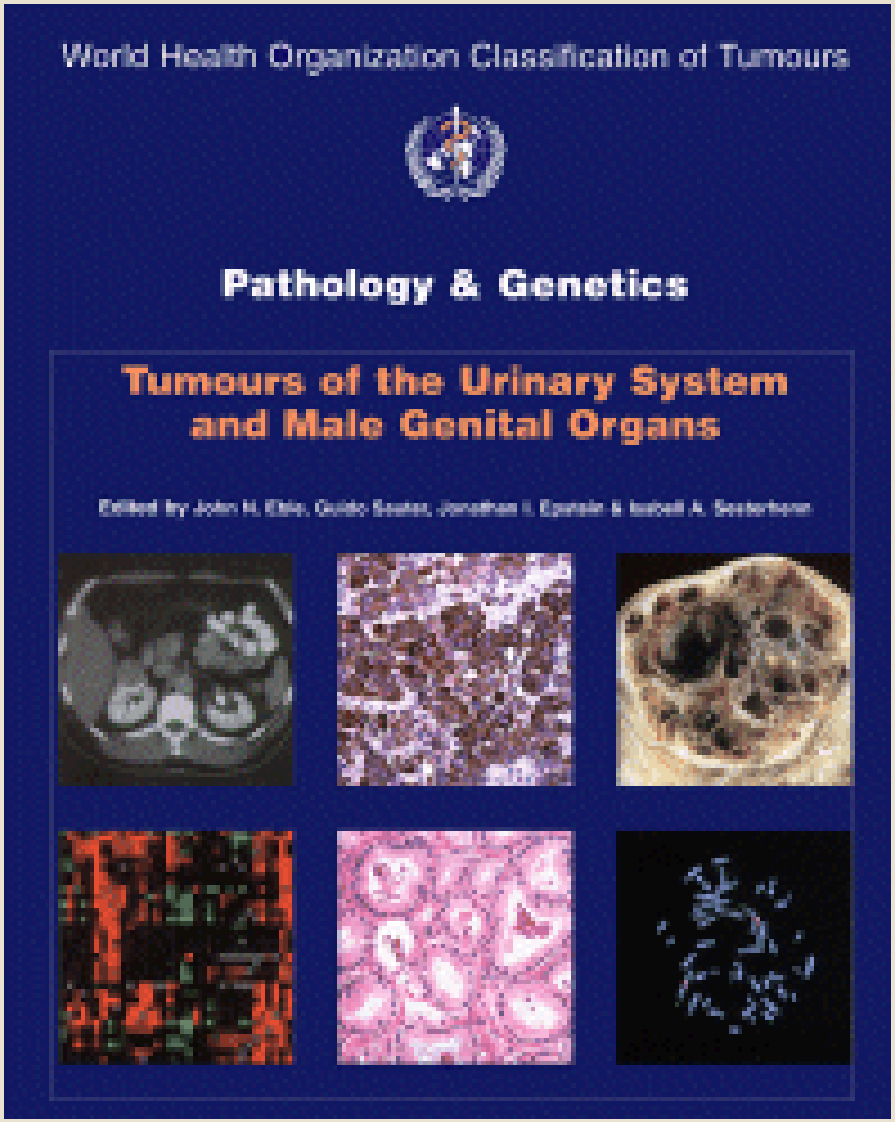
Neuroendocrine tumors

- Small cell neuroendocrine carcinoma (SmCC)
  - M>F
  - Urothelial origin
  - Overwhelming part of tumor has to be SmCC
  - Genetically unstable, *TP53* alterations+++
  - Bad prognosis (as > 65a, high pT, metastases)
- Large cell neuroendocrine carcinoma
  - High grade, mitosis+++, aggressive
- Well differentiated NET → Carcinoid
  - Small size, good prognosis
- No therapeutic guidelines





Thank You


World Health Organization Classification of Tumours
Pathology & Genetics
Tumours of the Urinary System and Male Genital Organs