WHO 4 – RENAL EPITHELIAL TUMOURS

Ed. by Holger Moch

STEWART FLEMING
UNIVERSITY OF DUNDEE

- MAJOR PARADIGM SHIFT IN EARLY 1990S IN UNDERSTANDING RENAL CANCER

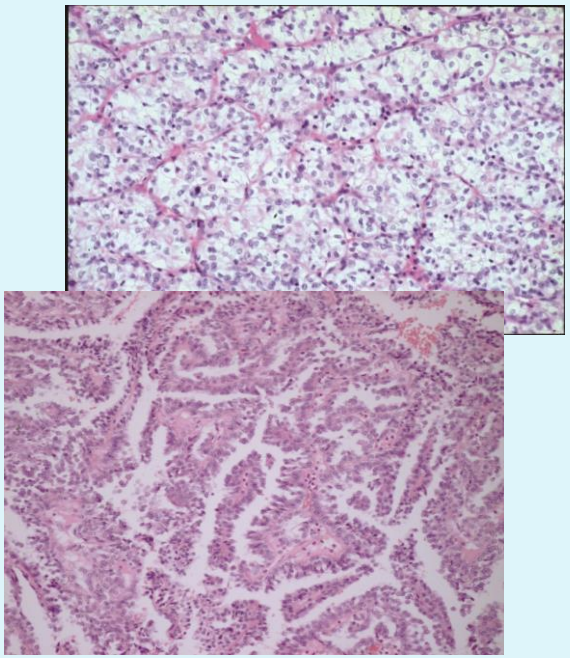
The impact of genetics on the classification of renal carcinoma

S.FLEMING
Department of Pathology, University of Edinburgh Medical School, Teviot Place, Edinburgh, UK

Molecular differential pathology of renal cell tumours
G. KOVACS

THE HEIDELBERG CLASSIFICATION OF RENAL CELL TUMOURS

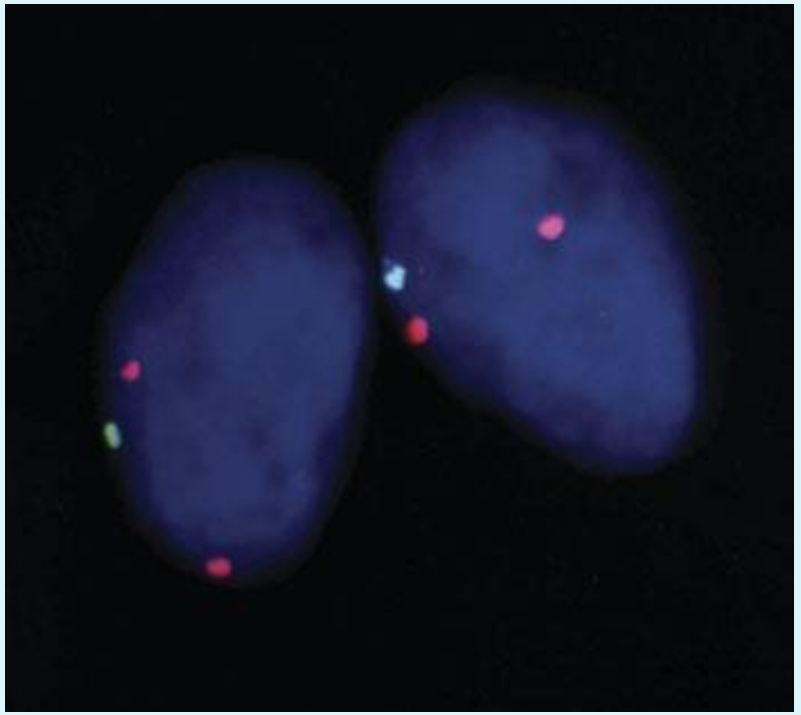
GYULA KOVACS[1]*, MOHAMMED AKHTAR[2], BRUCE J. BECKWITH[3], PETER BUGERT[1], COLIN S. COOPER[4], BRETT DELAHUNT[5], JOHN N. EBLE[6], STEWART FLEMING[7], BÖRJE LJUNGBERG[8], L. JEFFREY MEDEIROS[9], HOLGER MOCH[10], VICTOR E. REUTER[11], EBERHARD RITZ[1], GÖRAN ROOS[8], DIETMAR SCHMIDT[12], JOHN R. SRIGLEY[13], STEPHAN STÖRKEL[14], EVA VAN DEN BERG[15] AND BERT ZBAR[16]



A CLASSIFICATION …BASED ON UNDERSTANDING THE GENETIC ABNORMALITIES INVOLVED WILL BE ROBUST IN TERMS OF BIOLOGY, CLINICAL BEHAVIOUR AND RESPONSE TO THERAPY

GENETIC ALTERATION IN RCC CORRELATES STRONGLY WITH MORPHOLOGY

HISTOPATHOLOGY	3p LOSS		VHL MUTATION	
	Y	N	Y	N
CLEAR CELL	25	8	18	25
PAPILLARY	1	7	0	8
ONCOCYTOMA	2	3	0	5
CHROMOPHOBE	0	3	0	3



FOSTER ET AL 1994 Somatic mutations of the von Hippel - Lindau disease tumour suppressor gene in non-familial clear cell renal carcinoma

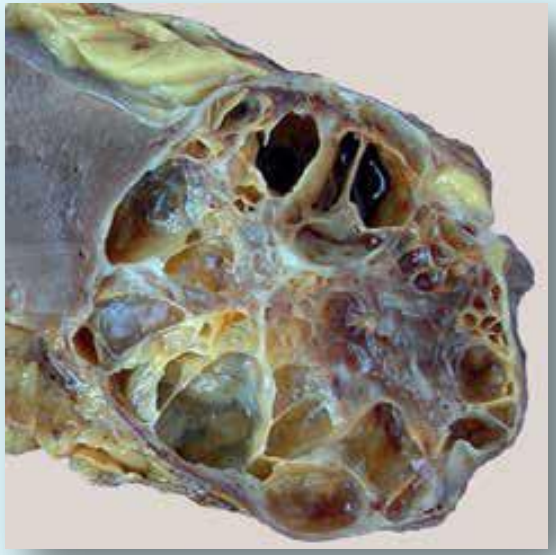
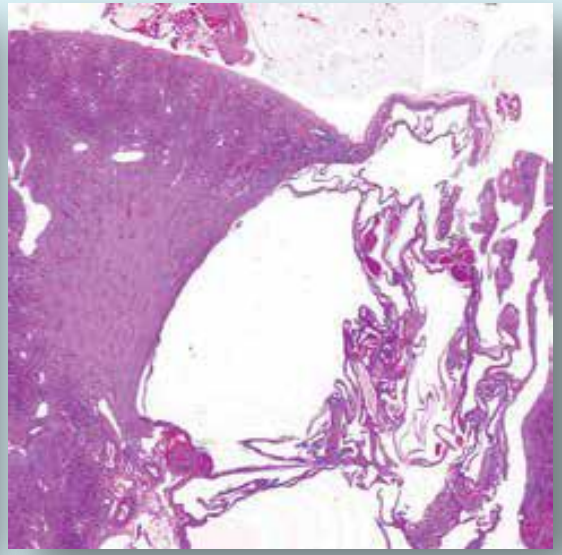
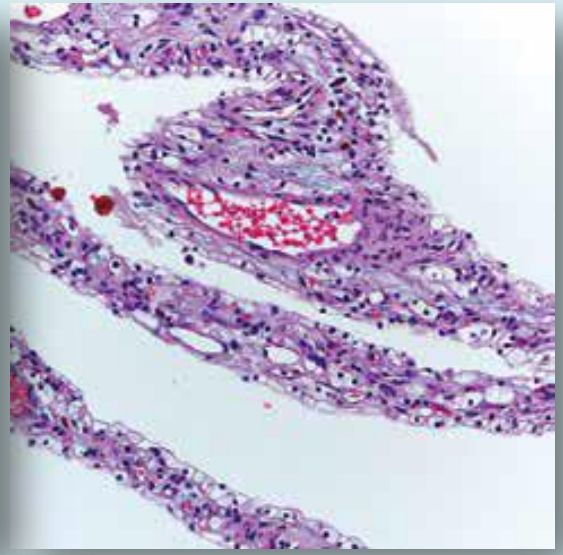
The Pathology and Genetics of Renal Tumours WHO v4

- Clear cell renal cell carcinoma VHL and 3p-
- Multilocular cystic renal neoplasm of low malignant potential
- Hereditary leiomyomatosis with RCC associated renal cell carcinoma Fumarate hydratase
- Papillary renal cell carcinoma c-met and chr 7+; Fumarate hydratase*
- Chromophobe renal cell carcinoma Multiple chromosome loss
  - Hybrid oncocytic chromophobe tumour Folliculin
- Collecting duct carcinoma
- Renal medullary carcinoma IN1 and sickle cell
- MiT family translocation renal cell carcinoma
  - Xp11 translocation renal cell carcinoma
  - t(6;11) renal cell carcinoma
- Mucinous tubular and spindle cell carcinoma Multiple chromosomal losses
- Tubulocystic renal cell carcinoma Fumarate hydratase*
- Acquired cystic disease associated renal cell carcinoma
- Clear cell papillary (tubulopapillary) renal cell carcinoma
- Succinate dehydrogenase deficient RCC SDHB, SDHC, SDHD
- Renal cell carcinoma, unclassified
- Papillary adenoma
- Oncocytoma

EPIDEMIOLOGY

- 350,000 CASES WORLD WIDE IN 2012
  - 10,000 pa IN UK
- RATE DOUBLING IN 20 YEARS
- ASSOCIATED WITH
  - OBESITY
  - CIGARETTE SMOKING
  - HYPERTENSION
- 2-4% FAMILIAL

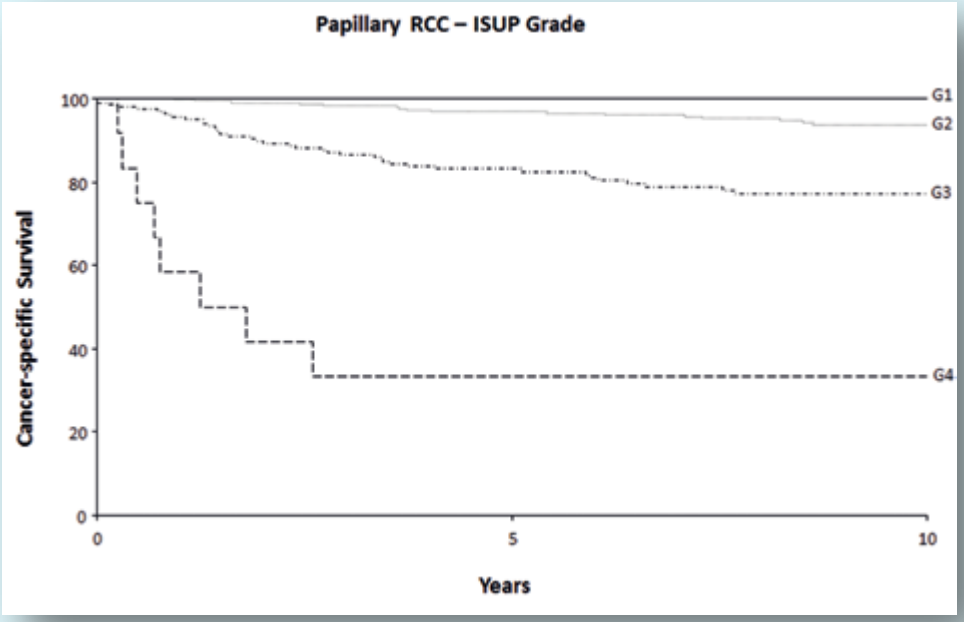
Multilocular cystic renal neoplasm of low malignant potential

Multilocular cysts, lined by a single layer of cells with evident clear cell morphology
No solid areas of clear cell carcinoma

PAPILLARY RCC

- TYPE 1, TYPE 2, MIXED
- NUCLEAR GRADE (ISUP)



NEW DEFINITION FOR PAPILLARY ADENOMA

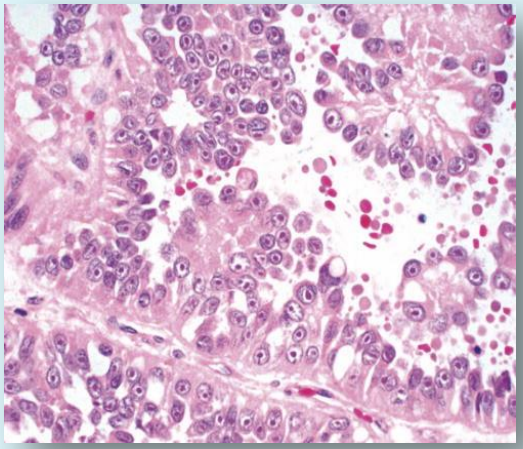
UNENCAPSULATED AND <15mm

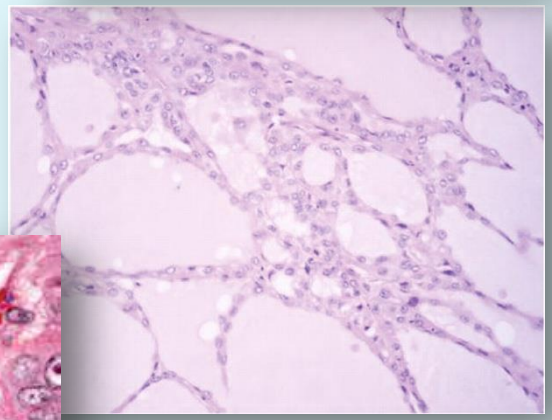
RENAL CANCER AND MITOCHONDRIA 2013

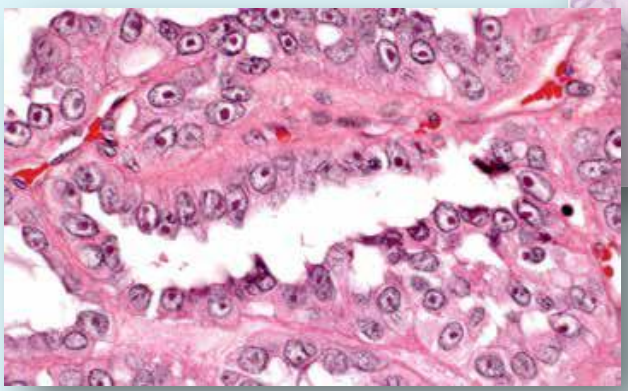
- THERE IS NOW EVIDENCE THAT MUTATIONS IN THE MITOCHONDRIAL SDH AND FH GENES PREDISPOSE TO DIFFERENT TYPES OF RENAL CANCER
- FIFTEEN YEARS AGO NO-ONE WOULD HAVE SUSPECTED THIS

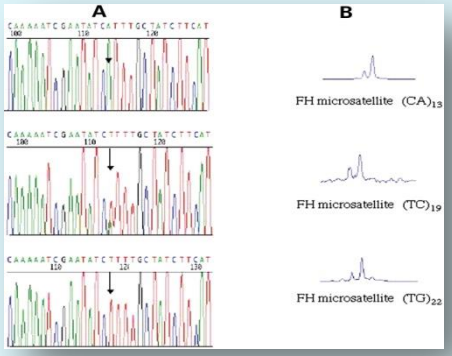
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated renal cell carcinoma and fumarate hydratase

- FIRST REPORT TYPE 2 PAPILLARY
- SECOND REPORT LOW GRADE CDC (TUBULOCYSTIC)
- SUBSEQUENT REPORTS ARCHITECTURE MAY BE TUBULAR, PAPILLARY, TUBULOCYSTIC OR MIXED
- USUALLY SOLITARY TUMOUR
- NUCLEOLAR MORPHOLOGY
- **MUTATION MUST BE DEMONSTRATED**









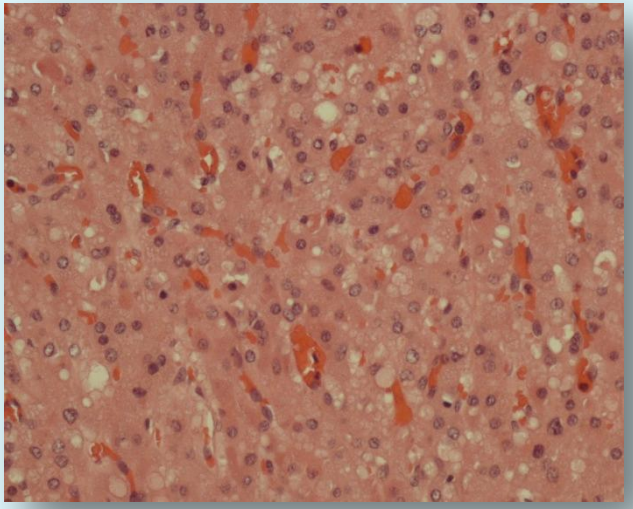
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated renal cell carcinoma and fumarate hydratase

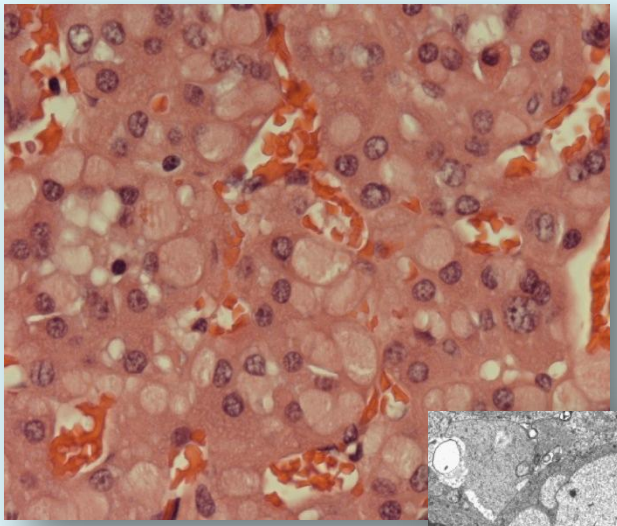
- TYPE 2 PAPILLARY, TUBULAR OR TUBULOCYSTIC NEOPLASM
- NUCLEOLAR MORPHOLOGY
- FAMILY HISTORY
- YOUNG PATIENT
- AGGRESSIVE TUMOUR BEHAVIOUR

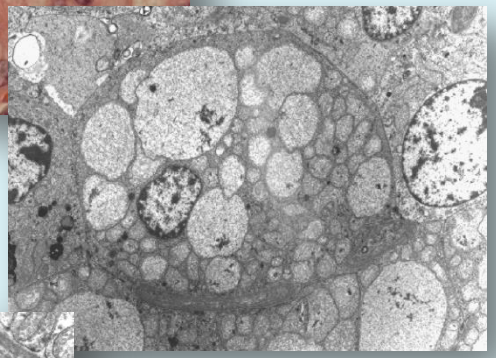
Succinate dehydrogenase–deficient renal carcinoma

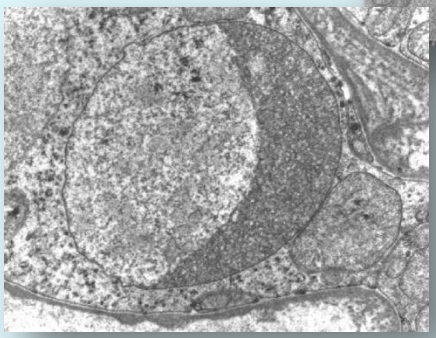
- RCC
  - OFTEN <30 YRS
  - POSSIBLE FEMALE PREPONDERANCE
  - MALIGNANT POTENTIAL
  - CHARACTERISTIC MORPHOLOGY
  - SDHB IMMUNOCYTOCHEMISTRY
  - HEAD AND NECK PARAGANGLIOMA
  - PHAEOCHROMOCYTOMA
  - DEMONSTRATE MUTATION IN GERMLINE AND SOMATIC LOSS

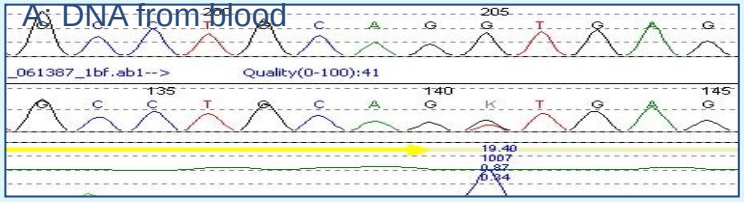
Succinate dehydrogenase–deficient renal carcinoma

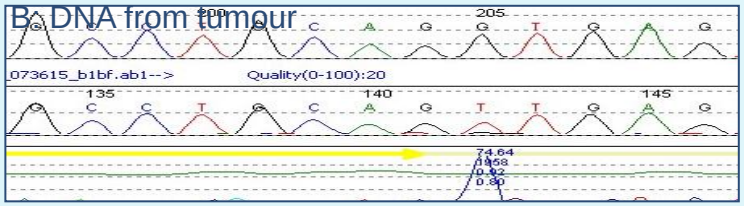




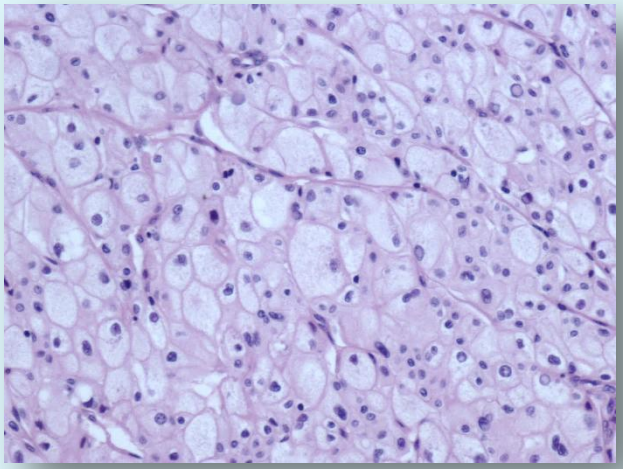


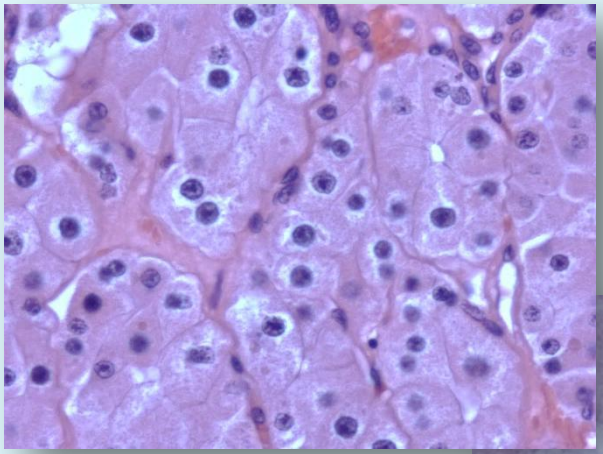


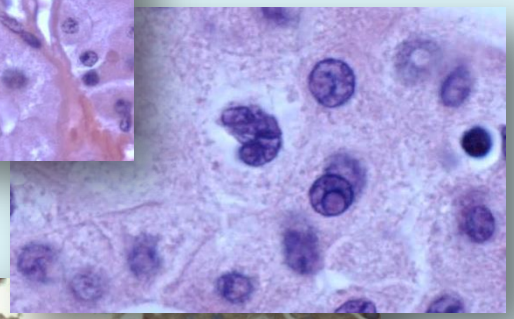


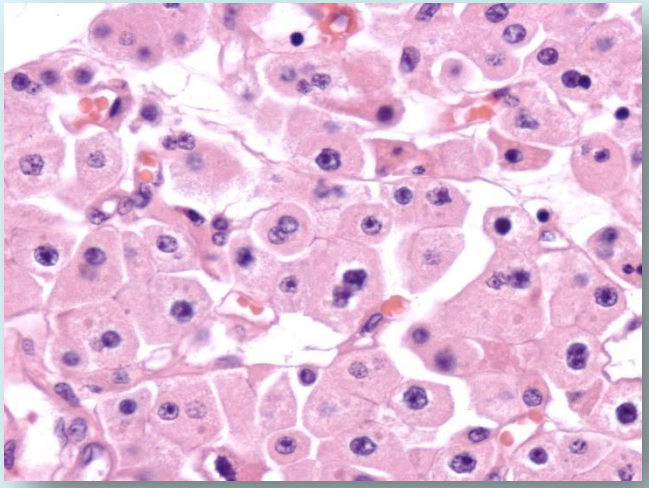


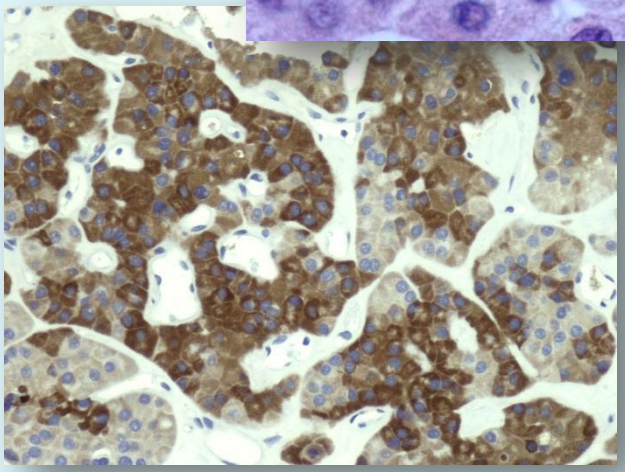
CHROMOPHOBE CARCINOMA











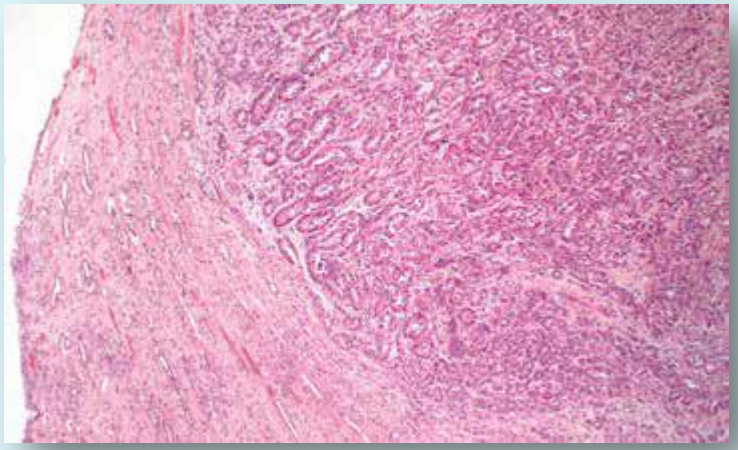
CK7

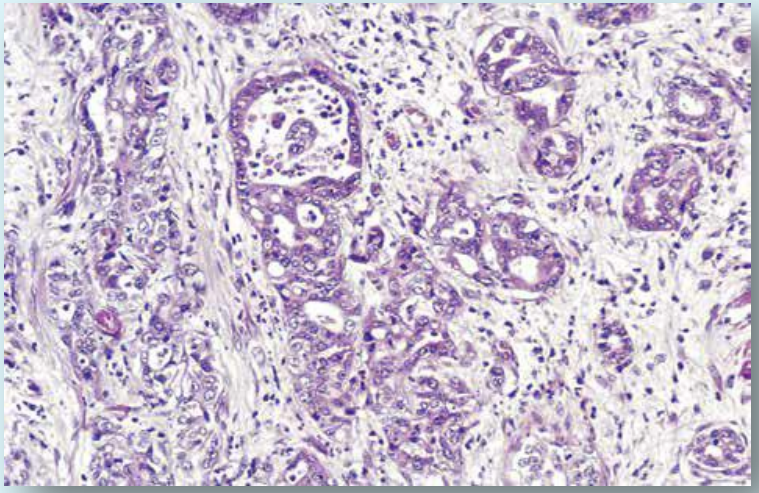
CHROMOPHOBE CARCINOMA

- GOOD PROGNOSIS
  - >90% 5 YEAR SURVIVAL
- ISUP GRADE NOT APPLICABLE
- CAREFULLY NOTE
  - SARCOMATOID MORPHOLOGY
  - NECROSIS
  - EXTENSION BEYOND KIDNEY

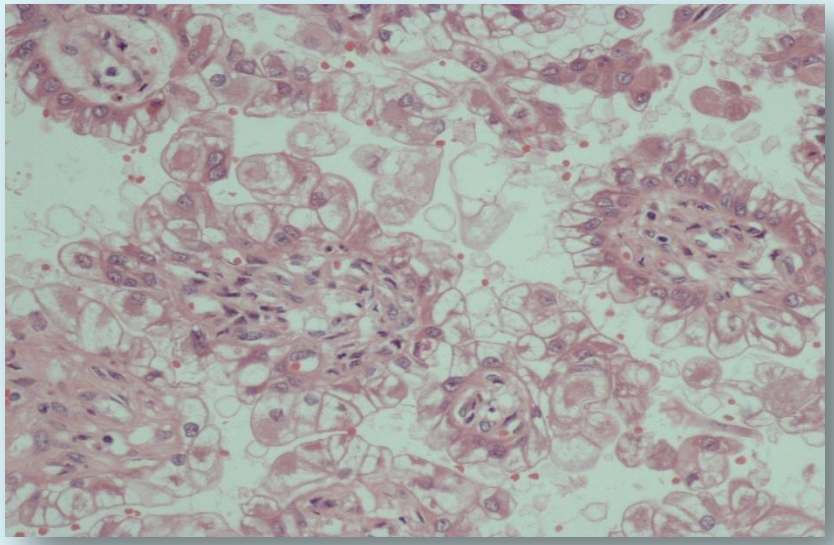
COLLECTING DUCT CARCINOMA

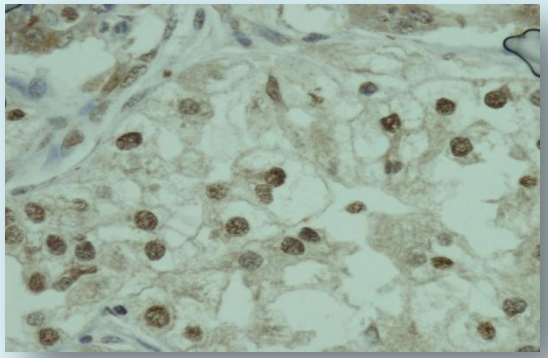
- Medullary involvement
- Predominant tubular morphology
- Desmoplastic stromal reaction
- Cytologically high grade
- Infiltrative growth pattern
- Absence of other RCC subtypes or urothelial carcinoma





MiT family translocation renal cell carcinomas

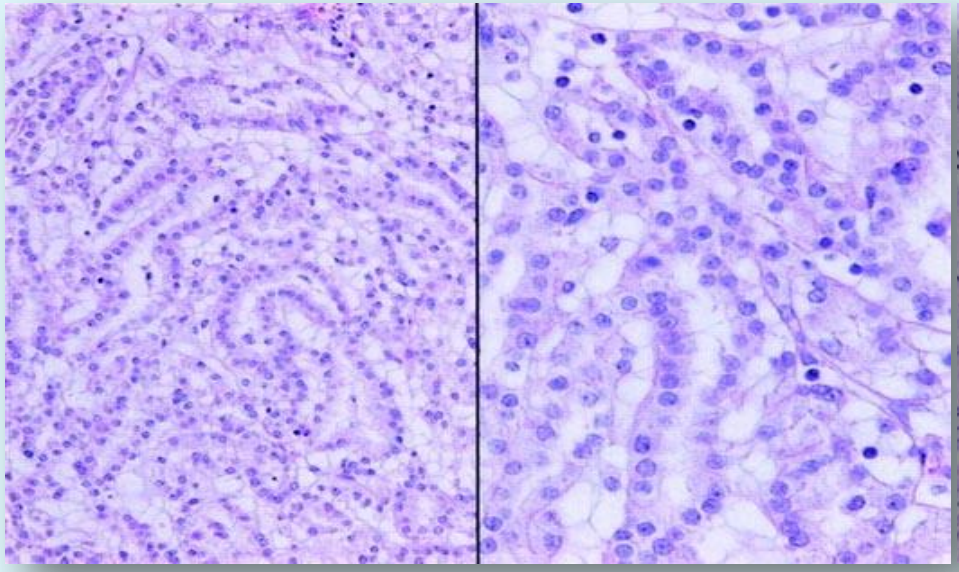




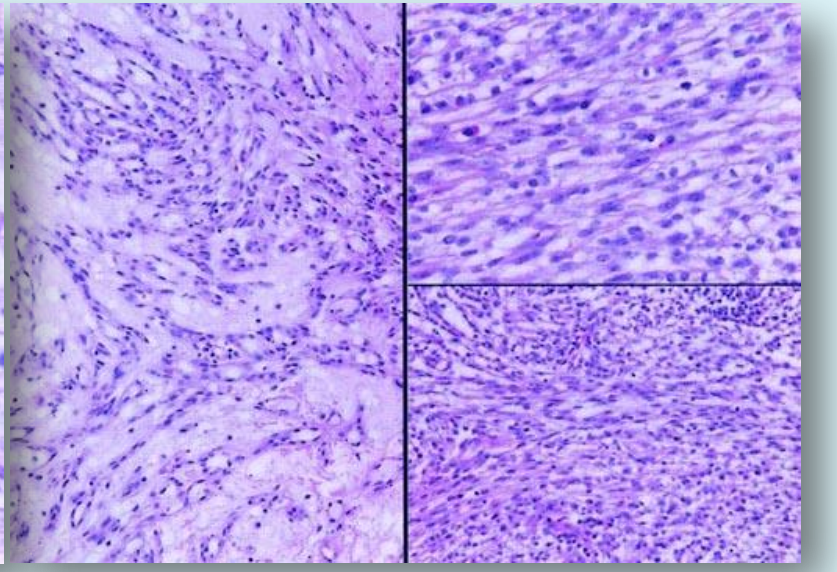
- YOUNGER PATIENTS
- MIXED CLEAR CELL AND PAPILLARY
- VOLUMINOUS CYTOPLASM
- PSAMMOMA BODIES
- TFE3, more rarely B or C in nucleus
- CATHEPSIN K

Xp11 TRANSLOCATIONS tX;11, tX;17
T6;11 – TFE B

MUCINOUS TUBULAR AND SPINDLE CELL RENAL CARCINOMA

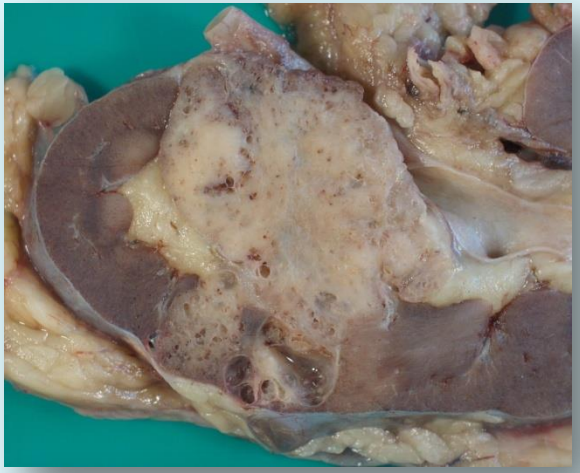


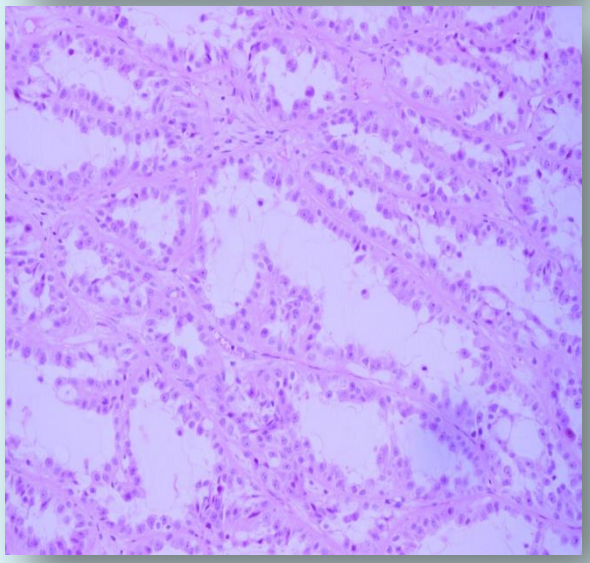
TUBULAR COMPONENT



SPINDLE CELL COMPONENT

TUBULOCYSTIC CARCINOMA OF KIDNEY





WELL CIRCUMSCRIBED

TUBULAR OR MICROCYSTIC

SINGLE LAYERED CUBOIDAL EPITHELIUM

MILD NUCLEAR PLEOMORPHISM

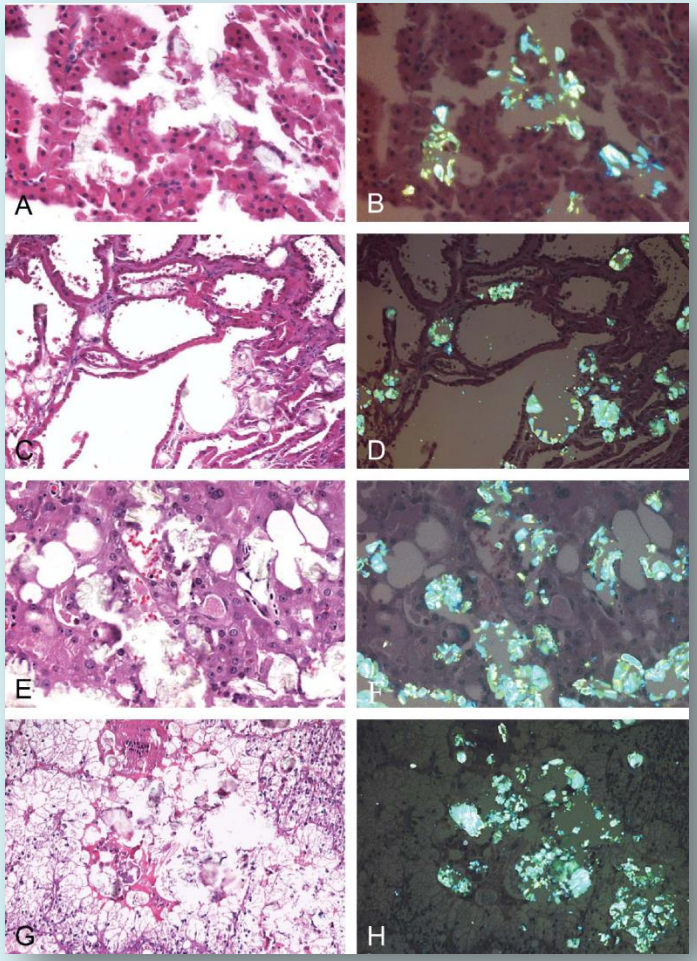
MAY HAVE PROMINENT NUCLEOLI

LOW METASTATIC POTENTIAL ~10%

Acquired cystic disease–associated renal cell carcinoma

- 30 YEAR HISTORY OF RCC IN ESRD
- PREVIOUSLY CONSIDERED TO BE MOSTLY PAPILLARY
- NOW AT LEAST TWO NEW TYPES OF RCC RECOGNISED IN THIS CLINICOPATHOLOGICAL CONTEXT
  - ACKD ASSOCIATED RCC
  - CLEAR CELL PAPILLARY RCC IN ESRD
- 60% OF RCC IN ESRD

Acquired cystic disease–associated renal cell carcinoma

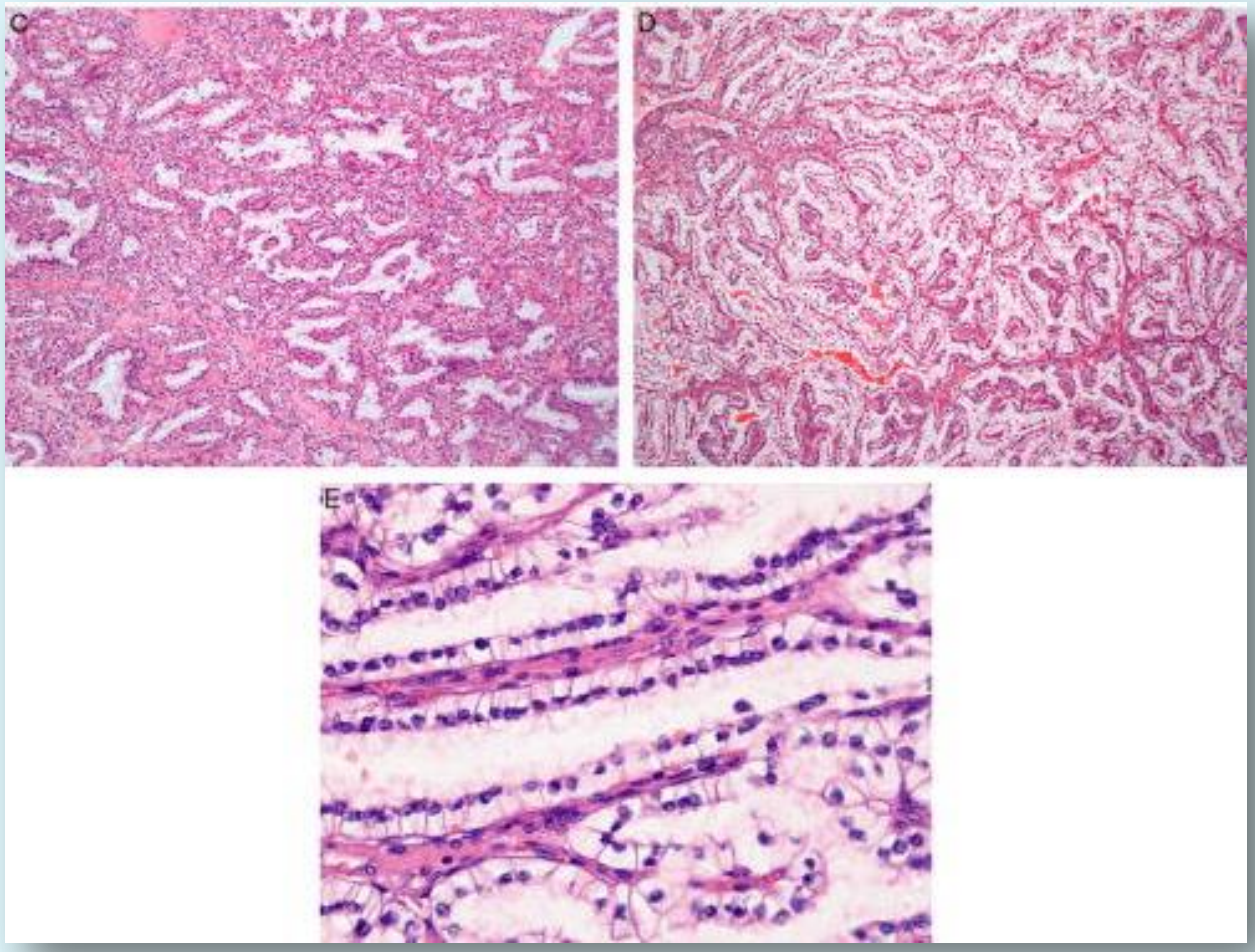


- OFTEN ENCAPSULATED
- OFTEN ARISING FROM CYST
- SOLID TUBULO-ACINAR MORE OFTEN THAN PAPILLARY ARCHITECTURE
- FINE LUMINAL SPACES
- CALCIFICATION & PSAMMOMA BODIES
- LARGE CELL WITH EOSINOPHILIC CYTOPLASM
- ONLY OCCASIONALLY CLEAR CELL

SULE et al 2005

CLEAR CELL PAPILLARY RCC

- ACKD OR NON-CYSTIC ESRD
- TUBULO-PAPILLARY ARCHITECTURE
- MAY BE CYSTIC
- CLEAR CELL CYTOLOGY
- SUBNUCLEAR CLEAR CYTOPLASM
  - MIMICKING SECRETORY ENDOMETRIUM
- NO VHL MUTATION NOR 3P LOSS
- NO TRISOMIES OF 7 AND 17
- POSITIVE CK7, HIF1a, CA IX (cup like pattern)
- NEGATIVE CD10, AMACR, TFE3

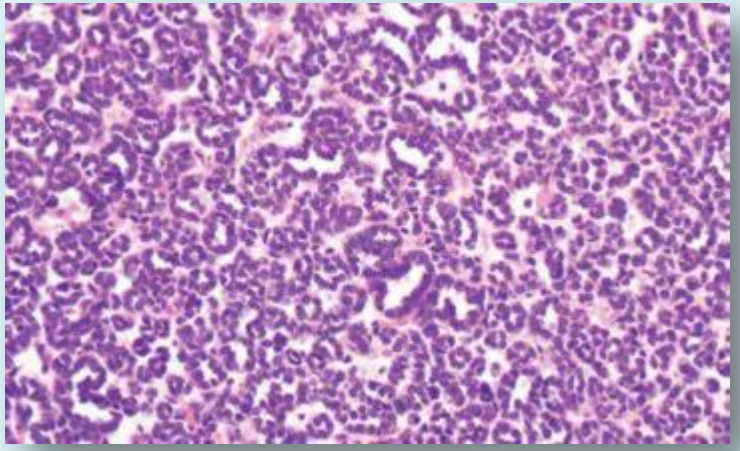


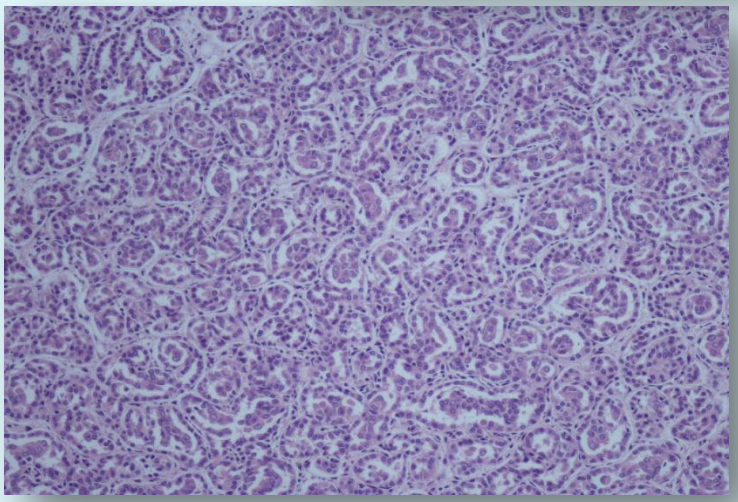
Aydin et al Am J Surg Path 2010

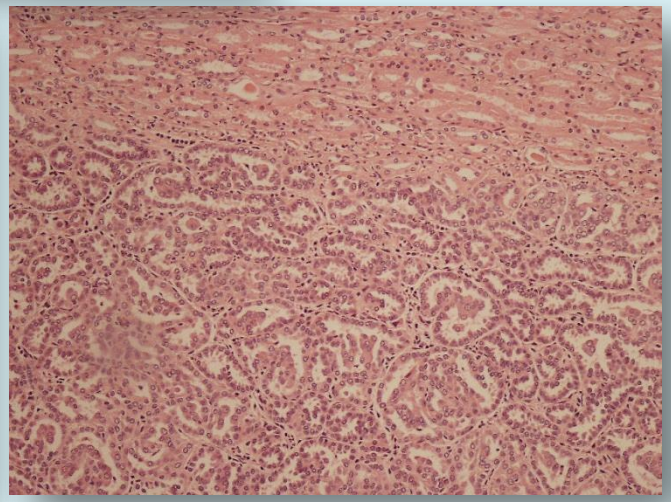
METANEPHRIC ADENOMA

- MAY PRESENT DIAGNOSTIC DIFFICULTY WITH PAPILLARY RCC
- USUALLY INCIDENTAL BUT CAN BE LARGE
- UNIFORM WHITE-GREY-TAN LESION
- HIGHLY CELLULAR
  - COMPOSED OF TIGHTLY PACKED SMALL ACINI
  - SMALL CELLS WITH BASOPHILIC NUCLEI LACKING PLEOMORPHISM
  - BRANCHING ANGULATED TUBULES COMMON
  - SOME FOCI OF PAPILLARY ARCHITECTURE
  - PSAMMOMA BODIES

METANEPHRIC ADENOMA







METANEPHRIC ADENOMA V PAPILLARY RCC

- CK7 FOCAL, MINOR
- WT1 70% +
- CD57 90% +
- AMACR 10-12% +

- CK7 >80% (TYPE 1 >2)
- WT1 12% +
- CD57 5% +
- AMACR 90% +

– CK7 AND AMACR FAVOUR PRCC WHILE CD57 FAVOURS MA

FISH

MA Usually normal copy number chr 7, 17

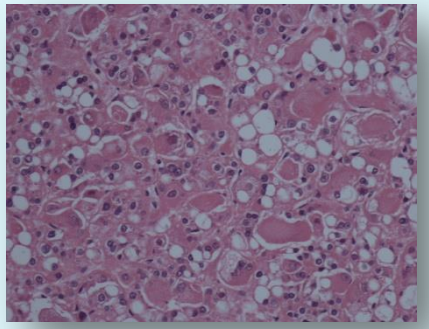
PRCC chr 7 + and 17+ in majority

90% OF MA HAVE THE BRAF V600E MUTATION

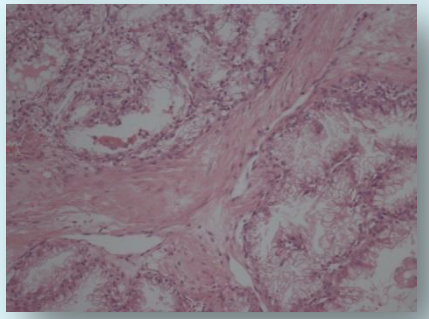
Unclassified renal cell carcinoma

- USUALLY HIGH GRADE OFTEN WITH SARCOMATOID OR RHABDOID MORPHOLOGY
- MAY ON OCCASION BE A LOW GRADE TUMOUR WITH NO RESEMBLANCE TO DEFINED ENTITIES
- AS A GROUP THESE HAVE A POOR PROGNOSIS
- GENETIC INVESTIGATIONS MAY HELP WITH CLASSIFICATION eg VHL MUTATION AND 3p-

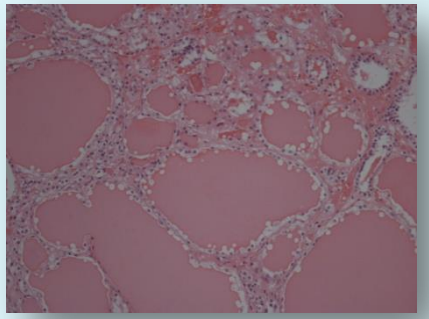
EMERGING ENTITIES



- ALK ASSOCIATED RCC
  - May be associated with sickle cell trait
  - Some indicative morphological features
  - ALK1 positive immunocytochemistry
  - t2:?? Translocation
    - Vin; EML4; TPM3; Copy number



- RCC WITH MONOSOMY 8
  - TCEB1 mutation and loss
  - Thick fibromuscular bands,
  - Clear cell cytology with voluminous cytoplasm
  - Clear cell renal cell carcinoma-like acinar areas tubular and focally papillary architecture



- THYROID FOLLICLE LIKE RCC
  - Characteristic thyroid like morphology
  - TTF-1 and thyroglobulin negative

International Agency for Research on Cancer

World Health Organization

UNIVERSITY OF DUNDEE

NHS Tayside