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HOW I APPROACH

How we approach paediatric renal tumour core needle biopsy in the setting of preoperative chemotherapy: A Review from the SIOP Renal Tumour Study Group

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Abstract

The International Society of Paediatric Oncology Renal Tumour Study Group (SIOP-RTSG) advocate treating children with Wilms tumour (WT) with preoperative chemotherapy, whereas the Renal Tumor Committee of the Children's Oncology Group (COG) advocates primary nephrectomy (without biopsy) when feasible. Successive SIOP-RTSG trial protocols recommended pretreatment biopsy of children with unilateral tumours only where there were features to suggest an increased probability of a non-WT requiring a change in management. The UK experience in the SIOP WT 2001 trial showed that an alternate approach of performing biopsies on all

Abbreviations: CCSK, clear cell sarcoma of the kidney; CN, cystic nephroma; CNB, core needle biopsy; COG, Children's Oncology Group; CPDN, cystic partially differentiated nephroblastoma; FNA, fine-needle aspiration; GPOH, Gesellschaft für pädiatrische Onkologie und Hämatologie; ICCC, International Classification of Childhood Cancer; MN, mesoblastic nephroma; RCC, renal cell carcinoma; RTK, rhabdoid tumour of the kidney; SIOP-RTSG, International Society of Paediatric Oncology Renal Tumour Study Group; TBM, tumour board meeting; WT, Wilms tumour; XGP, xanthogranulomatous pyelonephritis.

children with renal tumour masses to determine histology at diagnosis rarely changes management, and can result in misdiagnosis (particularly patients in the age range typical for WT). Although a more selective approach to biopsy has been routine practice in all other countries participating in SIOP-RTSG trials, there was variation between national groups. To address this variation and provide evidence-based recommendations for the indications and recommended approach to renal tumour biopsy within the SIOP paradigm, an international, multidisciplinary working group of SIOP-RTSG members was convened. We describe the resulting recommendations of this group, which are to be incorporated in the ongoing SIOP-RTSG UMBRELLA study.

KEYWORDS
oncology, renal tumours, Wilms tumour

1 | INTRODUCTION

Wilms tumour (WT) is the most common paediatric renal tumour, accounting for over 85% of all cases in children.[1] Under the International Society of Paediatric Oncology (SIOP) paradigm, WT are treated with neoadjuvant chemotherapy to reduce the risk of tumour rupture during surgery and allow for stratification of postoperative chemotherapy intensity and duration based on response to preoperative treatment.[2] By contrast, the Renal Tumor Committee of the Children's Oncology Group (COG) advocates primary nephrectomy where feasible. In COG protocols, biopsy is limited to unilateral cases where primary nephrectomy is not performed.

The management of other (non-Wilms) tumours varies from purely surgical approaches for benign tumours and localised renal cell carcinoma (RCC) to more intensive neoadjuvant chemotherapy regimens in the case of clear cell sarcoma of the kidney (CCSK) and rhabdoid tumour of the kidney (RTK). Experience from the United Kingdom suggests that mandating core needle biopsy (CNB) at diagnosis rarely changes management in the age typical for WT, and risks misdiagnosis of both WT and non-WT.[3]

The strategy of performing CNB only where there are features to suggest an increased probability of a non-WT requiring change in management has been used in many other countries participating in SIOP Renal Tumour Study Group (RTSG) trials, with some variation between national groups.[4] The criteria used for deciding primary CNB instead of presumptive chemotherapy were first based on SIOP trials' clinical data and mainly based on age at diagnosis, metastatic status, and differential diagnoses such as neuroblastoma. New available epidemiological data focusing on patients' age at diagnosis[1] and recent detailed retrospective imaging data[5,6] as well as tumour volumes data from the Gesellschaft für pädiatrische Onkologie und Hämatologie (GPOH) provide the opportunity to update the recommendations for the use of CNB in children with renal neoplasms.

Here, we describe the rationale for the biopsy recommendations within the International Society of Paediatric Oncology Renal Tumour Study Group (SIOP-RTSG) UMBRELLA study (Table 1). These recommendations are not for children with cancer predisposition syndromes who are diagnosed by screening programmes for specific tumours, as the pretest probabilities are very different in these cases.[7] This should be tailored to the tumour predisposition. For example, any new renal solid mass in a child at risk of WT is likely to be a WT or proliferating nephrogenic rest and may be treated without the need for diagnostic biopsy, whereas biopsy would be valuable in a child with tuberous sclerosis to differentiate between RCC and epithelioid angiomyolipoma.

2 | FACTORS INFLUENCING BIOPSY INDICATIONS

2.1 | Age

Based on international population level registry data, WT represents over 90% of all renal tumours in children under 7 years old.[1] RCC accounts for over 5% of cases in children aged 7 years, and the relative incidence increases in each subsequent year group, being over 20% of cases at 10 years and the predominant tumour type in children over 14 years (Figure 1). However, even in late adolescence, over 10% patients will have a WT. Determining a precise age cutoff at which to start routinely performing biopsy is complicated by the relative rarity of renal tumours in older children and the possibility of inclusion biases in trial cohorts; therefore, population-level data have been used. The small numbers of registered cases in regions outside of Europe and North America mean it is not possible to determine region-specific cutoffs.

Based on a German cohort containing 49 RCCs and 2560 WT, the clinico-radiological diagnosis of RCC was suspected by the local team in only 16% (5/32) of patients where reference radiology was available (N. Graf unpublished data), whereas CNB correctly identified all RCCs in both UK and French cohorts.[3,5] Consequently, the SIOP RTSG now recommends CNB for all children aged 10 years or older and in children 7–10 years with smaller volume tumours (see rationale below) to both spare younger children with RCC unnecessary chemotherapy while also identifying adolescents with WT who would benefit

TABLE 1 Summary of recommended indications for diagnostic core needle biopsy of renal neoplasms in children, adolescents and young adults without features of genetic predisposition, under SIOP-RTSG protocols

	Features typical of WT (i.e. *not* requiring biopsy) *all* criteria required	Biopsy *not* recommended if *any* of these criteria met	Biopsy recommended if *any* of these criteria met	Indication to be discussed in tumour board meetings if *any* of these criteria met
Clinical criteria	Age ≥6 months but <7 years, No infectious syndrome	Age <3 months (upfront surgery indicated)	Age ≥10 years, Age between 7 and 10 years, Tumour volume[a] <200 ml	Age ≥3 months but <6 months, Infectious syndrome, Urinary tract infection
Radiological criteria	Obvious renal origin, Unilateral tumour with volume over 80 ml, Solid or mixed (solid and cystic) without calcification, Metastases absent or limited to lungs and age >2 years	Totally cystic tumour (primary surgery, if indicated), Bilateral kidney tumours in children ≥6 months but <7 years and/or typical nephroblastomatosis at imaging (presumptive chemotherapy)	Uncertain renal origin, Atypical metastases: bones (any age), central nervous system (any age), pulmonary (<2 years)	Intratumour calcifications, Tumour volume under 80 ml, Large necrotic adenopathy, Bilateral kidney tumours and ≥7 years
Biochemical criteria	Normal urinary catecholamines, Normal serum calcium, LDH less than 4× upper limit of normal		Elevated urinary catecholamines, Hypercalcaemia *and* age <4 years	LDH over 4× upper limit of normal

Note: 6 months = 182 days life.
Abbreviations: LDH, lactate dehydrogenase; SIOP-RTSG, International Society of Paediatric Oncology Renal Tumour Study Group; WT, Wilms tumour.
[a]Tumour volume = length (cm) × width (cm) × thickness (cm) × 0.523.

from preoperative chemotherapy. Furthermore, CNB is recommended in adult patients with renal masses to resolve diagnostic uncertainty and determine optimal medical and surgical management[8,9] so CNB is recommended even in older adolescents where RCC is more likely than WT.

Epidemiological data are limited by the fact that benign tumours are often not routinely collected in cancer registries. Mesoblastic nephroma (MN) is a tumour of low malignant potential and typically benign clinical course that occurs in early infancy. Based on UK population-level data, including both malignant and benign tumours, MN represents over 70% of kidney tumours in children under 3 months, but beyond 3 months WT is the most common tumour.[10] Data from national trial cohorts and case series suggest the median age of diagnosis of MN to be under 3 months[11] and in previous SIOP-RTSG, UK and NWTSG studies, MN was less than 10% of all tumours diagnosed after 3 months of life (7% in 3–4 months, 4% in 4–5 months and 5% in 5–6 months).[12] Hence, upfront surgery is still recommended before the age of 3 months, but between 3 and 6 months, the clinical and radiological characteristics need to be discussed carefully within tumour board meetings (TBM) to make an optimal risk/benefit judgement regarding primary nephrectomy in the context of the most likely diagnosis. Classical MN usually demonstrates suggestive features,[13,14] whereas the cellular variant of MN and WT share similar radiological features.

2.2 | Biochemical features

A single-centre retrospective cohort of 317 patients provides the best evidence to support the biochemical features suggestive of non-WT[5]: 31% of patients with hypercalcaemia had a non-WT (RTK or MN). Isolated hypercalcaemia may be the only feature to suggest RTK in a child of the typical age for WT; however, as up to 7% with WT will also have hypercalcaemia, biopsy should be limited to the ages at which RTK is typical; 90% of all RTK occurs in children under 4 years, and fewer than 1% cases in each year group above this are RTK.[1]

Urinary catecholamine metabolites are elevated in over 90% cases of neuroblastoma[15] and so this test is crucial and should be obtained for every retroperitoneal paediatric tumour to avoid misdiagnosis.[16] Elevated lactate dehydrogenase (LDH) is seen in haematologic malignancies and high-risk neuroblastomas, but is also a frequent finding in WT; therefore, correlation with other features is advised.

Both renal abscesses and the pseudotumours formed by focal xanthogranulomatous pyelonephritis (XGP) may mimic WT[17,18]; therefore, urinary microscopy and culture is essential in the diagnostic workup of a paediatric renal mass when clinical or biological signs of infection are observed. However, fever, biological inflammatory syndrome or true urinary tract infection may co-exist with, and be part of the initial presentation of, classical WT, so discussion of the indications for biopsy in a TBM is required in these cases.

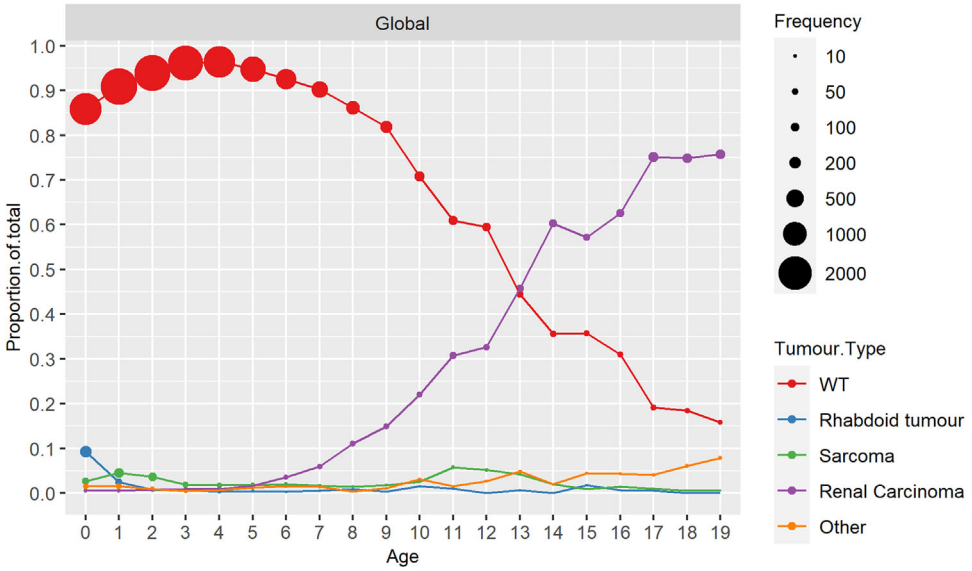

FIGURE 1 Population level histological distribution of renal tumours by age. Distribution of renal tumours recorded in International Classification of Childhood Cancer (ICCC) database 3rd Edition taken from Nakata et al. (2020).[1] Data are 15,320 cases in children (age 0–14 years) and 800 cases in adolescents (15–19 years) registered between 2001 and 2010. The size of each point is proportional to the number of cases. (importantly, mesoblastic nephroma [MN], cystic partially differentiated nephroblastoma [CPDN] and cystic nephroma [CN] are not included in the ICCC-3 as although they have diagnostic codes they are variably collected by national registries)

2.3 | Radiologic features

2.3.1 | Tumour site

Tumours arising from the upper renal pole may be difficult to differentiate from those arising from the adrenal gland such as neuroblastoma. When retroperitoneal tumours are very large, the normal residual renal parenchyma may be difficult to identify. Given that biochemical tests are not 100% sensitive for neuroblastoma and that biopsy is required for MYCN status in neuroblastoma, CNB is recommended whenever there is any uncertainty about the tissue of origin of a retroperitoneal tumour.

Conversely, bilateral tumours should usually not be biopsied. Although there are rare reports of bilateral cystic partially differentiated nephroblastoma (CPDN), cystic nephroma (CN),[19] RTK[20] and RCC,[21,22] the rarity of these entities means that after exclusion of haematologic malignancies, bilateral renal tumours in children under the age of 7 years are almost always WT or nephroblastomas and so can be treated with appropriate neoadjuvant chemotherapy. Bilateral WT is very rare in children 7 years and over.[1] Children over 7 years with bilateral tumours may have a non-WT and it should be discussed at a TBM.

2.3.2 | Imaging appearances

Imaging appearances are often contributory to deciding whether biopsy is indicated. The MRI features that can differentiate between different tumours have been described by a Delphi study of the RTSG radiology panel.[14]

Entirely cystic tumours are typically low-risk CPDN and CN, which occur with a median age at diagnosis of 12 and 16 months, respectively.[19] Both are adequately treated with upfront nephrectomy alone. The diagnostic yield from predominantly or exclusively cystic tumours is likely to be poor; therefore, CNB should not be performed in these cases. In rare cases of WT with a prominent cystic appearance treated with primary nephrectomy, adjuvant chemotherapy is delivered based on histologic risk and stage defined by the pathologists, according to SIOP guidelines.

Intratumoral calcifications related to tumour necrosis occur in 10% of WT,[5] but also in a wide range of non-WT renal tumours such as CCSK, RCC, RTK, and are typically observed in neuroblastomas. The radiologic depiction of few tumour calcifications is not by itself an indication for biopsy, but should raise TBM discussion about the probability of neuroblastoma or non-Wilms renal neoplasms.

Similarly, prominent enlarged hilar and retroperitoneal lymph nodes occur in aggressive tumours, both WT and other non-WTs. Therefore, either feature is suggestive of a higher probability of a non-WT (28% for calcifications and 17% for bulky adenopathy[5]). However, the size of lymph nodes alone is not predictive of the degree of tumour spread (i.e., enlarged nodes may be reactive and conversely small ones contain tumour deposits)[23] and so all cases of bulky lymphadenopathy should lead to a careful discussion in a TBM regarding the indication for CNB.

Renal calculi are typically associated with diffuse XGP but this could be mistaken for a large renal mass, so should prompt TBM discussion.

2.3.3 | Tumour volume

Tumour volumes in millilitres can be estimated from imaging studies using the elliptic approximation: length (cm) × width (cm) × thickness (cm) × 0.523. RCC and RTK are typically smaller at presentation than WT or CCSK.[5] However, the size of WT at presentation is dependent on the healthcare setting[24]; therefore, caution should be used when interpreting data from individual countries or centres. Analysis of a single-centre series suggested a volume cutoff of 70 ml as having good discriminatory value to identify RCC.[25] Unpublished data from a much larger GPOH series with more cases of RCC suggest that overall a tumour volume under 61 ml has a 90% sensitivity for RCC but 51% specificity, but in children above 7 years, an 80 ml cutoff is associated with a 90% sensitivity and a 61% specificity and no child between 7 and 10 years of age had an RCC >200 ml (N. Graf unpublished data). To ensure all children with RCC are identified, CNB is recommended in children 7–10 years of age with a tumour volume less than 200 ml, and younger children with tumours less than 80 ml should be discussed at TBM.

2.4 | Metastatic disease

Isolated lung metastases are present in over 75% children with metastatic WT,[26] but also 33% of metastatic RTK.[27] Based on the typical age at presentation of RTK and the rarity of stage IV WT in children under 2 years old, previous SIOP-RTSG trials have recommended CNB in children under 2 years with pulmonary metastases. Using this criterion, a third of patients are found to be RTK.[5] Multisite metastases are more common in RTK,[27] and the presence of metastases at sites uncommon for WT, such as bone and the central nervous system, in children of any age is a sufficient indication for biopsy to rule out RTK and CCSK.

3 | RECOMMENDED APPROACH

Percutaneous image-guided co-axial CNB through a retroperitoneal approach is the current recommendation for renal tumour biopsy, because of its high diagnostic accuracy and low complication rate, both in adults[28] for localised masses suspicious for RCC and in children to characterise masses suspicious for non-WT[3,5,6] (Table 2). Each centre is recommended to have a clear protocol imbedding these recommendations, written in conjunction with interventional radiology and pathology departments to ensure best practice and reduce the risk of complications.

Open surgical biopsy upstages all tumours to stage III disease under SIOP protocols and so is not recommended. In the very small number of cases done in the SIOP2001 trial, open biopsy was associated with poorer event-free survival on univariate (but not multivariate) analysis.[4]

CNB in children should be performed by trained interventional radiologists or surgeons under general anaesthesia, whereas local anaesthesia can be proposed in adolescents and young adults. Both ultrasound and CT scans may be used for guidance, but ultrasound offers several advantages: it can be performed in a conventional operating room (i.e., without need for specific interventional radiology unit), it allows real-time control of the biopsy tract to target areas of interest and avoids ionising radiation, especially in young children.

TABLE 2 Recommended approach

Under general anaesthesia: consider local anaesthesia only for adolescents or young adults
Ultrasound or computed tomography (CT) guidance: make sure to sample solid and viable tumour, avoid necrotic or cystic areas
Co-axial technique is mandatory
Retroperitoneal biopsy tract only (do not use transperitoneal access)
Use cutting needles with a size of 18 or 16 gauge to guarantee sufficient tissue for pathologic differentiation (provide typically 6 cores 15-mm long)
No direct fixation of all specimens (part of specimens in culture medium like RPMI or immediate freezing for molecular biology analyses)

A co-axial technique is highly recommended, allowing for multiple sampling from a single needle tract, hence reducing the risk of local complication, notably haemorrhage and tumour seeding.

A retroperitoneal (i.e., posterior) approach is mandatory to avoid the peritoneal cavity and the associated risk of peritoneal spillage, which adversely impacts prognosis. Anterior tumours can be accessed via normal kidney posteriorly using an introducer. Retroperitoneal hydrodissection should be used to avoid overlying bowel. The risk of needle tract recurrence after CNB (in the retroperitoneum or the lumbar wall) has always been a matter of debate. This risk is strongly associated with the biopsy technique used (needle diameter, ccoaxial approach or not), with operator's experience, and biased by adjuvant treatments, especially flank radiotherapy. In the most recent monocentric series of 88 CNB with a co-axial 18 G method, no needle recurrences were observed.[5] In the larger UK series of 552 CNB, only one needle tract recurrence occurred (after a transperitoneal approach).[29,30]

The needle diameter affects both the amount of tissue obtained and the complication rate. The widely accepted compromise is 18 or 16 gauge needles (i.e., 17 or 15 G ccoaxial introducer). In a paediatric series, the use of 18 G was reported as associated with no mortality and only 12% haematuria (93% grade 1),[5] whereas the use of needles as large as 14 G was associated with a higher rate of complications (20% fall in haemoglobin, 7% infection and one death),[30] whereas the rate of nondiagnostic material was relatively low in both series (8% and 6.5%, respectively).

The amount of tissue to be obtained is difficult to define and should be discussed on a case-by-case basis depending on the clinical scenario, balancing the need to acquire an optimal tissue volume against the risks of complications. Typically, six cores 15 mm long allow both pathologic diagnosis, molecular biology analyses and bio-banking for research purposes (consensus opinion). However, the optimal

procedure should be decided by consensus between pathologists, radiologists and the clinical team in each centre.

Fine-needle aspiration (FNA) performed with 22 G (or thinner) needles is less invasive than CNB and is reported as associated with high diagnostic accuracy in the few centres with cytopathologic expertise for paediatric neoplasms.[5,31] However, meta-analysis of mostly adult studies[32] and single-centre reports from paediatric centres suggest that FNA provides lower diagnostic accuracy than percutaneous CNB.[5,33] Nevertheless, the combined use of FNA and CNB is feasible with the ccoaxial approach and is used by some paediatric and adults teams, as it may reduce the nondiagnostic rate of CNB and provides additional material (cell suspensions) for both fast cytologic analysis and molecular biology.[5,34]

Spontaneous retroperitoneal haemorrhage may occur at diagnosis of renal tumours. When this results in haemodynamic instability, which cannot be corrected with resuscitative measures, immediate nephrectomy or embolisation is mandatory. However, where haemorrhage is limited, restrained in the retroperitoneum and clinically well tolerated, biopsy can be performed if indicated.

Coagulopathy is not an absolute contraindication to biopsy, but should be corrected prior to biopsy. Consensus recommendations are to correct an INR to less than 1.5 and transfuse to achieve a platelet count $>50 \times 10^9$/L.[35] There is no consensus approach to an elevated APTT in the absence of heparin treatment and so local haematology advice should be followed.

In the cases where CNB is not diagnostic, we recommend repeating it after further discussion in a TBM, ensuring that results of all other investigations necessary for differential diagnosis are available.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Herve J. Brisse chaired the working group. Thomas J. Jackson drafted the manuscript. All members of the working group contributed revisions and agreed on the final version.

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