Renal tumours
WHO 4
• MAJOR PARADIGM SHIFT IN EARLY 1990S IN UNDERSTANDING RENAL CANCER

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

<table>
<thead>
<tr>
<th>HISTOPATHOLOGY</th>
<th>3p LOSS</th>
<th>VHL MUTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLEAR CELL</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>PAPILLARY</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>ONCOCYTOMA</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>CHROMOPHOBIE</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

FOSTER ET AL 1994 Somatic mutations of the von Hippel - Lindau disease tumour suppressor gene in non-familial clear cell renal carcinoma
TUMOUR HISTOLOGY MATTERS BECAUSE IT REVEALS THE UNDERLYING GENETICS

WHO v4

- Clear cell renal cell carcinoma VHL and 3p-
  - Multilocular clear cell renal cell neoplasm of low malignant potential
- Papillary renal cell carcinoma c-met and chr 7+; Fumarate hydratase
- Chromophobe renal cell carcinoma Multiple chromosome loss
  - Hybrid oncocyctic chromophobe tumour Folliculin
- Carcinoma of the collecting ducts of Bellini
- Renal medullary carcinoma IN1 and sickle cell
- MiT family translocation renal cell carcinoma
  - Xp11 translocation renal cell carcinoma
  - t(6;11) renal cell carcinoma
- Carcinoma associated with neuroblastoma
- 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
- Hereditary leiomyomatosis associated renal cell carcinoma Fumarate hydratase
- SDHB associated RCC SDHB
- RCC with monosomy 8 Monosomy * TCEB1
- ALK associated RCC ALK translocation or amplification
- Thyroid follicle like RCC
- Renal cell carcinoma, unclassified
INHERITED RCC

- VHL
- FAMILIAL PAPILLARY RCC
- BIRT HOGG DUBE SYNDROME
- TUBEROUS SCLEROSIS
- HLRCC
- SDHB
- NON-SYNDROMIC FAMILIAL RCC
WHO CLASSIFICATION PROCESS

ISUP CONSENSUS – REPORT – CONSULTATION – WHO REPORT - 2016
CONSOLIDATING DIAGNOSTIC CRITERIA

• PAPILLARY RCC
  – TYPE 1, TYPE 2, MIXED – ALSO GRADE

• 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
New entities

- Consensus sought for renal tumours described since 2004 (2002) (or renamed)
- Entities presented
- Discussion
- Voting
- Accepted, rejected, emerging
TUBULOCYSTIC CARCINOMA OF KIDNEY

- WELL CIRCUMSCRIBED
- TUBULAR OR MICROCYSTIC
- SINGLE LAYERED CUBOIDAL EPITHELIUM
- MILD NUCLEAR PLEOMORPHISM
AGGRESSIVE TUBULOCYSTIC RCC

• AGGRESSIVE TUBULOCYSTIC
• MORPHOLOGY OF FOCAL CDC LIKE
• YOUNG PATIENT

• THINK HLRCC
ESRD ASSOCIATED RCC

• 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

• Atypical cyst or cyst with (atypical) epithelial proliferation
OXALATE AND ACKD RCC

- 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
- AMACR – BUT CK7 +
CLEAR CELL PAPILLARY RCC

- NO VHL MUTATION NOR 3P LOSS
- NO TRISOMIES OF 7 AND 17
- POSITIVE CK7, HIF1a, CaIX
- NEGATIVE CD10, AMACR, TFE3
FUMARATE HYDRATASE AND RCC

• FIRST REPORT TYPE 2 PAPILLARY
• SECOND REPORT LOW GRADE CDC (TUBULOCYSTIC)
• SUBSEQUENT REPORTS ARCHITECTURE MAY BE TUBULAR, PAPILLARY TUBULOCYSTIC OR MIXED
• MUTATION MUST BE DEMONSTRATED
TRANSLOCATION ASSOCIATED RCC

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

TO BE RENAMED MiT family translocation renal cell carcinoma
MUCINOUS TUBULAR AND SPINDLE CELL RENAL CARCINOMA

TUBULAR COMPONENT

SPINDLE CELL COMPONENT
ACCEPTED

- TUBULOCYSTIC RCC
- ESRD ASSOCIATED RCC
- CLEAR CELL PAPILLARY RCC
- HLRCC RENAL TUMOUR
- MiT FAMILY TRANSLOCATION RCC
- MUCINOUS TUBULAR AND SPINDLE CELL CARCINOMA
Emerging

- SDH associated RCC
- ALK positive RCC
- Thyroid follicle like RCC
SDH MUTATION

- RCC
  - OFTEN <30 YRS
  - POSSIBLE FEMALE PREPONDERANCE
  - OUTCOME UNDEFINED
  - CHARACTERISTIC MORPHOLOGY
  - SDHB IMMUNOCYTOCHEMISTRY
  - HEAD AND NECK PARAGANGLIOMA
  - PHAEOCHROMOCYTOMA
SDH HISTOLOGY
MITOCHONDRIAL MORPHOLOGY
ALK 1 translocation RCC

- Rare only four cases in literature
- May be associated with sickle cell trait
- Some indicative morphological features
- ALK1 positive immunocytochemistry
- t2:?? Translocation
  - Vin; EML4; TPM3; Copy number
Alk associated RCC
TUMOUR GRADE PREDICTS BIOLOGY
ISUP NUCLEOLAR GRADE

- Not applicable
- Grade X - Cannot be assessed
- Grade 1 - Nucleoli inconspicuous or absent at high power magnification
- Grade 2 - Nucleoli evident at high power magnification
- Grade 3 - Nucleoli large and prominent at low power magnification
- Grade 4 - Nuclei bizarre and/or multilobated, sarcomatoid or rhabdoid morphology

- Grade should be assigned according to the worst grade regardless of extent.
- This system has been validated for clear cell and papillary renal cell carcinoma. It has not been validated for chromophobe and other types of renal cell carcinoma.

HOW DOES IT REFLECT GENETICS?
CAN WE DEFINE TREATMENT PATHWAYS BY IDENTIFICATION OF DRIVER MUTATIONS?

DOES TUMOUR EVOLUTION CONFOUND THAT AIM?

RENAL CELL CARCINOMA
WHAT REALLY MATTERS?

It's the economy, stupid.
(Bill Clinton)

-genetics-