



# The diagnostic accuracy and clinical utility of pediatric renal tumor biopsy: Report of the UK experience in the SIOP UK WT 2001 trial

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## Abstract

**Introduction:** The International Society of Paediatric Oncology (SIOP) protocols recommend preoperative chemotherapy appropriate for Wilms tumors (WTs) in children with renal tumors aged  $\geq 6$  months, reserving biopsy for "atypical" cases. The Children's Cancer and Leukaemia Group (CCLG) joined the SIOP-WT-2001 study but continued the national practice of biopsy at presentation.

**Method:** Retrospective study of concordance between locally reported renal tumor biopsies and central pathology review nephrectomy diagnoses of children enrolled by CCLG centers in the SIOP-WT-2001 study.

**Results:** Biopsy reports were available for 552/787 children with unilateral tumors. 36 of 552 (6.5%) were nondiagnostic: 2 normal tissue, 12 necrotic, 9 insufficient sample, and 13 indeterminate results (disproportionately non-WTs). The sensitivity and specificity of biopsy to identify tumors that did not require SIOP empirical preoperative chemotherapy were 86.0% and 99.6%, respectively. 13 of 548 (2.4%) biopsy results were discordant with nephrectomy; non-WTs other than renal cell carcinoma and clear cell sarcoma of the kidney (CCSK) were poorly recognized. In children aged 6-119 months, 480 of 518 (91.6%) had WT or nephroblastomatosis. 5 of 518 (1%) had benign tumors, and only one diagnosed on biopsy. Biopsy results correctly changed clinical management in 25 of 518 (4.8%), including identifying 19 of 20 CCSKs, but would have led to overtreatment in 5 of 518 (1%) or undertreatment in 4 of 518 (0.8%). In children aged  $\geq 10$  years, biopsy correctly changed management in 5 of 19 (26%) cases with no discordance.

**Conclusion:** Biopsy is less effective at identifying non-WTs than WTs and rarely changes management in younger children. Biopsy should be reserved in SIOP protocols for children  $\geq 10$  years and in younger children with clinical or radiological features inconsistent with WT.

## KEYWORDS

diagnostic accuracy, pediatric, renal biopsy, sensitivity and specificity

## 1 | INTRODUCTION

Renal tumors represent 7% of pediatric cancers, with Wilms tumor (WT) the most common, accounting for about 90% of renal cancers in European Cancer registries.<sup>1,2</sup> WT has a median age of diagnosis of 3 years and generally has a good prognosis with 5-year overall

survival 93% and 2-year event-free survival 87%.<sup>3</sup> Non-WTs are rare in children and predominantly include mesoblastic nephroma (MN), clear cell sarcoma of the kidney (CCSK), rhabdoid tumor of the kidney (RTK), and renal cell carcinoma (RCC). MN is a tumor of low malignant potential usually requiring no further treatment than nephrectomy. It is the most common renal tumor among neonates but after 3 months of

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age, MN represents fewer than 10% of renal tumors,<sup>4</sup> and in total 75% all MNs in the UK occur under the age of 6 months.<sup>5</sup> CCSK has a similar age distribution to WT but requires more intensive chemotherapy to achieve similar 5 year outcomes compared with WT.<sup>6,7</sup> RTK typically presents in the first 1-2 years and has a considerably poorer prognosis, despite more intensive chemotherapy, with median survival less than 1 year.<sup>8</sup> RCC typically presents in adolescence, is chemotherapy resistant, and requires effective surgical clearance, with molecular targeted therapy used in appropriate cases.

There are two philosophies for the initial management of pediatric renal tumors. The Children's Oncology Group (COG) protocols advocate upfront nephrectomy to achieve an accurate tissue diagnosis prior to postoperative chemotherapy. The International Society of Paediatric Oncology (SIOP) Renal Tumour Study Group (SIOP-RTSG) protocols use preoperative chemotherapy to minimize the risk of preoperative tumor rupture, give a more favorable stage distribution, and to allow histological response to chemotherapy to be included in risk stratification of postoperative treatment.<sup>9,10</sup> Upfront nephrectomy is advocated only for children under 6 months of age where there is a much higher incidence of tumors that do not require cytotoxic treatment. There are no significant differences in overall survival between concurrent COG and SIOP renal tumor trials.<sup>3</sup>

The UK and Irish Children's Cancer and Leukaemia Group (CCLG) changed from immediate nephrectomy to a preoperative chemotherapy approach when they joined the SIOP WT 2001 trial after the UKW3 trial compared the two approaches.<sup>11</sup> However, we continued using percutaneous biopsy (PCNB) prior to commencing chemotherapy in all cases to reduce the risk of giving inappropriate chemotherapy to children with non-WTs. For other countries participating in the SIOP WT 2001 trial, biopsy was not recommended routinely but only permitted when there was clinical diagnostic uncertainty.

Biopsy carries risks that may not outweigh the clinical benefits of identifying non-WTs, especially in the age range where WT is the most likely diagnosis. The largest study of pediatric biopsy associated morbidity in 182 cases enrolled in UKW3 found 19% of patients suffered pain, 7% infection, and 5% postprocedure bleeding.<sup>12</sup> A further concern is that biopsy poses a risk of local tract seeding, but only a few cases are reported in the literature.<sup>13,14</sup> Large adult series (>10,000 patients) suggest needle track recurrence occurs in <0.01% cases<sup>15</sup> compared with 0.5% in the above pediatric series.<sup>12</sup> In the UKW3 trial, biopsy was not significantly associated with risk of local relapse in multivariate analysis.<sup>16</sup>

In this study, we analyzed the diagnostic accuracy of locally reported biopsies compared to the central pathology review (CPR) nephrectomy diagnoses, and assessed the implications of any discordancy for the clinical effectiveness of a policy of universal renal biopsy for pediatric renal tumors by age group.

## 2 | METHODS

A retrospective study of children enrolled through the CCLG in the SIOP WT 2001 trial.<sup>10</sup> Children were eligible for inclusion if they had a unilateral renal tumor that had been biopsied at presentation. Biopsy

**TABLE 1** Grouping of tumors according to how a correct diagnosis on biopsy would have changed initial management

Group	Description	Tumors included
A	Benign tumors requiring surgery but not chemotherapy	Mesoblastic nephroma Cystic nephroma Cystic partially differentiated nephroblastoma Nontumor
B	Malignant tumors usually treated by initial surgery	Renal cell carcinoma
C	Malignant tumors "under-treated" by the standard SIOP-RTSG preoperative chemotherapy regimen for localized WT	Clear cell sarcoma of the kidney Rhabdoid tumor of the kidney Anaplastic sarcoma Desmoplastic small round CELL tumor Primitive neuroectodermal tumor
D	Tumors appropriately treated by the standard SIOP-RTSG preoperative chemotherapy regimen	Wilms tumor Nephroblastomatosis/bulky nephrogenic rests that have imaging appearances of a proliferating tumor

SIOP-RTSG, International Society of Paediatric Oncology Renal Tumour Study Group.

was recommended using a 12-14G cutting needle under ultrasound guidance and with consideration of using a coaxial technique.

The pathology reports of renal tumor biopsies were obtained retrospectively from participating CCLG centers by requesting to provide all biopsy reports for the children they had enrolled, and trial case files of G. Vujanic (Chair of the CCLG Pathology Panel) for biopsies that were sent for CPR (note that biopsies were not required to be sent routinely for CPR). Biopsies were reported locally prior to nephrectomy.

Each local pathology report was coded by a nonpathologist (TJJ) into one of 15 categories (Supporting Information File S1) and the type of the biopsy (fine needle aspirate, PCNB or open) was recorded based on the description in the report. Five of the categories were considered as types of "nondiagnostic": "normal renal tissue," "necrotic sample," "insufficient sample," "indeterminate diagnosis," and "indeterminate diagnosis—not a WT." A case was classed as "indeterminate" if the pathologist offered a differential diagnosis or stated they were not confident of a single diagnosis. The full local pathology report of all cases classified as "indeterminate diagnosis" was reviewed by an expert pediatric pathologist (GMV).

The CPR nephrectomy diagnoses were extracted from the SIOP UK WT 2001 trial and study database held at the Cancer Research UK Clinical Trials Unit, University of Birmingham.

Patients were divided into four clinically meaningful groups to assess the ability of biopsy to correctly identify cases, which would require a different management than the standard SIOP preoperative chemotherapy approach<sup>3</sup> (Table 1). Group A comprised benign tumors for which chemotherapy is unnecessary, Group B comprised RCCs, Group C comprised other malignant tumor types requiring more intensive chemotherapy regimens (mainly CCSK and RTK), Group D comprised WT and hyperplastic nephrogenic rests that would be treated appropriately by the standard SIOP chemotherapy. A binary classification sensitivity-specificity analysis was performed comparing

Group D versus those that required alternative management (Groups A-C). Data are presented as a  $3 \times 2$  contingency table as recommended by Simel.<sup>17</sup> The worst-case sensitivity was defined as treating all Groups A-C cases with a biopsy that was nondiagnostic or indeterminate and included WT in the differential as false negatives and the worst case specificity as treating nondiagnostic/indeterminate biopsies in Group D cases as false positives: the analysis used a modified version of the “intention to diagnose” approach<sup>18</sup> based on the intention to discriminate between WT and non-WT. Overall concordance between first biopsy and subsequent nephrectomy diagnosis was assessed. A more detailed assessment within each clinically relevant group was then performed as some discordant results would not result in incorrect management.

Subgroup analyses were performed for three specific age groups: the first were children under the age of 6 months, for whom upfront nephrectomy is already advised, the second between 6 months and 9 years and 11 months, and the third group children aged 10 years or over, where the relative incidence of non-WTs starts to increase.

Analyses were performed in the R statistical environment<sup>19</sup> with graphical output produced using ggplot2.<sup>20</sup> Exact binomial 95% confidence intervals (CI) were calculated for sensitivity, specificity, nondiagnostic, and accuracy estimates.

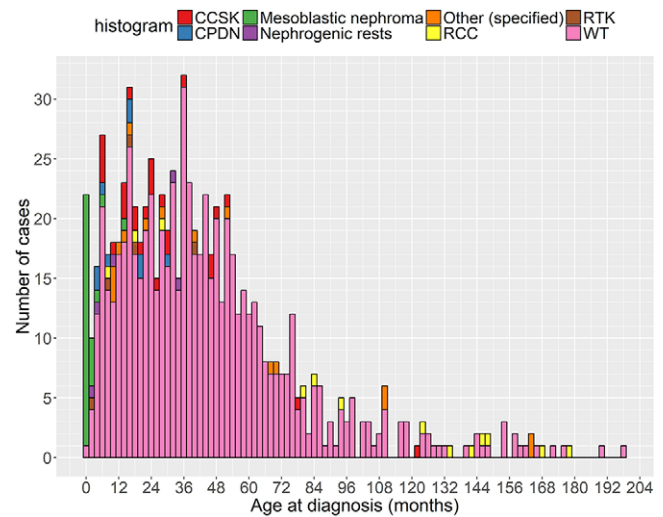
### 3 | RESULTS

#### 3.1 | Inclusion

There were 849 cases enrolled by 25 centers (22 UK, 1 Irish, 1 Australian, 1 New Zealand) into the CCLG database for the SIOP WT 2001 trial, from March 2002 to December 2011. The upper age limit for this trial was 18 years. We excluded 62 children with bilateral (stage V) disease, 64 cases with upfront nephrectomy, and 169 cases without a biopsy report either because a biopsy was not performed or the report was not provided by the recruiting center (19 centers provided copies of original biopsy reports). In one case, biopsy of a metastatic site was used for primary diagnosis. One child had tumor rupture associated with biopsy, therefore an emergency nephrectomy was performed without local reporting of the biopsy material. Of the remaining 552 cases, there were three cases where the pathology panel could not give a definitive diagnosis and one child died prior to nephrectomy. Accordingly, 548 cases were included in the concordance analysis (Supporting Information Figure 1). A histogram showing the relative distribution of different tumors types in children of different ages enrolled in the trial is presented in Figure 1, with the biopsy population showing a similar distribution (Supporting Information Figure 2). There was no significant difference in the proportion of non-WTs for cases where a biopsy report was obtained compared to where it was not (49/548 vs 12/163, Fisher's exact test,  $P = 0.633$ ).

#### 3.2 | Type of biopsy

Of the 552 initial biopsies, 541 were PCNB, 10 open, and in one case the type of biopsy could not be determined from the pathology report and was missing from the registration case report form.



**FIGURE 1** Stacked histogram for the age at presentation for all unilateral cases. Bin width = 2 months

#### 3.3 | Nondiagnostic and indeterminate biopsy results

Thirty-six of 552 (6.5%; 95% CI, 4.6-8.9%) biopsies were nondiagnostic; two had only normal renal tissue, 12 were wholly necrotic, and nine were an insufficient sample. Thirteen reports were considered indeterminate by a pathologist, of which two had a differential diagnosis that only included non-WTs. A biopsy was repeated in seven of 36 cases, of which six were diagnostic (five WTs and one neuroblastoma). Patients with indeterminate biopsies were more likely to have a final diagnosis in Groups A-C than Group D—six of 49 (12.2%) versus seven of 539 (1.3%) (Fisher's exact test,  $P = 0.00029$ ). However, there was no such difference for biopsies that were nondiagnostic because of procedure failure (sampling normal tissue, necrotic regions or having an insufficient sample)—two of 49 (3.9%) versus 21 of 539 (4.1%) (Fisher's exact test,  $P = 1.00$ ).

#### 3.4 | Sensitivity analyses

The overall sensitivity of biopsy to identify tumors that needed alternative treatment from the recommended preoperative treatment for WT was 86.0% [95% CI, 72.0-94.7%], with a specificity for biopsy correctly identifying WT/NR of 99.6% [95% CI, 98.4-99.9%]. The worst-case sensitivity was 75.5% [95% CI, 61.1-86.7%] and worst-case specificity 94.0% [95% CI, 91.5-95.9%] (Figure 2).

#### 3.5 | Concordance

The concordance between biopsy and nephrectomy is detailed in Supporting Information File S3. Counting all WT subtypes as one category, biopsy was discordant in 13 of 548 (2.4%) cases and fully concordant in 499 of 548 (91.1%). This gives an overall accuracy of 499 of 512 (97.5%, 95% CI, 95.7-98.6%) for a diagnostic sample.

A discordant biopsy result was recorded for eight of 49 (16.3%) of the non-WT compared with five of 499 (1.0%) in Group D (WT/NRs). One of the Groups A-C cases with a discordant biopsy was an anaplastic sarcoma of the kidney, which at the time of presentation was not a

		NEPHRECTOMY DIAGNOSIS	
		GROUPS A-C	GROUP D
BIOPSY DIAGNOSIS	GROUPS A-C	37	2
	GROUP D	6	469
	Nondiagnostic	6	28
	TOTAL	49	499

Metric	Definition	Value
Sensitivity	TP/(TP+FN)	86.0%
Specificity	TN/(TN+FP)	99.6%
Worst-case sensitivity	TP/(NDP+TP+FN)	75.5%
Worst-case specificity	TN/(NDN+FP+TN)	94.0%

TP	FP
FN	TN
NDP	NDN

**FIGURE 2** 3 × 2 contingency table for the sensitivity and specificity of biopsy to distinguish “Groups A-C tumors” (i.e., those that do not require the standard pre-operative SIOP regimen) from Group D tumors (that do). “Worst case” calculations are on an intention to diagnose principle. Far right panel corresponds to definitions of each square in the 3 × 2 grid: TP, true positive; TN, true negative; FP, false positive; FN, false negative; NDP, nondiagnostic positive; NDN, nondiagnostic negative

recognized entity in the literature so a pathologist could not have been expected to recognize it. Three of the five discordant cases in Group D were nephrogenic rests diagnosed as WT on biopsy (which cannot easily distinguish these two entities and their initial management usually includes the same preoperative chemotherapy used for WT). After accounting for the two caveats above, there remains a statistically significant difference in discordance rate between Groups A-C and D (7/48; 14.6% vs 2/499; 0.4%, Fisher's exact test,  $P = 5.0 \times 10^{-7}$ ).

The concordance between biopsy diagnosis and nephrectomy based on clinically relevant groups is summarized in Table 2 and as follows:

*Group A: Five of nine (55.6%) benign tumors were correctly identified on biopsy with two nondiagnostic cases. Of the remaining two of nine cases with discordance between biopsy and final nephrectomy, one was reported as CCSK on biopsy but was an MN on nephrectomy, and the other was a cystic partially differentiated nephroblastoma (CPDN) diagnosed as WT on biopsy.*

*Group B: Eight of 10 (80%) RCCs were correctly identified and the other two biopsies suggested an alternative diagnosis (one as a WT and one as a metanephric adenoma).*

*Group C: Twenty of 30 (66.7%) other malignant non-WTs were correctly identified, 19 of these were cases of CCSK, which accounted for two-thirds of all cases in Group C. In four cases, a biopsy suggested a diagnosis of WT with the ultimate nephrectomy histology RTK in two cases and one case each of anaplastic sarcoma and desmoplastic small round cell tumor (DSRCT).*

*Group D: This was the largest group, consisting of WT (495 cases) and nephrogenic rests (four cases). In 20 cases (4.0%), the biopsy failed to provide diagnostic material and in three of four cases diagnosed as nephrogenic rests on the nephrectomy specimen, the initial biopsy suggested WT. Anaplasia was not reported in 27 of 30 (90%) of adequate biopsies from children with diffuse anaplastic WT. Overall, in 466 of 499 (93.4%) cases, the biopsy correctly identified WT/NR, both appropriate for preoperative chemotherapy with vincristine and actinomycin D. In two of 499 (0.4%) cases, the biopsy suggested an alternative malignant histology (one CCSK and one RTK).*

### 3.6 | Subgroup analyses

Cases were subgrouped based on the different age distributions of tumors. In the age range at which WT is commonest (6-119 months group), 10 of 518 (2%) children had tumors requiring only surgery (five benign tumors and five RCCs) compared with five of 19 (26.3%) children aged 10 years and over (all RCCs). Similarly, 480 of 518 (92.6%) cases of tumors in children aged 6-119 months were Group D (i.e., no management change required) versus 12 of 19 (63.2%) cases of tumors in the older age group. Compared with the whole cohort, the sensitivity of biopsy to identify Groups A-C (non-WT) in children 6-119 months is reduced to 82.4% (95% CI, 65.5-93.2%) with worst-case sensitivity of 73.7% (95% CI, 56.9-86.6%) (Figure 3).

### 3.7 | Clinical implications

Overall, 37 of 548 (6.7%) children had a non-WT and the biopsy identified a diagnosis that required a change from the standard SIOP preoperative chemotherapy management (“clinical effectiveness”). Furthermore, six cases of non-WT were not detected by biopsy and 28 cases of WT/NR had nondiagnostic biopsies (Table 3 and Supporting Information File S2).

The biopsy result would have changed management for 28 for 518 children (5.4%) in the 6-119 months group (24 were correctly

**TABLE 2** Summary of the concordance between biopsy and nephrectomy for all cases, grouped according to how a correct biopsy diagnosis could have changed management (diagnostic groupings are per Table 1)

	Group A— chemotherapy unnecessary	Group B—RCC	Group C—requires alternative, more intensive chemotherapy	Group D—requires standard SIOP WT preoperative chemotherapy regimen
Concordant biopsy	5	8	20	466
Discordant biopsy	2	2	4	5
Nondiagnostic result	2	0	6	28
Total	9	10	30	499



		NEPHRECTOMY DIAGNOSIS	
		GROUPS A-C	GROUP D
BIOPSY DIAGNOSIS	GROUPS A-C	28	2
	GROUP D	6	450
	Nondiagnostic	4	28
	TOTAL	38	480

Metric	Definition	Value
Sensitivity	TP/(TP+FN)	82.4%
Specificity	TN/(TN+FP)	99.6%
Worst-case sensitivity	TP/(NDP+TP+FN)	73.7%
Worst-case specificity	TN/(NDN+FP+TN)	99.6%

TP	FP
FN	TN
NDP	NDN

**FIGURE 3** 3 × 2 contingency table for the sensitivity and specificity of biopsy to distinguish “non-Group D tumors” in children aged greater than or equal to 6 months but less than 10 years. Format is the same as shown in Figure 2

diagnosed—19 CCSK, one DSRCT, three RCC, one benign tumor—with one RCC misdiagnosed as a metanephric adenoma, an MN thought to be CCSK, and two malignant tumors where WT was excluded but the diagnosis was uncertain) compared with five of 19 (26%) children in the 120 months+ group (all RCCs). In the 6-119 months group, five of 518 (1%) children with discordant biopsy results would have resulted in overtreatment (one MN, one CPDN, two WT, and one RCC). Four of 518 children would be undertreated (one anaplastic sarcoma, one DSRCT, and two RTK). There were no cases of discordant results in the 120 months+ group (Table 3 and Supporting Information File 2). Five of 518 (1%) children in the 6-119 months group had benign lesions not requiring chemotherapy, of which only one was correctly identified.

## 4 | DISCUSSION

This is the largest study of the diagnostic accuracy of pediatric renal tumor biopsy. In addition to calculating estimates of concordance and nondiagnostic rates, we also report on how effective biopsy (per-

formed by PCNB in 98% of cases) is in identifying tumors that require a change in management from the standard SIOP approach.

The overall concordance between biopsy and final nephrectomy (91.7%) is slightly lower than the 94% figure found in Vujanic et al's study from UKW3.<sup>12</sup> However, Vujanic et al's study only included cases where both the biopsy and nephrectomy were sent for CPR and so may represent a biased subgroup analysis. This suggests that where biopsy is performed, CPR may help improve diagnostic accuracy, as is the case for nephrectomy specimens.<sup>21</sup>

We found that 6.5% of all biopsies were nondiagnostic, which is slightly higher than the 4% figure found in the UKW3 study,<sup>12</sup> but not dissimilar to a pooled estimate of 6% for biopsy inadequacy from a systematic review of PCNB of pediatric tumors.<sup>22</sup> Importantly, we report the rates of different types of nondiagnosis. “Invalid” nondiagnostic results, whereby the test procedure fails to provide material required for diagnosis (“insufficient sample,” “wholly necrotic tissue,” “normal renal tissue”), are different from valid nondiagnostic results (where the procedure was adequate but there was diagnostic uncertainty—an “indeterminate result”) as the latter may provide some clinically useful information (e.g., this is a malignant neoplasm that is not a WT, but it is not clear which non-WT).<sup>23</sup> While PCNB alone may lead to unrepresentative material (an invalid non-diagnostic result), this risk is minimized by using an image-guided coaxial technique to sample material from the most suspicious areas of the tumor.<sup>24</sup>

Note that 36% of the nondiagnostic results in this study were indeterminate results. It is unclear whether this was because pathologists were less certain of the diagnosis or more prepared to admit diagnostic uncertainty in SIOP UK 2001 than UKW3 or whether the different researchers in each paper classified pathology reports differently. For example, the degree of diagnostic certainty associated with identical phraseology can be interpreted differently between surgeons and pathologists.<sup>25</sup>

The SIOP approach is to treat all pediatric renal tumors (unless they are completely cystic on imaging studies or occur in children under 6 months of age or clinical features are atypical) with empirical preoperative chemotherapy appropriate for the most likely diagnosis of WT. Hence, the potential utility of biopsy is to correctly identify non-WTs

**TABLE 3** Summary of the concordance between biopsy and nephrectomy shown separately for patients aged between 6-119 months and ≥10 years (120 months)

	Group A benign—chemotherapy not needed		Group B RCC		Group C requires alternative/more intensive chemotherapy		Group D requires standard SIOP WT preoperative chemotherapy regimen	
	6-119 months	120 months <sup>+</sup>	6-119 months	120 months <sup>+</sup>	6-119 months	120 months <sup>+</sup>	6-119 months	120 months <sup>+</sup>
Correct diagnosis	1	0	3	5	20	0	448	12
Discordant diagnosis— appropriate treatment	0	0	1	0	0	0	2	0
Discordant diagnosis—VA would be “over treatment”	2	0	1	0	0	0	2	0
Discordant diagnosis—VA would be “under treatment”	0	0	0	0	4	0	0	0
Nondiagnostic	2	0	0	0	4	2	28	0
Total	5	0	5	5	28	2	480	12

Groups are as described in Table 1, according to how a correct biopsy diagnosis could have changed management.

to permit an early change in management. However, the sensitivity of biopsy to identify these tumors is considerably poorer than the specificity to avoid misdiagnosis of WT. There were also higher levels of diagnostic uncertainty with non-WT cases. Identification of high-risk tumors that require chemotherapy other than CCSK was particularly poor (although these cases, such as RTK and DSRCT, are a minority of all high-risk tumors).

Our data suggest that overall biopsy would be expected to correctly change management in 6.7% cases. If we confine the analysis to the 6-119 months age group and include CCSK in the group that are considered to be adequately treated by vincristine and actinomycin-D preoperative chemotherapy, this drops to six of 518 (1.2%) cases. This is a reasonable analysis as although there are no trials comparing the different regimens for CCSK, there are no survival differences between the UK (where the CCLG advocates AVD preoperatively if a CCSK is identified) and Germany, where biopsy is rarely employed and thus an AV regimen is de facto used or between SIOP and NWTs/COG approaches.<sup>26</sup>

Ultimately, the percentage of cases in which biopsy will change management is lower than the incidence of procedural complications previously reported.<sup>12</sup> Our data suggest that biopsy in children over 6 months is not effective in avoiding unnecessary chemotherapy in children with benign tumors but it is clearly effective in identifying RCCs (an important diagnosis to make to avoid unnecessary chemotherapy and allow timely surgical resection). Based on European population based registry data, RCC accounts for 34% of all renal cancers in 10-14 years old compared with 4.3% in 5-9 years old but WT is still the most common diagnosis in both age groups.<sup>2</sup> We find using a cut-off of 10 years and above increases the clinical effectiveness of biopsy to 26%, with all cases of RCC being correctly identified. Comparing the distribution of histological diagnoses of cases registered in the trial with the national cancer registry of England confirms the suitability of this age threshold for our population (Supporting Information Figure 3). Furthermore, recent reviews of the use of PCNB in adult RCC suggest that this technique is safe and provides adequate diagnostic information to guide subsequent surgical management.<sup>27</sup>

There are some limitations of this study. First, we achieved partial capture of the intended cohort as some centers did not respond to requests to provide biopsy reports. Some patients from nonresponding centers were included as they also had biopsies sent for CPR. If pathologists were more likely to send diagnostically challenging cases for CPR, this may have increased the nondiagnostic rate. Second, this study was confined to cases recruited to a trial focused on WT, hence benign tumors may be underrepresented and some tumor types that also occur in nonrenal sites were registered in other trials. As such, the estimates of concordance are not fully generalizable to all pediatric renal tumors. Third, changes in pathological practice over the last 15 years, such as the use of specific immunohistochemistry and molecular biology techniques to distinguish between different non-WTs, may mean that the nondiagnostic and discordance rates may be overestimated compared to current practice. As the use of CPR is associated with increased diagnostic accuracy,<sup>21</sup> our estimates cannot be applied to situations where biopsies are subject to CPR. We used the local biopsy reports as it was not part of the trial protocol for biopsies to

be sent routinely for CPR (unlike all nephrectomies). Some biopsies were sent for CPR concurrently with the nephrectomy specimens and so were not blinded. Fourth, our estimates for clinical effectiveness are inferred from the biopsy data rather than the actual treatment decisions made locally. In practice, a biopsy result is always taken in the context of imaging results and the child's clinical picture. Finally, our results may not be generalizable to contexts where biopsy is used more selectively.

In summary, this study provides estimates for the diagnostic accuracy and clinical utility of pediatric renal tumor biopsy in the context of a preoperative chemotherapy approach. Our results suggest that for children aged under 10 years, biopsy is unlikely to change clinical management under SIOP protocols, and other than for CCSK is not always helpful in identifying high-risk tumors (both malignant non-WT and anaplastic WT) and risks misdiagnosis and overtreatment of WT. Furthermore, biopsy is associated with some risks and delaying the start of chemotherapy. On this basis, we have amended our national clinical guidelines, which follow the SIOP approach, to recommend that no biopsy is necessary for children aged 6 months-10 years with typical clinical and imaging presentation for WT. Biopsy should be reserved for cases where there are clinical or radiographic features to suggest a non-WT and performed routinely where the child is 10 years or older under image guidance and using modern coaxial percutaneous cutting needle biopsy techniques.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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