



Original Research

# Evaluation of needle biopsy as a potential risk factor for local recurrence of Wilms tumour in the SIOP WT 2001 trial



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Received 20 November 2018; received in revised form 25 March 2019; accepted 10 April 2019

Available online 1 June 2019

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<https://doi.org/10.1016/j.ejca.2019.04.027>

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**KEYWORDS**

Wilms tumour;  
Local relapse;  
Biopsy;  
SIOP WT 2001

**Abstract Rationale:** The impact of biopsying Wilms tumour (WT) at diagnosis on assigning the tumour stage and recommended treatment remains controversial. To address this important question, we analysed the potential association of all types of biopsy with local recurrence in patients treated in the SIOP WT 2001 trial, where needle biopsy was permitted without ‘upstaging’ the tumour to stage III. Only open biopsy required treatment as stage III.

**Methods:** Among 2971 patients with unilateral WT (stages I–IV), 420 relapsed (139 local). Risk factors for recurrence were analysed by Cox proportional hazard methods.

**Results:** Biopsy was performed in 969 of 2971 (33%) patients (64% cutting needle, 30% fine needle aspiration [FNA] and 6% open biopsy). Biopsied patients were older, with larger tumours and a greater proportion with high-risk histology. In multivariate analysis that included all factors associated with local recurrence in univariate analysis, only high-risk histology (hazard ratio [HR] = 2.32; 95% confidence interval [CI]: 1.58–3.42,  $p < 0.0001$ ), age  $\geq 2$  years (HR = 2.24; 95% CI: 1.22–4.09,  $p = 0.01$ ) and preoperative tumour volume (HR = 1.07 per 100 ml; 95% CI: 1.02–1.12,  $p = 0.01$ ) were significant. The HR for the association of local recurrence and event-free and overall survival with biopsy was not significant (HR = 1.4; 95% CI: 0.9–2.17,  $p = 0.13$ ; HR = 1.1; 95% CI: 0.85–1.42,  $p = 0.46$  and HR = 1.13; 95% CI: 0.79–1.62,  $p = 0.51$ , respectively). These results were not materially different whether FNA or open biopsy were included in the biopsy group or not.

**Conclusions:** This *post hoc* analysis provides some reassurance that needle biopsy is not an independent adverse factor for either local recurrence or survival after adjustment for all relevant risk factors. Needle biopsy should not be an automatic criterion to ‘upstage’ WT.

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## 1. Introduction

The clinical impact of biopsy on Wilms tumour (WT) staging is controversial because of debated results on the possible relationship between biopsy and the risk of local recurrence. Based on the results of the National Wilms Tumour Study (NWTS) 3–4 trials, showing that patients with stage II disease and local spillage had worse outcome than those with no spillage, the Children’s Oncology Group (COG) AREN0532 protocol now considers any patient with local spillage to have a stage III tumour [1,2]. Any biopsy, regardless of the type—fine needle aspiration (FNA), percutaneous cutting needle biopsy (PCNB or ‘Trucut’) or open surgery—is considered as tumour spillage [2]. By contrast, the most recent trial of the International Society of Paediatric Oncology Renal Tumour Study Group (SIOP–RTSG, trial protocol SIOP WT 2001) permitted tumour biopsy by FNA or PCNB without affecting tumour stage assignment, with the latter determined by the pathological stage of the nephrectomy specimen [3].

In the UKW3 randomised trial, that compared immediate nephrectomy with a preoperative chemotherapy approach, UK clinicians had routinely biopsied patients assigned to delayed nephrectomy using PCNB without affecting tumour staging [4]. Therefore, when the UK joined the SIOP WT 2001 trial, this national group had continued their national practice of biopsying patients before starting chemotherapy [4,5]. However, concerns about a higher rate of local relapse in the UKW3 trial led to a *post hoc* analysis that showed equivocal results

with an association between biopsy and local relapse on univariate analysis (UVA) that lost statistical significance on multivariable analyses after adjustment for other known risk factors for recurrence [6]. Interpretation was made more difficult by the small number of events and the fact that the biopsy group contained an excess of larger and more advanced stage tumours in older patients [6].

The SIOP WT 2001 trial data set provides a unique opportunity to analyse the potential association of biopsy as a risk factor for local recurrence or adverse survival outcome in a cohort of patients treated uniformly with a preoperative chemotherapy approach, taking into account multivariable analysis (MVA) of the confounding factors that influence prognosis. We, therefore, conducted a retrospective *post hoc* analysis of the SIOP WT 2001 trial database, using the same patient inclusion/exclusion criteria that had been applied to the UKW3 trial data set, to test the hypothesis that biopsy may be an independent risk factor for local recurrence.

## 2. Methods

### 2.1. Eligible patients

Between 2001 and 2011, 3313 patients were registered in the SIOP WT 2001 trial with localised or metastatic unilateral WT (Supplemental Fig. 1). Thirty patients were excluded because of missing information on whether and how biopsy was performed. As the main

outcome was risk factors for local recurrence, patients whose tumours were not treated by the standard approach of total unilateral nephrectomy after preoperative chemotherapy (n = 312, including 133 who had nephron-sparing surgery and one case of extrarenal tumour) were excluded. Metachronous relapse was not considered as recurrence as it is likely to represent a new primary tumour because of genetic predisposition. The final study population consisted of 2971 patients.

The SIOP WT 2001 trial was approved through relevant national ethical and regulatory processes in each country. All participants or their parents provided informed consent that included use of their clinical data for research.

## 2.2. Definition of biopsy

Patients were categorised with respect to the ‘biopsy’ variable recorded on the relevant case report form (CRF). The registration options were ‘no biopsy’, FNA, PCNB or open (surgical) biopsy.

## 2.3. Definition of tumour rupture

This was taken from the CRFs where the presence of any rupture could be reported, regardless of its timing as preoperatively or perioperatively.

## 2.4. Classification of relapse

The site of relapse was recorded on CRFs as either ‘primary site (tumour bed)’, ‘other abdominal site’, ‘lung’, ‘liver’, or ‘extra-abdominal site’. ‘Primary site’ and ‘other abdominal site’ were assumed to represent direct physical spread and were considered as ‘local relapse’, as in the UKW3 analysis [6]. Abdominal relapse that was confined to the liver was categorised as ‘distant’ relapse because of haematogenous spread and grouped together with relapse in the lung or other non-abdominal sites. ‘Combined’ relapse was defined as a combination of local and distant relapse within the same patient.

## 2.5. Analysis restricted to patients with low- and intermediate-risk stage I and II WT

The use of doxorubicin and radiotherapy may negate the adverse effect of biopsy. To mitigate this effect, we performed an analysis restricted to 797 patients with stage I and II, low- and intermediate-risk histology WT who received only vincristine and actinomycin D and no doxorubicin in both preoperative and postoperative chemotherapy and no radiotherapy. This cohort excluded any patients documented to have had open biopsy, positive lymph nodes and tumour capsule rupture and those who received radiotherapy to the flank or ‘high-risk’ postoperative chemotherapy regimens.

## 2.6. Statistical methodology

Time to an event was calculated from the date of diagnosis. Survival curves were made using the Kaplan–Meier technique. Cox proportional hazard regression analysis was used to investigate the association of potential prognostic factors with each of the four outcome variables (local relapse, distant relapse, any event and overall survival). The very first event was considered and was local relapse, distant relapse or a combination of both (any event). No death occurred without prior relapse. Overall survival was considered separately. Factors were tested for proportionality and linearity in case of continuous variables (age was categorised as 6 months to 1.99 years, 2 – 3.99 years and 4 and older). Results were expressed in terms of hazard ratio (HR), 95% confidence interval (CI) and p-value. All multivariable models are stratified by ‘national country’. For univariable and multivariable Cox proportional hazards models, missing values were imputed with either the median value (continuous covariate) or with the most common value (categorical covariate) in the following covariates: rupture at surgery yes/no (22% missing values), volume at diagnosis (13% missing values) and volume at surgery (10% missing values).

## 3. Results

### 3.1. Clinical characteristics

Among 2971 patients included in the analysis, 969 (33%) had a biopsy, 288 (29.7%) by FNA, 620 (64.0%) by PCNB and 61 (6.3%) by open surgery. Ninety-seven percent of UK patients had a biopsy compared to only 8% of German patients. All other participating countries had a global biopsy rate of around 20%–26% (Table 1). Only patients with open biopsy required treatment as stage III.

The ‘no biopsy’ and ‘biopsy’ groups exhibited some differences, with older patients, larger tumours at diagnosis and surgery and more patients with a higher abdominal tumour stage and/or metastases in the ‘biopsy’ group (Table 2). There were slightly more high-risk

Table 1  
Biopsy type by the national centre.

Group	No biopsy		FNA		PCNB		Open biopsy	
	No.	%	No.	%	No.	%	No.	%
Total	2002	<b>67</b>	288	<b>10</b>	620	<b>21</b>	61	<b>2</b>
Brazil	257	<b>79</b>	29	<b>9</b>	30	<b>8</b>	8	<b>3</b>
Germany	694	<b>92</b>	60	<b>8</b>	0	<b>0</b>	0	<b>0</b>
France	477	<b>79</b>	78	<b>13</b>	39	<b>6</b>	12	<b>2</b>
SIOP-NL	558	<b>74</b>	87	<b>12</b>	92	<b>12</b>	14	<b>2</b>
UK	16	<b>3</b>	34	<b>6</b>	459	<b>86</b>	27	<b>5</b>

FNA: fine needle aspirate.

<sup>a</sup> UK continued its established national practice from the UKW3 trial of recommending percutaneous cutting needle biopsy (PCNB) prior to chemotherapy in all patients.

Table 2  
Patient and tumour characteristics by biopsy group.

Biopsy	No	Yes	P values
Total	2002	969	
Sex			0.7
Male	933 (46.7%)	444 (45.9%)	
Female	1065 (53.3%)	524 (54.1%)	
Age			< 0.001
0.5–1.99	567 (28.3%)	192 (19.8%)	
2–3.99	718 (35.9%)	317 (32.7%)	
4–17.5	717 (35.8%)	460 (47.5%)	
Category			< 0.001
Localised	1752 (87.5%)	777 (80.2%)	
Metastatic	250 (12.5%)	192 (19.8%)	
Side			0.187
Right	953 (47.6%)	487 (50.3%)	
Left	1049 (52.4%)	482 (49.7%)	
Volume at diagnosis (ml) (Median & IQR)	410 (220–670)	570 (310–880)	< 0.001
Volume at surgery (ml) (Median & IQR)	140 (50–300)	180 (70–410)	< 0.001
Abdominal stage			< 0.001
I	1025 (53.6%)	374 (40.0%)	
II	455 (23.8%)	227 (24.3%)	
III	433 (22.6%)	334 (35.7%)	
Margin status			< 0.001
Negative	1782 (89.0%)	766 (79.1%)	
Positive	220 (11.0%)	203 (20.9%)	
Lymph node status			< 0.001
Negative	1793 (89.6%)	817 (84.3%)	
Positive	209 (10.4%)	152 (15.7%)	
Tumour rupture			0.004
No	1339 (91.1%)	739 (87.2%)	
Yes	131 (8.9%)	108 (12.8%)	
Histological risk group (panel review/local pathol.)			0.027
Low risk	111 (5.8%)	54 (5.9%)	
Intermediate risk	1558 (81.9%)	731 (78.3%)	
High risk	234 (12.3%)	149 (15.8%)	

IQR, interquartile range.

histology tumours in the ‘biopsy’ group (15.8% versus 12.3%) and features making a tumour stage III were also more frequent (Table 2). Preoperative chemotherapy consisted of three drugs in 25% of patients being biopsied compared to 14% of patients in the ‘no biopsy’ group. A greater proportion of patients in the biopsy group had postoperative chemotherapy with the four-drug regimen (20% versus 12%) (Supplemental Table 1).

### 3.2. Outcome

At a median follow-up of 6 years, 420 (14.1%) patients experienced a relapse, 86 (20%) local, 222 (53%) distant and 53 (13%) combined. In 59 patients, the relapse site was not further specified (Table 3, Figs. 1–2).

### 3.3. Local relapse risk factors

On univariable analysis of risk factors for local recurrence, the following were significantly associated with a higher risk: age >2 years, tumour volume at diagnosis

Table 3  
Relapses and deaths by biopsy group.

Type of relapse	No Biopsy (n = 2002)	Biopsy (n = 969)	Total (n = 2971)
Local relapse only	45 (2.2%)	41 (4.2%)	86 (2.9%)
Combined relapse	31 (1.5%)	22 (2.3%)	53 (1.8%)
<b>All local relapses</b>	<b>76 (3.8%)</b>	<b>63 (6.5%)</b>	<b>139 (4.7%)</b>
Distant relapse only	131 (6.5%)	91 (9.4%)	222 (7.5%)
Unknown site	49 (2.4%)	10 (1.0%)	59 (2.0%)
<b>Any relapse</b>	<b>256 (12.8%)</b>	<b>164 (16.9%)</b>	<b>420 (14.1%)</b>
Death	107 (5.3%)	97 (10.0%)	204 (6.9%)

and at surgery, histological risk group, abdominal tumour pathological stage III, positive lymph nodes (LNs), tumour rupture, biopsy (yes/no) and type of biopsy (PCNB and open only) (Table 4).

On MVA, only age >2 years (HR = 2.24), high-risk histology (HR = 2.32) and tumour volume at surgery (HR = 1.07 per 100 ml) remained significantly associated with an increased risk of local relapse. The HR for the association with biopsy had reduced in value and lost significance, from HR = 1.7; 95% CI: 1.21–2.37, p = 0.002 in UVA to HR = 1.4; 95% CI: 0.9–2.17, p = 0.13 in MVA (Table 4).

### 3.4. Distant relapse risk factors

On UVA, age >2 years, volume at diagnosis and at surgery, left side, high-risk tumour, metastatic status, stage III abdominal tumour, positive LN, positive margin status, biopsy and type of biopsy (PCNB and open only) were associated with an increased risk of distant recurrence (Supplemental Table 2), whereas on MVA, only age >2 years (HR = 2.01), high-risk histology (HR = 2.82), abdominal stage II and III (HR = 1.58 and HR = 1.52, respectively), initial metastases (HR = 2.5) and tumour volume at surgery

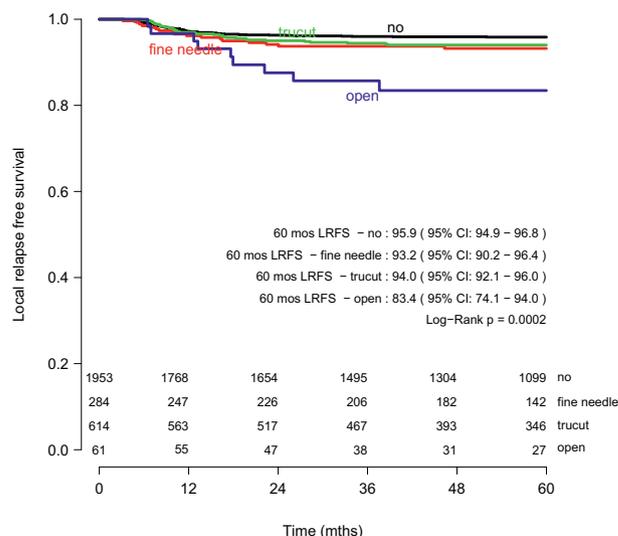


Fig. 1. Local relapse-free survival (LRFS) Kaplan-Meier curve.

(HR = 1.08 per 100 ml) remained significant (Supplemental Table 2).

### 3.5. OS and EFS of the whole cohort

The 5-year Overall survival/Event-free survival (OS/EFS) for patients having no biopsy versus those having a biopsy whether we include FNA or not in the ‘no biopsy’ group were very similar (Supplemental Table 3).

On UVA, both OS and EFS were significantly associated with age, tumour volume at diagnosis and at surgery, metastatic status, histological risk group, pathological abdominal stage, positive LN, tumour capsule rupture, positive margin status, biopsy and type of biopsy (PCNB and open) (Supplemental Table 4 + 5).

On MVA, the HR for association with biopsy lost significance for both EFS and OS (HR = 1.1 and HR = 1.13, respectively). OS remained associated with age >4 years (HR = 1.64), tumour volume at surgery (HR = 1.08/100 ml), metastatic status (HR = 3.4), high-risk histology (HR = 4.82), pathological abdominal stage III (HR = 2.32) and tumour rupture (HR = 1.52) (Supplemental Table 4), whereas for EFS, age >2 years (HR = 1.43), tumour volume at surgery (HR = 1.08 per 100 ml), metastatic status (HR = 1.91) and high-risk tumour (HR = 2.27) were still significant (Supplemental Table 5).

### 3.6. Analysis restricted to patients with no open biopsy

The study population of this subgroup was 2910 patients because 61 patients with open biopsies were excluded. There were no differences in clinical characteristics and in chemotherapy delivered preoperatively and postoperatively. No other risk factors appeared in the univariate and multivariate analyses for the four different outcome variables. The HR for biopsy was similar between the whole group and the subgroup with no open biopsy (Supplemental Table 6).

### 3.7. Analysis restricted to patients with low and intermediate risk stage I and II WT

If we restricted the analysis to 797 patients with low and intermediate risk histology, stage I and II WT who did not receive any doxorubicin or radiotherapy, no patient had an open biopsy, 73 (9.1%) had FNA and 180 (22.6%) had PCNB. Patients having a biopsy (n = 253) were significantly older (39.6 months versus 30.2 months in the ‘no’ biopsy group,  $p < 0.001$ ) with a larger median tumour volume at diagnosis (470 ml versus 350 ml,  $p < 0.001$ ) and after preoperative chemotherapy (190 ml versus 140 ml,  $p < 0.018$ ). Biopsy was the only significant risk factor associated with local relapse-free survival (HR = 2.65; 95% CI: 1.28–5.45;  $p = 0.01$ ) in UVA and remained positive in MVA (HR = 2.67; 95% CI: 1.07–6.67,  $p = 0.04$ ). However, if we included age

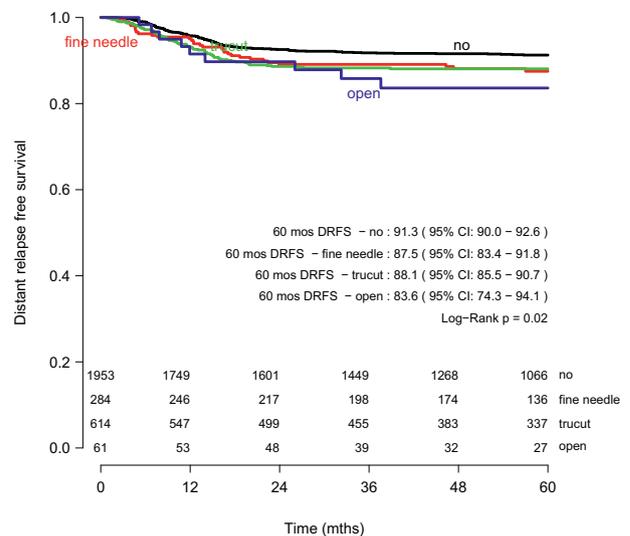


Fig. 2. Distant relapse-free survival (DRFS) Kaplan-Meier curve.

as a cofactor in the MVA, because it had met the criteria to be included in all other MVA, the HR for biopsy reduced and lost statistical significance (HR = 2.4; 95% CI: 0.95–6.05,  $p = 0.06$ ) (Table 5).

## 4. Discussion

This *post hoc* analysis of all patients with unilateral WT treated with preoperative chemotherapy in the SIOP WT 2001 trial showed that while there was a significant association of biopsy with local recurrence in UVA, this lost significance in MVA. The latter took account of other known factors (high-risk histology, higher tumour stage and volume and older age at diagnosis) associated with adverse outcome that were overrepresented in the biopsied population. This finding is similar to that of the *post hoc* analysis of the UKW3 trial but provides greater power because of the larger number of patients analysed [6].

Although biopsy was performed routinely in the UK, in the other participating countries, biopsy was recommended only when there was unusual clinical or radiological presentation. Therefore, as patients were not randomised to have a biopsy or not, the two groups were not comparable in their age, tumour size and metastatic status at diagnosis. Open biopsy appeared to be associated with a higher risk of recurrence but was only performed in a very small number of patients. The results for needle biopsy were similar for FNA and PCNB. From these results, we recommend that open biopsy should be avoided and needle biopsy reserved for cases of diagnostic uncertainty when histological confirmation is desired prior to initiating chemotherapy.

The increased risk associated with high-risk histology was substantial. This is consistent with many previous reports describing unfavourable (anaplastic) or high-risk histology (anaplastic and blastemal-type WT) as one of the strongest predictors of poor outcome in WT [7–13].

Table 4

Univariate and multivariable analysis of risk factors of recurrence for any local relapse.

Risk factor		No. with local relapse	Univariate analysis			Multivariable analysis		
			HR	95% CI	p-value	HR	95% CI	p-value
Biopsy	No	76	1		0.002	1		0.13
	Yes	63	1.70	1.21–2.37		1.40	0.9–2.17	
Age (years)	0.5–1.99	14	1		<0.001	1		
	2–3.99	46	2.37	1.30–4.32		2.24	1.22–4.09	0.01
	4–17.5	79	3.60	2.04–6.36		2.78	1.55–4.99	0.001
Risk	Low + intermediate	100	1		<0.0001	1		
	High	39	2.83	1.95–4.1		2.32	1.58–3.42	<0.0001
Volume at surgery (per 100 ml)		139	1.11	1.07–1.16	<0.0001	1.07	1.02–1.12	0.01
Volume at diagnosis (per 100 ml)		139	1.09	1.06–1.13	<0.0001			
Lymph node status	Negative	114	1		0.03			
	Positive	25	1.60	1.03–2.46				
Tumour Rupture <sup>a</sup>	No	119	1		0.004			
	Yes	20	1.96	1.22–3.15				
Abdominal stage	I	59	1		0.06			
	II	32	1.14	0.74–1.76				
	III	48	1.57	1.07–2.30				
Site	Right	67	1		0.94			
	Left	72	1.01	0.72–1.41				
Margin status	Negative	117	1		0.62			
	Positive	22	1.12	0.71–1.76				
Gender	Male	61	1		0.57			
	Female	78	1.10	0.78–1.54				
Category	Localised	114	1		0.25			
	Metastatic	25	1.28	0.83–1.98				
Biopsy done	No	76	1		0.0002			
	Fine needle	17	1.61	0.95–2.74				
	Trucut	37	1.52	1.03–2.26				
	Open	9	3.92	1.96–7.83				

HR, hazard ratio; CI, confidence interval.

<sup>a</sup> In a sensitivity analysis in which the value of ‘yes’ rather than ‘no’ was imputed for the patients with missing data for ‘rupture at surgery’, the hazard ratio and p value for any association of local recurrence with biopsy were 1.175 and 0.37, respectively, adding further weight to the lack of significant association of this parameter in the multivariable analysis.

Abdominal stage III was associated with an over 1.5-fold increased risk of local recurrence, but in MVA, only overall survival was negatively impacted. Abdominal stage III, whatever the reason to be stage III and despite slightly different definitions of stage III between SIOP and COG, has been reported to carry a higher risk of relapse: 27% of COG and 19.6% of the German Society of Pediatric Oncology group stage III patients experienced a relapse [14,15]. The Italian group provided further evidence that stage III tumours due to LN metastases had a worse outcome than stage III tumours with tumour rupture and positive margins [16]. Abdominal stage III was also an independent risk factor for adverse outcome in patients with blastemal-type WT included in the SIOP WT 2001 trial, along with age at diagnosis and tumour volume at surgery [17].

Larger tumour volume at diagnosis and after preoperative chemotherapy was a significant adverse factor for all outcomes but only volume after chemotherapy was significant in MVA. Tumour size was unequally distributed between both groups, a clinically expected finding also seen in the UKW3 study, where the median tumour diameter was 12.3 cm in the biopsy group compared to 10.7 cm in the no-biopsy group [6].

Older age at diagnosis was an independent adverse factor for any relapse and EFS (age threshold > 2 years) and death (age threshold > 4 years). This is in contrast to the NWTS-4 study, where older age at diagnosis was a prognostic factor (HR = 2.6) in UVA but failed to achieve significance when adjusted for histology and LN involvement [7]. Similarly in the SIOP 93-01/GPOH study, while median age at first diagnosis for patients experiencing a relapse was significantly older than for patients in complete continuous remission (4.5 versus 3.1 years), age lost significance in MVA [8]. However, in the UKW2 and 3 trials, age older than 4 was also considered as an adverse prognostic factor in stage I favourable histology WT treated with vincristine only [18].

When we restricted the analysis to patients with stage I and II, low- and intermediate-risk histology tumours who receive no doxorubicin, the small number of local recurrences meant that the statistical power to interpret such a *post hoc* analysis is weak. However, in this subgroup, where chemotherapy is minimal in intensity (only vincristine and actinomycin D preoperatively and postoperatively) and duration (4 weeks preoperatively and 4 weeks (stage I) or 27 weeks (stage II) postoperatively), it is possible that any potential association of biopsy with

Table 5

Univariate and multivariable analysis of risk factors for local recurrence restricted to patients with intermediate-risk stage I and II WT who received no doxorubicin and no radiotherapy (n = 797)<sup>a</sup>.

Risk factor		No. with local relapse	Univariate analysis			Multivariable analysis		
			HR	95% CI	p-value	HR	95% CI	p-value
Biopsy	No	13	1		0.01	1		0.06
	Yes	17	2.65	1.28–5.45		2.40	0.95–6.05	
Age (years)	0.5–1.99	6	1		0.12	1		
	2–3.99	11	1.81	0.67–4.90		1.80	0.67–4.88	0.25
	4–17.5	13	2.68	1.02–7.05		2.31	0.87–6.14	0.09
Biopsy done	No	13	1		0.05			
	Fine needle	4	2.29	0.74–7.03				
	Trucut	13	2.78	1.29–6.00				
Volume at surgery	(per 100 ml)	30	1.004	0.88–1.14	0.96			
Volume at diagnosis	(per 100 ml)	30	1.06	0.97–1.17	0.16			
Abdominal stage	I	22	1		0.29			
	II	8	1.54	0.68–3.74				
Site	Right	14	1		0.82			
	Left	16	1.08	0.53–2.23				
Gender	Male	12	1		0.32			
	Female	18	1.44	0.69–3.00				

HR, hazard ratio; CI, confidence interval.

<sup>a</sup> This cohort excluded any patients documented to have had open biopsy, positive lymph nodes and tumour capsule rupture and those who received radiotherapy to the flank or 'high-risk' postoperative chemotherapy regimens.

recurrence is stronger. Age appeared as a confounding factor for the statistical significance of biopsy in this setting, but as it was a major risk factor of survival in the other survival analyses, we included it in the MVA even though it did not reach significance in the UVA.

Limitations of the study include lack of information on potential molecular biomarkers and missing data, especially for the site of relapse, tumour rupture, tumour volume at diagnosis and preoperatively. The latter was taken into account in the statistical analysis to input the missing data with either the median value for continuous covariate or with the most common value for the categorical covariate.

Hence, while caution is needed in interpreting our findings for clinical use, we conclude that needle biopsy (FNA or PCNB) does not clearly increase the risk of local relapse of Wilms tumour in the setting of preoperative chemotherapy. We suggest that needle biopsy can be ignored for tumour staging purposes, providing it is performed according to modern standards, under image guidance with coaxial technique. Taking account of the level of evidence of our analysis, we further recommend that needle biopsy be reserved for children whose clinical presentation or imaging are atypical for WT and where histological confirmation is desired before starting any chemotherapy [19]. The current criteria recommended by the SIOP–RTSG for when biopsy should be considered are older age at diagnosis (10 years and older); presence of lung metastases in a child aged younger than 2 years; metastases in sites other than the lung or liver; urinary infection; high serum calcium or LDH levels and on imaging: psoas inflammation; presence of calcification; voluminous lymphadenopathy; no visible renal parenchyma or where the tumour appears to be almost totally

extrarenal. The restriction of biopsy to these criteria will decrease the number of indications for biopsy that should be performed with FNA or PCNB. Implementation of our suggestions should be based on national and international study group consensus, treatment approach and prospective monitoring of outcomes.

#### Conflict of interest statement

None declared.

#### Acknowledgements

The SIOP WT 2001 study was funded by Cancer Research UK (grant C1188/A8687), the UK National Cancer Research Network and Children's Cancer and Leukaemia Group (CCLG) (who supported the UK section), Société Française des Cancers de l'Enfant and Association Leon Berard Enfant Cancéreux and Enfant et Santé (who supported the French section), Gesellschaft für Pädiatrische Onkologie und Hämatologie and Deutsche Krebschilfe (grant 50-2709-Gr2, who supported the German section), Grupo Cooperativo Brasileiro para o Tratamento do Tumour de Wilms and Sociedade Brasileira de Oncologia Pediátrica (who supported the Brazilian section), the Spanish Society of Paediatric Haematology and Oncology and the Spanish Association Against Cancer (who supported the Spanish section) and the International Society of Pediatric Oncology coordinating centre in the Netherlands (SIOP-NL). K.P.-J. is partly supported by the National Institute for Health Research Biomedical Research Centre Funding Scheme. The authors acknowledge the

enormous efforts made by more than 1000 clinicians working at the 251 childhood cancer treatment centers in this study from 26 countries who enrolled and followed up patients in this study and the patients and their families for their participation.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2019.04.027>.

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