PITFALLS AND TRAPS IN THE DIAGNOSIS AND STAGING OF RENAL TUMOURS OF CHILDHOOD

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Cardiff, U.K.
# Renal Tumours of Childhood - Classification (2016)

<table>
<thead>
<tr>
<th>Nephroblastic Tumours</th>
<th>Mesenchymal Tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilms Tumour</td>
<td>Clear Cell Sarcoma of Kidney</td>
</tr>
<tr>
<td>Nephrogenic rests</td>
<td>Rhabdoid Tumour of Kidney</td>
</tr>
<tr>
<td></td>
<td>Mesoblastic Nephroma</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Metanephric Tumours</th>
<th>Epithelial Tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metanephric Adenoma</td>
<td>Renal Medullary Carcinoma</td>
</tr>
<tr>
<td>Metanephric Adenofibroma</td>
<td>Papillary Renal Cell Carcinoma</td>
</tr>
<tr>
<td>Metanephric Stromal Tumour</td>
<td>RCC Associated with Translocations</td>
</tr>
<tr>
<td></td>
<td>Ossifying Renal Tumour of Infancy</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Others</th>
</tr>
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<tbody>
<tr>
<td>PNET</td>
</tr>
<tr>
<td>DSRCT</td>
</tr>
<tr>
<td>Synovial Sarcoma</td>
</tr>
<tr>
<td>Anaplastic Sarcoma of Kidney</td>
</tr>
<tr>
<td>Others</td>
</tr>
</tbody>
</table>
RENAL TUMOURS OF CHILDHOOD

- **WILMS’ TUMOUR** 85%
  - Non-anaplastic 75-80%
  - Anaplastic 5-10%

- **MESOBLASTIC NEPHROMA** 3-4%

- **CCSK** 3-4%

- **RTK** 2%

- **OTHERS** 5-7%

- 120 cases p.a. in the UK (~60 m population)
- 20 paediatric pathology centres
WILMS TUMOUR (NEPHROBLASTOMA)

- The most common renal tumour in children
- 1 in 10,000 children 0 – 15 years of age
- 0.16% neonatal, rare in adults
- Rarely extra-renal
- Peak 3 - 4 years of age
- F > M
- Racial differences

- 5-8% bilateral
- 10% associated with congenital syndromes
- 1% familial

- The most treatable tumour in children (85% - 95%)
WILMS TUMOUR

Histological features

- Blastemal component
- Epithelial component
- Stromal component

- Triphasic (mixed, classical) WT
- Biphasic and monophasic WT

- Degree of differentiation
- Line of differentiation

- Innumerable number of patterns
WT - Epithelial type
WT – Stromal type
ANAPLASTIC WT

- 1978 Beckwith & Palmer

- Criteria
  - Atypical tri- or multipolar mitoses
  - Nuclear enlargement (3x)
  - Hyperchromasia

- All three criteria must be met
- Each cell type may be anaplastic
- Focal and Diffuse anaplasia
The histological criteria for anaplasia:

- atypical mitoses
- nuclear enlargement (3x)
- hyperchromasia
CHEMOTHERAPY-INDUCED CHANGES

► Pathological evaluation of post-treatment WTs is critical for therapeutic decisions and prognostic assessment in the SIOP trials

► Pre-operative Cx is part of many therapeutic protocols in tumours in children
  ▶ Osteosarcoma, Ewing sarcoma
  ▶ Rhabdomyosarcoma, Neuroblastoma, Hepatoblastoma
‘dead’ blastema
WILMS TUMOUR

- Favourable vs. unfavourable histological features
  - Anaplasia – unfavourable feature in NWTS/COG and SIOP trials
    - Focal vs. Diffuse anaplasia
  - Post-Cx blastemal type WT – unfavourable (high risk) in SIOP trials
  - 100% post-Cx necrosis - low risk (in SIOP)
1) **Pre-operative chemotherapy** (2-drugs 4 weeks)

2) **Surgery (nephrectomy)**

3) **Post-operative therapy**
   - histological type (or group)
   - local (and overall) stage

   - molecular biology markers
WILMS TUMOUR

- Risk-adapted treatment (SIOP 1984 -)
  - Low risk tumours
  - Intermediate risk tumours
  - High risk tumours
Role of the pathologist

- To make the diagnosis

- To subclassify a tumour as
  - Low
  - Intermediate
  - High risk

- To stage a tumour at nephrectomy
SIOP Classification (2001)

LOW RISK TUMOURS

• (CMN, CPDN)

• COMPLETELY NECROTIC WT

INTERMEDIATE RISK

• EPITHELIAL TYPE WT

• STROMAL TYPE WT

• MIXED TYPE WT

• REGRESSIVE TYPE WT

• FOCAL ANAPLASIA WT

HIGH RISK TUMOURS

• BLASTEMAL WT

• DIFFUSE ANAPLASIA WT

• CCSK, RTK
WILMS TUMOUR

- Problems with the differential diagnosis (WT vs. non-WT)
- Problems with sub-classification of WTs
- Problems with staging
## SIOP 2001 – PATHOLOGY
(2001 – 2011)

<table>
<thead>
<tr>
<th>Discrepancies in dg</th>
<th>Relevant</th>
<th>Irrelevant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>490/2125 (23%)</td>
<td>201/2125 (9.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Discrepancies in stage</th>
<th>Up-stage</th>
<th>Down-stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (2216)</td>
<td>344/2216 (15.5%)</td>
<td>165/2216 (7.4%)</td>
</tr>
</tbody>
</table>
IMPORT STUDY
(UK – 2012 - )

- 325 patients with nephrectomy
- 27/325 (8.3%) with significant Dx discrepancy
- 15/325 (4.6%) with non-significant Dx discrepancy
- 39/325 (12%) with Stage discrepancy
- 18% with discrepancy in assessment of blastema
- 314/325 (97%) submitted for Rapid CPR
**SIOP 2001 / IMPORT Study**

**Post-operative treatment of WTss**

<table>
<thead>
<tr>
<th></th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Risk</strong></td>
<td>NFT</td>
<td>-</td>
<td>AV (27w)</td>
</tr>
<tr>
<td><strong>Intermediate Risk</strong></td>
<td>AV (4w)</td>
<td>AV (27w)</td>
<td>RT + AV (27w)</td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td>AVD (27w)</td>
<td>RT+AVDC (34w)</td>
<td>RT + AVDC (34w)</td>
</tr>
</tbody>
</table>
# SIOP Classification (2001)

## Low Risk Tumours
- (CMN, CPDN)
- Completely Necrotic WT

## High Risk Tumours
- Blastemal WT
- Diffuse Anaplasia
- CCSK, RTK

## Intermediate Risk
- Epithelial Type WT
- Stromal Type WT
- Mixed Type WT
- Regressive Type WT
- Focal Anaplasia
SIOP CLASSIFICATION (2001)

1st step - % of CIC
- if no viable tumour – completely necrotic (low risk tumour)
- if CIC >2/3 – regressive type (intermediate risk tumour)
- if CIC <2/3 – sub-classify on the basis of histological components

2nd step - % of histological components
- epithelial type (IR)
- stromal type (IR)
- mixed type (IR)
- regressive type (IR)
- blastemal type (HR)
- anaplasia (FA – IR and DA - HR)

3rd step - stage the tumour
- viable vs non-viable tumour in the renal sinus, perirenal fat, RMs, LN
Table 1. Histological criteria for Wilms’ tumour subtyping in SIOP WT 2001

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Histological features (% of a tumour)</th>
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<tbody>
<tr>
<td></td>
<td>CIC</td>
</tr>
<tr>
<td>Completely necrotic</td>
<td>100%</td>
</tr>
<tr>
<td>Regressive</td>
<td>&gt;66%</td>
</tr>
<tr>
<td>Mixed</td>
<td>&lt;66%</td>
</tr>
<tr>
<td>Epithelial</td>
<td>&lt;66%</td>
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<tr>
<td>Stromal</td>
<td>&lt;66%</td>
</tr>
<tr>
<td>Blastemal</td>
<td>&lt;66%</td>
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CIC - chemotherapy-induced changes
WT - Epithelial type

- > 1/3 viable

- > 2/3 of the viable tumour consists of epithelial structures

- The stromal component may comprise the rest of the viable tumour

- Only small scattered foci of blastema comprising < 10% of the tumour may be present

- If >10% blastema = mixed type
Anaplastic WT

The histological criteria for anaplasia

- atypical mitoses
- nuclear enlargement (3x)
- hyperchromasia
Anaplastic WT - Dx discrepancies

- 28/102 (27.5%) cases dg as non-AWTs re-classified as AWTs (UK cases)
  - 17 cases FA
  - 11 cases DA

- Another 12 cases were classified as AWTs by the institutional pathologists but re-classified as
  - * non-AWTs - 9 cases
  - * DSRCT - 1 case
  - * RTK - 1 case
  - * ASK - 1 case

- 6 cases dg of FA changed to DA by the Panel

- NWTS 5 – anaplastic WTs – 39% dg discrepancy
Viable vs. non-viable tumour
Genuine tumour stroma vs. CIC
Rare rhabdomyoblasts in hypocellular stroma
Blastema vs. epithelium
Blastema vs. epithelium
WT vs. CCSK

- Associated syndromes
- Bilateral/multicentric
- Metastases (bone, brain)
- Nephrogenic rests
- Heterologous cell types (skeletal muscle)
- Genuine renal tubules
- Botryoid intra-pelvic growth
- Renal vein and IVC growth
MESOBLASTIC NEPHROMA vs. CCSK

- Age (MN <6mo, CCSK >1yr)
- Cartilage in MN
- Tumour-kidney border (infiltrative vs. pushing)
- Entrapment of normal renal parenchyma (islands vs nephrons)
- Mitotic rate (high in MN)
- Vascular pattern (slit-like vs. arborising)
- ICC: MN + desmin, SMA, CCSK negative but NGFR +
  - Cyclin D1 – 100% CCSK, but also in MN
- DD: WT – stromal type
SIOP 2001 - Staging criteria

- Differ from NWTS/COG
- Non-viable ('dead') tumour tissue not important if completely resected
- Non-viable tumour at RM and LN = positive
Viable tumour thrombus – Stage II

Non-viable tumour thrombus – Stage I
CIC in perirenal fat – Stage I

Viable tumour in perirenal fat with pseudocapsule – Stage I
Viable tumour at RM – Stage III
Non-viable tumour at RM – Stage III
CIC in LN – Stage III
## Post-operative treatment of WTs

<table>
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# Renal Tumours of Childhood

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<th>Age</th>
<th>Most common</th>
<th>Possible</th>
<th>Rare</th>
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<tbody>
<tr>
<td>0-3 m</td>
<td>MN, RTK</td>
<td>WT</td>
<td>-</td>
</tr>
<tr>
<td>4-6 m</td>
<td>WT, MN</td>
<td>RTK</td>
<td>CCSK, RCC</td>
</tr>
<tr>
<td>7-12 m</td>
<td>WT</td>
<td>RTK, CCSK, MN</td>
<td>RCC</td>
</tr>
<tr>
<td>1-5 yrs</td>
<td>WT</td>
<td>CCSK</td>
<td>RTK, (MN), RCC</td>
</tr>
<tr>
<td>6-10 yrs</td>
<td>(A)WT</td>
<td>CCSK, RCC</td>
<td>-</td>
</tr>
<tr>
<td>11-15 yrs</td>
<td>(A)WT</td>
<td>RCC, PNET</td>
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RENAL TUMOURS OF CHILDHOOD

Diagnostic clues:

- Age (MN, RTK)
- Unilateral vs. Bilateral (WT)
- Unicentric vs. Multicentric (WT)
- Metastases (bones, brain, lungs)
- Nephrogenic rests (WT)
- Tumour’s tubules (WT)
- Skeletal muscle (WT)
RENAL TUMOURS OF CHILDHOOD

- Rare tumours, especially non-Wilms’ tumours
- Even paediatric pathologists see very few cases in their professional lives
- Histopathological diagnosis and stage are critical for adequate treatment
- Treatment in centres participating in multicentre trials according to established protocols