



# Renal Tumours of Childhood – a Review

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## Abstract

Renal tumours of childhood are rare, although they are one of the most common solid tumours in children. They include numerous entities, which have different clinical, histological, molecular biological and prognostic features, so their precise diagnosis and staging are critical for appropriate treatment. The most common is Wilms' tumour (WT) with ~80-85 % of all cases, whereas other entities including mesoblastic nephroma, clear cell sarcoma, rhabdoid tumour, renal cell carcinoma, metanephric tumours and others are very rare (2-4 % each) which explains why they represent a big diagnostic challenge for diagnostic pathologists. They are subclassified into three risk groups – low, intermediate and high – which have different treatments and prognosis. There are two big study groups which have different approaches but remarkable similar outcomes. The International Society of Paediatric Oncology approach (followed in most of the world) is based on preoperative chemotherapy, followed by surgery and further therapy, whereas the Children's Oncology Group approach (followed mainly in the United States and Canada) is based on primary surgery, followed by postoperative treatment.

**Key words:** Renal tumours; Wilms' tumour; Prognostic groups; Clinico-pathological features.

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### ARTICLE INFO

Received: 26 June 2022

Revision received: 4 August 2022

Accepted: 4 August 2022

## Introduction

Renal tumours comprise about 7 % of all tumours in children up to 15 years of age.<sup>1</sup> Wilms tumour (WT) (nephroblastoma) is by far the most common (80-85 % of all renal tumours), whereas all other tumours are very rare (2-4 % each). The rarity of these tumours has been the main reason that, for more than 50 years, they are being treated in multicentre studies in the United States (through the Children's Oncology Group - COG) and Europe (International Society of Paediatric Oncology – SIOP),<sup>2</sup> which follow different treatment strategies. The COG treatment strategy includes primary nephrectomy followed by postoperative therapy, whereas the SIOP strategy typically includes preoperative chemotherapy followed by nephrectomy and postoperative therapy. In both

approaches postoperative therapy primarily depends on histological subtype and stage. Because histological criteria for subtyping and staging of WT differ between COG and SIOP, it is not possible to simply compare the results type-for-type and stage-for-stage, but nevertheless their survival results are remarkably similar.<sup>2</sup> The current SIOP and COG classifications distinguish three treatment groups: low-, intermediate- and high-risk tumours (Table 1).<sup>3,4</sup> The correct assignment of tumour stage is one of the most critical and demanding responsibilities of the pathologist.<sup>5</sup> The staging criteria have changed over time as the significance of different findings have become apparent.<sup>6</sup>

**Table 1:** Histological risk classifications for Wilms' tumour

International Society of Paediatric Oncology (SIOP)	Children's Oncology Group (COG)
<b>Low risk</b>	<b>Low risk</b>
- Cystic partially differentiated nephroblastoma*	- Cystic partially differentiated nephroblastoma*
- Completely necrotic Wilms' tumour	
<b>Intermediate risk</b>	<b>Intermediate risk</b>
- Epithelial, stromal, mixed, regressive types	- Favorable histology Wilms' tumour
- Focal anaplasia	- No evidence of anaplasia
<b>High risk</b>	<b>High risk</b>
- Diffuse anaplasia	- Diffuse anaplasia
- Blastemal type	- Focal anaplasia

\* Cystic partially differentiated nephroblastoma treated with surgery only

## Wilms' tumour

WT is a malignant embryonal tumour developing from nephrogenic blastema and histologically it resembles the foetal kidney. It is typically diagnosed in children 3-4 years of age, it is uncommon in neonates and infants and exceptionally rare in adults.<sup>7</sup> It shows racial differences and the prevalence rate is the same in Europeans and North Americans (8 per million), but it is more common in Africans and least common in East Asian population. There is a slight female predominance.<sup>7</sup>

Clinically, it is usually discovered as an asymptomatic abdominal mass, but in 20-30 % of cases it may present with clinical signs and symptoms including abdominal pain, haematuria, hypertension and anaemia. Although the majority of patients are non-syndromic, in 10-15 % of patients it is associated with syndromes and congenital anomalies.<sup>8</sup> Syndromes with a high-risk (> 20 %) of developing WT are WAGR (WT – aniridia – genitourinary anomalies – range of intellectual disabilities) and Denys-Drash syndrome (congenital nephropathy, WT and intersex disorders), moderate risk (5-20 %) is associated with Beckwith-Wiedemann syndrome, Simpson-Golabi-Behmel syndrome and Fraiser syndrome and low-risk is associated with Bloom syndrome, DICER1 syndrome, Li-Fraumeni syndrome and isolated hemihypertrophy. Recognition of these predisposition syndromes is important for clinical follow up of affected children. In 1-2 % of cases, WT is familial.<sup>9</sup>

Pathologically, WT presents as a large, solitary mass, however, in 10 % of cases it is multinodular.

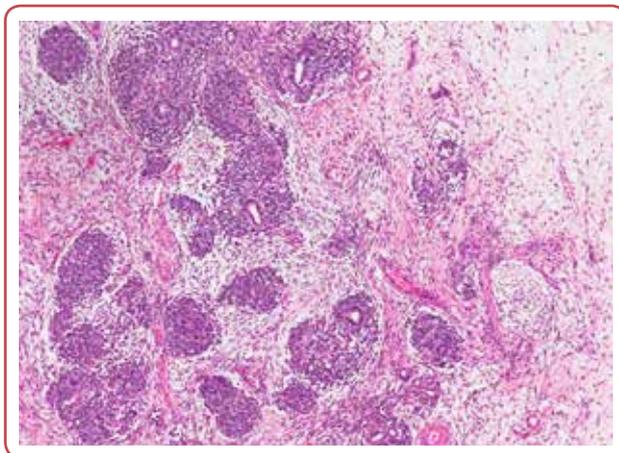
In 5-10 % of patients it presents as bilateral disease.<sup>10</sup> Histologically, classical/typical WT consists of three components: blastemal, epithelial and stromal (Figure 1), but many WT contain only two or one component. These components may be present in various proportions and each one may show a different line and degree of differentiation, resulting in numerous histological appearances. Preoperative chemotherapy may modify original histological features by destroying different tumour cells and inducing maturation of other components.<sup>11</sup> Some WTs show prominent heterologous differentiation of their components (skeletal muscle, adipose tissue, cartilage, bone, squamous epithelium, mucinous epithelium, etc.) resulting in so-called 'teratoid' appearance.<sup>12</sup> In the SIOP classification, WT are subclassified into types depending on the percentages of the chemotherapy-induced changes and viable tumour components, resulting in eight types and three risk groups (Table 2).<sup>4</sup> In the COG classification, the only histological feature of adverse prognostic significance is anaplasia, which is found in about 8-10 % of cases.<sup>13</sup> Anaplasia may occur in any cell type and it is defined as the presence of large atypical multipolar mitoses, together with marked nuclear enlargement and hyperchromasia (Figure 2).<sup>14</sup> Anaplasia is further subclassified as focal (FA) and diffuse anaplasia (DA). FA is defined as the presence of anaplastic changes in one or a few sharply demarcated foci within the primary tumour, without evidence of marked nuclear atypia elsewhere in the tumour. DA is defined as non-localised anaplasia and/or anaplasia beyond the original tumour capsule; FA with marked nuclear atypia elsewhere in the tumour; anaplasia that is not clearly demarcated from non-anaplastic tumour; anaplasia in intrarenal vascular extensions, extrarenal invasive sites or metastases; and anaplasia in a random biopsy sample.<sup>14</sup> Despite relatively simple criteria, diagnosis of anaplasia is still a big diagnostic problem for practising pathologists, with 30-50 % of cases being misdiagnosed by institutional pathologists.<sup>15</sup> In COG, FA and DA are regarded as high-risk tumours, whereas in the SIOP classification FA is subclassified in the intermediate-risk group and DA in the high-risk group.<sup>4</sup> Diffuse anaplasia is associated with a poor prognosis, especially at the higher stage. Anaplasia is not obliterated or induced by preoperative chemotherapy. It is associated with p53 mutations and is often positive on p53 immunohistochemical staining. In the SIOP classification of WTs treated with preoperative chemotherapy, blastemal-type WT is also subclassified into the high-risk group.<sup>4</sup>

WT most commonly metastasizes to the lungs and lymph nodes, whereas bone and brain metastases are rare.

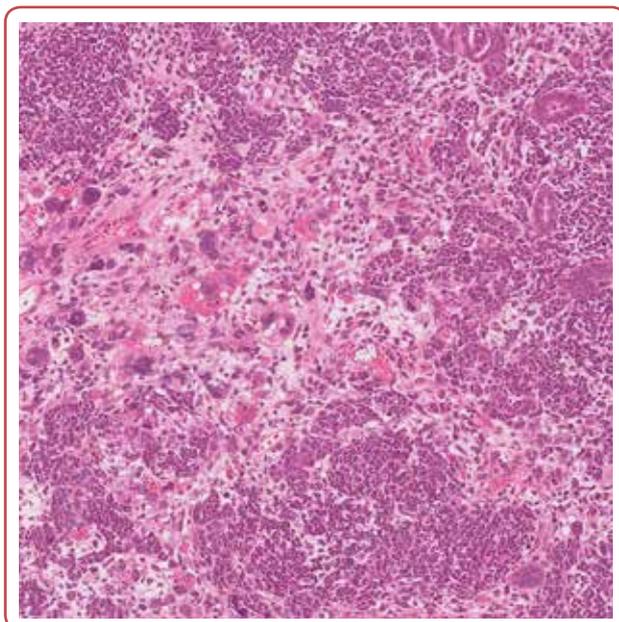
**Table 2:** Histological criteria for Wilms' tumour subtyping in SIOP classification

Tumour type	Histological features (% of a tumour)			
	CIC	Epithelium	Stroma	Blastema
Completely necrotic	100	0	0	0
Regressive	> 66	0 - 33	0 - 33	0 - 33
Mixed	< 66	0 - 65	0 - 65	0 - 65
Mixed	< 66	0 - 89	0 - 89	0 - 10
Epithelial	< 66	66 - 100	0 - 33	0 - 10
Stromal	< 66	0 - 33	66 - 100	0 - 10
Blastemal	< 66	0 - 33	0 - 33	66 - 100

CIC - chemotherapy-induced changes; SIOP - International Society of Paediatric Oncology;



**Figure 1:** Wilms' tumour, mixed type, consisting of blastemal, epithelial and stromal components



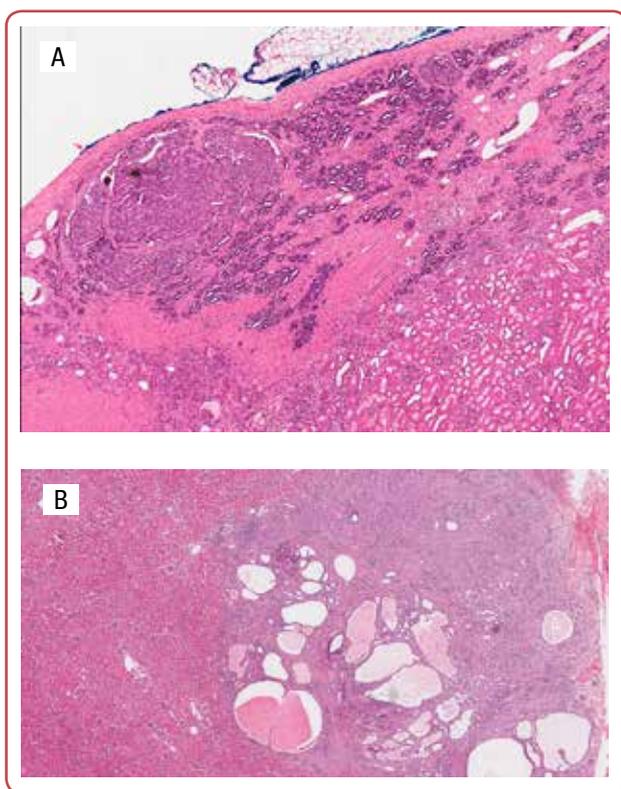
**Figure 2:** Wilms' tumour, anaplastic type, showing atypical mitoses, nuclear enlargements and hyperchromasia

In several studies, significance of impaired regulation of genes and their protein products involved in cell cycle control and DNA repair has been investigated for prognostic and therapeutic stratification of different histological types of WT, using immunohistochemical and genetic methods. Although the results of some p53 mutation studies have shown that their detection could contribute to the stratification of prognostic risk, especially associated with anaplastic WT,<sup>16-18</sup> the practical significance of such testing has not been established.

Also, although some association of surviving and cyclin A immunopositivity levels with histological types of WT was demonstrated, the differences observed were not statistically significant.<sup>19, 20</sup>

WT develops from precursor lesions which are called nephrogenic rests (NR) which represent abnormally persistent (after 36 weeks of gestation) foci of embryonal cells.<sup>15</sup> NR are found in 30-40 % of unilateral and in over 90 % of bilateral WT,<sup>21, 22</sup> and are subclassified into perilobar and intralobar NRs, depending on their localisation within the renal lobe. Both types are further subclassified into dormant, sclerosing and hyperplastic NRs and they may regress to fibrous tissue or progress to WT.<sup>15</sup> Perilobar NR are associated with overgrowth syndrome (hemihypertrophy, Beckwith-Wiedemann syndrome); they are found at the renal lobe periphery and are composed of epithelial, stromal and blastemal structures (Figure 3a). Intralobar NR are often associated with WAGR and Denys-Drash syndromes.<sup>21</sup> They are found within the renal lobe, usually contain abundant stroma and typically bland with the adjacent kidney (Figure 3b).

The genetics of WT shows a significant degree of heterogeneity – there are different tumour suppressor genes and different genetic mechanisms, with losses and gains of chromosomal material, some translocations and methylation and imprinting changes.<sup>23</sup> The only identified WT gene is *WT1*, on chromosome 11p13, its prevalence is 10-20 % and it is associated with stromal differentiation in WT. The second gene, *WT2* is almost certainly on chromosome 11p15, but it is still to be identified. Epidemiological studies suggest at least three types of genetic pathway in WT pathogenesis.<sup>23</sup> The NWT5 5 trial showed that loss of heterozygosity on both chromosomes 16q and 1p was associated



**Figure 3a, 3b:** Nephrogenic rests: A. perilobar nephrogenic rest; B. intralobar nephrogenic rest

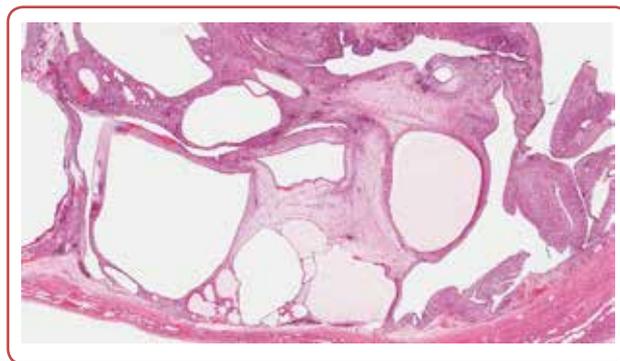
with an unfavourable outcome,<sup>24</sup> and this has been introduced in COG treatment stratification. However, only ~5 % of patients with non-anaplastic WT show these abnormalities, making it irrelevant for the majority of patients with WT. On the other hand, 1q gain has been found in 28-40 % of patients with WT and it has been shown to be associated with poor prognosis, prompting CG to introduce it as a new prognostic stratifier, whereas in SIOP UMBRELLA 2016 Study it is being prospectively studied.<sup>25</sup>

The prognostic factors in WT in COG and SIOP are tumour histological type and stage. In addition, in SIOP, prognostic factors also include tumour volume before and after preoperative chemotherapy in defined cases and responsiveness of lung metastases to initial chemotherapy in some groups. In COG, additional prognostic factors are age, tumour weight, rapidity of lung nodule response and molecular markers.<sup>26</sup>

Relapses occur in ~15 % of children and the majority within 2 years of diagnosis. The overall survival for patients with WT is now over 90 %; therefore, at present the focus is reduction of treatment in order to reduce therapy-related sequelae.<sup>27,28</sup>

### Cystic renal tumours

Entirely cystic renal tumours include cystic partially differentiated nephroblastoma (CPDN) and cystic nephroma (CN). They are rare and although they share many histological features (sharp demarcation from the renal parenchyma, cysts of different shapes and sizes, septa are the only solid parts and they may contain tubules and, in CPDN, foci of blastema (Figure 4), they are unrelated entities with CN belonging to DICER 1-related tumours,<sup>29</sup> whereas CPDN is part of a WT spectrum. They are both treated with surgery only and have excellent prognosis. Other renal tumours may show a prominent cystic appearance (but are almost never completely cystic), such as pre-treated WTs, mesoblastic nephroma, clear cell sarcoma of the kidney (CCSK) and even rhabdoid tumour of the kidney (RTK) and since their treatment and prognosis are very different, it is critical to diagnose them accurately.



**Figure 4:** Cystic partially differentiated nephroblastoma

### Mesoblastic nephroma

Mesoblastic nephroma (MN) accounts for 2-3 % of all paediatric renal neoplasms and is regarded as a low-grade mesenchymal/myofibroblastic tumour of the kidney. It typically occurs in infancy and it is often congenital. About 90 % of cases present in the first nine months of life, whereas it nearly never occurs after 3 years of age.<sup>30</sup> MN presents as an abdominal mass (~75 % of cases), hypertension (~20 %) and haematuria (~10 %).<sup>31</sup> It is not associated with nephrogenic rests, or with syndromes or congenital anomalies typical for WT and it is never metastatic or bilateral at presentation.

Macroscopically, it is presented as a solitary mass near the renal sinus. Histologically, it shows classical, cellular type and mixed pattern. The classical type (~25 % of cases) consists of

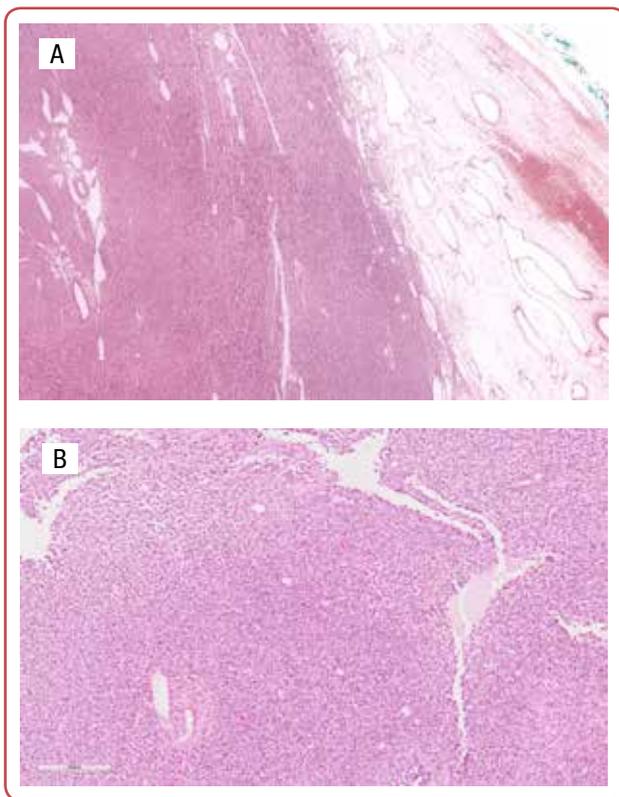


Figure 5a, 5b: Mesoblastic nephroma: A. classical type; B. cellular type

spindled cells with low mitotic activity, arranged in intersecting fascicles (Figure 5a), shows no capsule and infiltrates the renal parenchyma, renal sinus or perirenal fat. *EGFR* internal tandem duplication is a consistent and recurrent genetic event.<sup>32</sup> The cellular type (~65 % of cases) consists of densely packed plump, round cells with vesicular nuclei and a small to moderate amount of cytoplasm (Figure 5b). Although it has no capsule, it is usually sharply demarcated from the renal parenchyma. It shares the same genetic abnormality as infantile fibrosarcoma: a t(12;15)(p13;q25) translocation with resultant *ETV6-NTRK3* fusion.<sup>33</sup> MN is treated with complete surgical excision, resulting in excellent survival.<sup>34</sup> Rare local recurrences, particularly of cellular type, are due to incomplete resection and exceptionally rare cases of distant metastases have been reported.<sup>34</sup> They all develop within 12 months after the diagnosis, so patients should be followed up closely for at least 1 year. Relapses are treated with surgery too and chemotherapy is used only if tumours are inoperable. The differential diagnosis includes metanephric stromal tumour, clear cell sarcoma of the kidney and stromal-type WT. The correct diagnosis should be established on the basis of clinical, histological and molecular features of these tumours.

### Clear cell sarcoma of the kidney

Clear cell sarcoma of the kidney (CCSK) represents ~3 % of renal tumours of childhood. Its peak incidence is between 2 and 4 years of age and it shows a male-to-female predominance of around 2:1.<sup>35</sup> Clinically, it presents as a palpable abdominal mass, rarely with pain and gross haematuria. It is not associated with syndromes or congenital anomalies, it is never bilateral at presentation and no familial cases have been described.

Histologically, CCSK shows a wide histological spectrum of different patterns, including classical, epithelioid, spindled, sclerosing, palisading, myxoid, cystic and pleomorphic, which explains why it is the most frequently misdiagnosed renal tumour of childhood. Different patterns are usually found within the same tumour. The classical pattern is characterised by well-defined cords or nests of undifferentiated large cells with bland, empty-looking nuclei containing finely dispersed chromatin and usually no nucleoli. However, this pattern is seen in only ~30 % of cases. The most distinguishing feature is the delicate vascular network (Figure 6), which separates tumour cells into trabeculae or nest.<sup>36</sup>

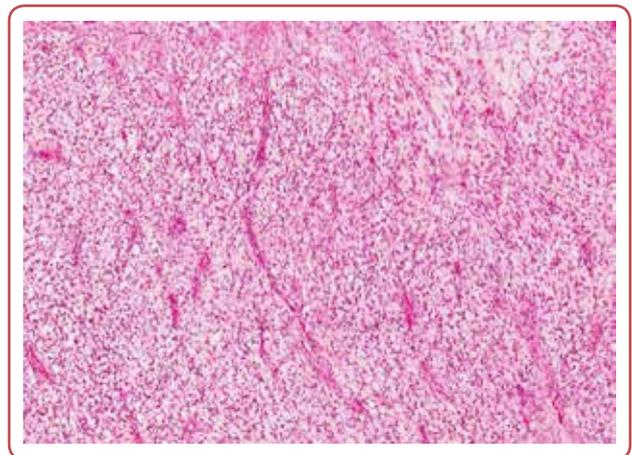


Figure 6: Clear cell sarcoma of the kidney showing characteristic vascular pattern

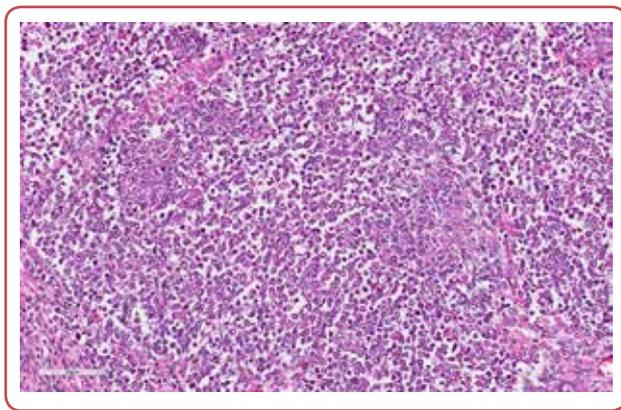
Recent molecular studies revealed that 80-90 % of CCSK show internal tandem duplications within exon 16 of *BCOR* (*BCOR* ITD), ~5 % the t(10;17)(q22;p13) translocation (resulting in a *YWHAE-NUTM2* fusion) and *BCOR-CCNB3* gene fusion - these genetic alterations appear to be mutually exclusive. The remaining ~5 % of CCSK shows no genetic abnormalities and they may not be genuine CCSK.<sup>37,38</sup>

Local lymph nodes are the most common

metastatic site at presentation for CCSK, but the bone is the commonest site for metastatic relapse.<sup>35</sup> The introduction of doxorubicin has resulted in a remarkable improvement in the prognosis of stage I-III tumour.<sup>35</sup>

### Rhabdoid tumour of the kidney

Rhabdoid tumour of the kidney (RTK) accounts for about 2 % of paediatric renal tumours. The mean age at diagnosis is 1 year and the median age is 11 months. Over 80 % of cases are diagnosed in the first 2 years of life and the diagnosis is debatable after the age of 5 years.<sup>39</sup>



**Figure 7:** Rhabdoid tumour of the kidney, showing non-cohesive cells with large nuclei, prominent nucleoli and abundant cytoplasm

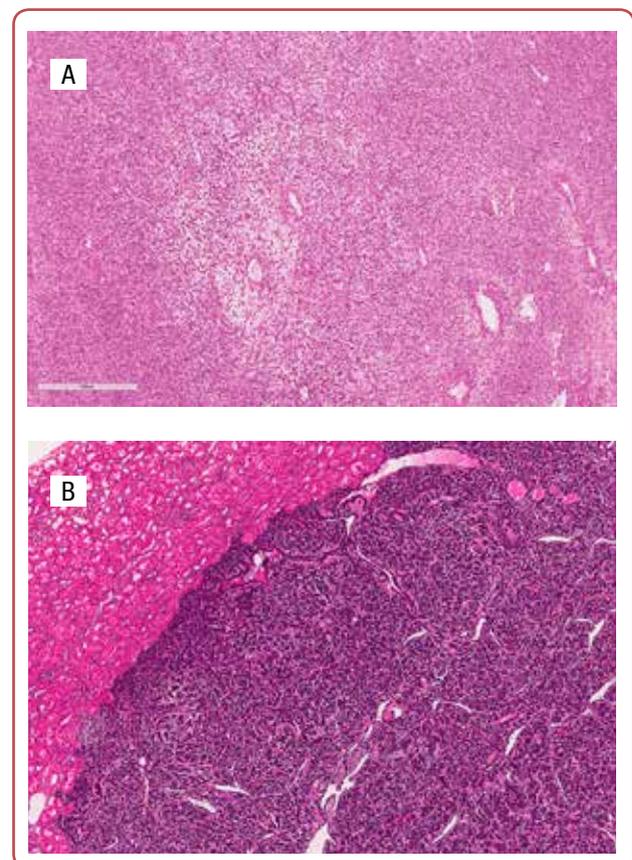
The tumour is associated with hypercalcaemia and synchronous or metachronous brain tumours. Characteristic histological features are the presence of large, non-cohesive tumour cells with eccentric large nuclei and very prominent eosinophilic central nucleoli (present in virtually all cases) and hyaline intracytoplasmic inclusions (often seen only focally) (Figure 7). In addition to the classical pattern, the tumour may show numerous other patterns, including classical, sclerosing, epithelioid, clear cell sarcoma-like, lymphomatoid, vascular, pseudopapillary and cystic patterns.<sup>40</sup> Immunohistochemically, in addition to vimentin (positive in all cases), RTK co-expresses different markers, including desmin, myoglobin, EMA, NSE, neurofilaments, S100 protein and CD99 (which are usually focally positive and not present in all cases).<sup>41</sup> However, the diagnostic immunohistochemical feature is absence of immunoreactivity for INI1 marker in the tumour cell nuclei. Genetic abnormalities of *hSNF5/INI1* tumour suppressor gene on chromosome 22q11.12 has been identified in children with renal and extra-renal rhabdoid tumours and the atypical teratoid

rhabdoid tumour of the brain.<sup>42</sup> The differential diagnosis of RTK includes renal medullary carcinoma (also INI1 negative tumour), cellular mesoblastic nephroma, CCSK, blastemal WT and Ewing sarcoma. RTK is a highly invasive, lethal neoplasm which gives early metastases in lung, lymph nodes, liver, bone and brain. The prognosis is very poor with 80-90 % of patients dying within a few months of the diagnosis.<sup>39</sup>

### Metanephric tumours

Metanephric tumours include a spectrum of rare entities, including metanephric stromal tumour (MST), metanephric adenofibroma (MAF) and metanephric adenoma (MA).<sup>43</sup>

Histologically, MST is a pure stromal tumour showing characteristic hypo- and hypercellular areas (resulting in a nodular appearance on low power view) (Figure 8a), concentric collarets of tumour around entrapped tubules and blood vessels which may show angiodyplasia. It occurs from 2 days to 156 months of age (median 13 months) and it should be considered in the differential diagnosis of stromal tumours in children older than 3 years of age, when MN does



**Figure 8:** Metanephric tumours: A. metanephric stromal tumour; B. metanephric adenoma

not occur. It is treated with surgery only and has the same excellent prognosis as MN.<sup>43</sup>

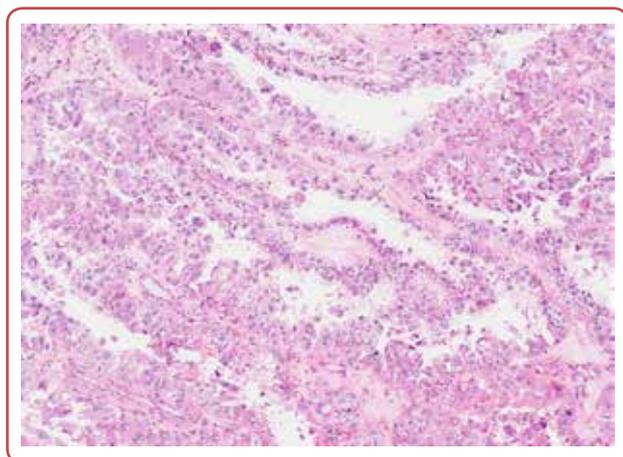
MAF occurs in children and young adults and exhibits a mixture of stromal elements (identical to those in MST) and well-defined areas of immature epithelium (tubules and papillae).<sup>43</sup>

Finally, MA is more commonly found in adults than in children. It is usually small (up to 2 cm) and composed of monotonous small, closely packed tubules which show no mitoses.

Characteristically, there is no capsule between the tumour and the adjacent renal parenchyma (Figure 8b). MA may be difficult to distinguish from epithelial-predominant WT and there may be a close pathogenetic relationship.<sup>43</sup>

### Renal cell carcinomas

Renal cell carcinomas (RCC) represent 3.5 % of renal tumours in children aged 0-14 years and 70 % in children aged 15-19 years. They show significant clinical, histological and genetic differences from RCC seen in adults.<sup>44</sup> The most common type in children is translocation-associated RCC (MiT-RCC) (Figure 9), followed by papillary type RCC, whereas clear cell RCC, which is the most common type in adults, is very rare in children.



**Figure 9:** Renal cell carcinoma associated with MiT translocation

They usually present with haematuria, abdominal and/or flank pain and abdominal/flank mass. The majority of patients (48 %) presents as stage I and ~10 % as metastatic (stage IV) disease. The most common metastatic sites are lung and liver.<sup>44</sup> After differences in malignant potential have been observed within rare RCC groups, histological, immunohistochemical and genetic characteristics that could contribute

to prognostic risk stratification have been underway for many years.<sup>45</sup>

Localised RCC is curable with surgery alone and their prognosis is very good (~90 % overall survival). High-stage RCC (stage III-IV) show a dismal prognosis (~22 % overall survival). Recent studies showed an improved prognosis with adjuvant therapy and this should now be considered as standard.<sup>44</sup>

Renal medullary carcinoma is a rare, highly aggressive tumour occurring in children and young adults with sickle cell trait or disease. Patients usually present with widespread metastases and show no response to chemo- or radiotherapy, resulting in a poor survival (mean 4 months).<sup>46</sup>

### Other entities

Several other rare tumours have been recently identified in the kidney. Some have been recognised by the application of molecular biology techniques, such as Ewing sarcoma,<sup>47</sup> desmoplastic small round cell tumour,<sup>48</sup> and synovial sarcoma,<sup>49</sup> whereas others, such as anaplastic sarcoma of the kidney<sup>50</sup> and mixed epithelial and stromal tumour of the kidney,<sup>51</sup> have been recognised on the basis of their characteristic clinicopathological features observed by examination of large series of cases from the multicentre studies.

## Conclusion

Renal tumours of childhood are a fascinating group of tumours where a remarkable progress in classification, treatment and understanding of molecular biology has been made. This has only been possible because of close collaboration between patients, clinicians, pathologists and molecular biologists and their participation in national and international multicentre trials where all data have been systematically and meticulously collected and studied. Since these tumours are rare, they still represent a diagnostic problem and central pathology review in multicentre trials is essential for assigning the appropriate treatment. Molecular biology markers are likely to play an even more important role in future trials.

## Acknowledgements

None.

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## Conflict of interest

None.

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