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RESEARCH ARTICLE

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How to improve initial diagnostic accuracy of kidney tumours in childhood?—A non-invasive approach

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Abstract

Non-invasive differentiation of paediatric kidney tumours is particularly important in the SIOP-RTSG protocols, which recommend pre-operative chemotherapy without histological confirmation. The identification of clinical and tumour-related parameters may enhance diagnostic accuracy. Age, metastases, and tumour volume (TV) were retrospectively analysed in 3306 patients enrolled in SIOP/GPOH 9, 93-01, and 2001 including Wilms tumour (WT), congenital mesoblastic nephroma (CMN), clear cell sarcoma (CCSK), malignant rhabdoid tumour of the kidney (MRTK), and renal cell carcinoma (RCC). WT was diagnosed in 2927 (88.5%) patients followed by CMN 138 (4.2%), CCSK 126 (3.8%), MRTK 58 (1.8%) and RCC 57 (1.7%). CMN, the most common localized tumour (71.6%) in patients younger than 3 months of age, was

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diagnosed earliest and RCC the latest (median age [months]: 0 and 154, respectively) both associated with significantly smaller TV (median TV [mL]: 67.2 and 45.0, respectively). RCC occurred in >14% of patients older than 120 months or older than 84 months with TV <100 mL. Receiver operating characteristic analyses discriminated WT from CMN, RCC and MRTK regarding age (AUC = 0.976, 0.929 and 0.791) and TV (AUC = 0.768, 0.813 and 0.622). MRTK had the highest risk of metastasis (37.9%) despite young age, whereas the risk of metastasis increased significantly with age in WT. Age and TV at diagnosis can differentiate WT from CMN and RCC. MRTK must be considered for metastatic tumours at young age. Identification of CCSK without histology remains challenging. Combined with MRI-characteristics, including diffusion-weighted imaging, and radiomics and liquid biopsies in the future, our approach allows optimization of biopsy recommendations and prevention of misdiagnosis-based neoadjuvant treatment.

KEYWORDS
biopsy, kidney neoplasms in childhood, neoadjuvant therapy, radiology, Wilms tumour

What's new?

Non-invasive differentiation of paediatric kidney tumours is a key aspect in the SIOP-RTSG protocols, which recommend preoperative chemotherapy without histological confirmation. This retrospective study shows that age and tumour volume at diagnosis are reliable parameters to help distinguish between Wilms tumour, congenital mesoblastic nephroma, renal cell carcinoma, and malignant rhabdoid tumour of the kidney. Consideration of these parameters allows for a higher proportion of patients treated correctly with preoperative chemotherapy, while reducing the biopsy rate to <15%. Combined with magnetic resonance imaging, radiomics, and liquid biopsies, the approach may further enhance the non-invasive discrimination of paediatric kidney tumours.

1 | INTRODUCTION

Wilms tumour (WT) is the most common malignant paediatric kidney tumour, accounting for over 90% of all kidney tumours in children.[1] However, other rare benign and malignant non-Wilms tumours (non-WT) occur in 10% of cases.[1] Unlike the Children's Oncology Group (COG), who advocates upfront-surgery in localized kidney tumour patients, the International Society of Paediatric Oncology Renal Tumour Study Group (SIOP-RTSG) protocols start in kidney tumour patients >6 months and <16 years, with pre-operative chemotherapy to downstage the tumour and to reduce the risk of rupture. Post-operative treatment is based on risk-stratification of histology and tumour stage after response to pre-operative chemotherapy.[2–4] Fine-needle or tru-cut biopsies are reserved for patients with unusual clinical presentation or atypical imaging findings.[3] Therefore, exact non-invasive diagnosis is essential and accurate initial imaging studies are required,[3,5] including abdominal ultrasound (US), cross sectional magnetic resonance imaging (MRI) with and without contrast enhancement and computed tomography (CT) of the lungs, to detect atypical features that should prompt biopsy and to determine overall tumour stage.[2,6] MRI plays a key role for the detection of a kidney mass, of venous invasion and synchronous contralateral kidney lesions.[7,8] WT presents as a large mostly solid and heterogeneous tumour of the kidney often with intra-tumoural bleeding and is characterized by a high signal intensity on T2- and intermediate signal intensity on T1-weighted images. The tumour can be delineated from the kidney parenchyma by a typical pseudo-capsule best seen on MRI images.[9] Recently, within the SIOP-RTSG radiology panel, efforts have been made to identify characteristic MRI features also for non-WT, and some important results have been obtained.[8,10,11]

However, as specific radiological criteria for non-WTs are still lacking, the question remains if age, tumour volume (TV), bilaterality, and metastasis at diagnosis may predict a correct histological diagnosis.[5] Hence, we performed a retrospective analysis of patients with WT, congenital mesoblastic nephroma (CMN), clear cell sarcoma (CCSK), malignant rhabdoid tumour (MRTK), and renal cell carcinoma (RCC), aiming to identify clinical and tumour-related parameters to discriminate between the different entities at the time of diagnosis.

2 | PATIENTS AND METHODS

2.1 | Study population, design

This retrospective analysis included 3306 (100%) patients with paediatric kidney tumours from Germany, Austria and Switzerland treated

according to the SIOP/GPOH 9, 93-01 and 2001 studies between 1989 and 2017. We focused on the five most common malignant paediatric kidney tumours, including 2927 WT and 379 non-WT patients (RCC, CCSK, MRTK and CMN). MRI was the diagnostic base and contrast-enhanced-MRI was mandatory in the diagnostic MRI protocol in this study. Patients were divided into those with unilateral and bilateral, and with localized and metastatic tumours. Patients with a known cancer predisposition syndrome (CPS) were only included in the analysis of clinical data.

2.2 | Statistical analysis

For statistical analysis the whole dataset was pseudonymized. IBM SPSS Statistics, version 27, was used for descriptive analyses (histograms, boxplots, frequency charts and bar charts) and statistical comparisons (*T*-test for independent samples, Levene test, chi-square test, linear- and logistic regression, Mann–Whitney-*U*-test, Spearman correlation for non-normally distributed variables and receiver operating characteristic [ROC] curves with the Youden-Index). The area under the curve (AUC) values were classified regarding their prediction value for discrimination according to the following generally accepted approach: AUC <0.60 poor, AUC 0.60–0.75 possibly helpful, AUC ≥0.75 clearly helpful, and AUC values ≥0.9 outstanding discrimination.[12] Two-sided *p*-values of .05 or below were considered statistically significant. TV was measured in coronal and transversal MRI using the ellipsoid formula ($TV = L_{ength} \times H_{igh} \times D_{epth} \times 0.523$). In 808 (24.4%) patients, CT scans were used for tumour measurement instead of MRI, especially for patients registered on SIOP 9 and 93/01.

3 | RESULTS

WT accounted for 88.5% of patients, followed by CMN (4.2%), CCSK (3.8%), MRTK (1.8%) and RCC (1.7%). Patients with CMN and MRTK were significantly younger and patients with RCC significantly older at diagnosis than WT patients. CMN, MRTK and RCC were associated with significantly smaller TV at diagnosis (Figure 1, Table 1).

Metastases at diagnosis were most common in patients with MRTK (37.9%) and occurred with decreasing frequency in patients with WT (18.1%), RCC (15.8%), and CCSK (12.7%). In metastatic patients, MRTK was diagnosed earlier and RCC later than WT (Figure 1, Table 1). In contrast to metastatic WT and CCSK, metastatic RCC patients were younger at diagnosis than patients with localized disease (Table 1). None of the patients with CMN had metastasis at diagnosis.

Of 254 (7.7%) patients with bilateral tumours only one patient had CCSK (Table 1). Patients with unilateral CCSK were significantly younger at diagnosis than patients with unilateral WT (median age: 33 vs. 38 months, respectively; Figure 1, Table 1). Both were associated with significant larger TV compared to the other entities (Figure 1, Supplemental Figure 1). A CPS or congenital malformation was more often known at diagnosis in WT compared to the total group of non-WT (Table 1).

3.1 | Localized unilateral kidney tumours

Of 1935 patients with localized unilateral kidney tumours 87.3% had WT, 4.9% CMN, and 4.9% CCSK (Table 2). RCC (1.6%) and MRTK (1.3%) were less common. Above 1 month of age only WT and CCSK occurred in all age groups. CMN was diagnosed earliest and in 20 patients prior to birth (Supplemental Table 2), followed by MRTK, CCSK, WT, and RCC (Tables 2 and 1).

CCSK patients presented with the largest TV, followed by WT, MRTK, CMN, and RCC having the smallest TV. Only 7.4% of CCSK patients had TV <100 mL, of whom five were younger than 36 months. TV >1000 mL occurred only in WT and CCSK (Table 2).

3.1.1 | Age group <36 months

Half of all tumours were diagnosed within the first 36 months of life. WT was present in 82.6%, followed by CMN (9.6%), CCSK (5.7%), and MRTK (2.1%). No RCC was diagnosed in this age group. Up to the age of 1 month, only CMN and WT were present and up to 3 months, CMN was the most common tumour (Supplemental Table 2, Supplemental Figure 2). Both tumours showed no significant differences in TV at this very young age. Above 6 months, CMN was present in only 1.6% and none was older than 36 months. Between 6 and 36 months CCSK occurred second most frequently (6.6%) and presented with the largest TV (354 mL) with 12.1% of patients with TV over 1000 mL having CCSK. These patients were diagnosed in more than 70% between 12 and 36 months (Supplemental Table 2). MRTK patients younger than 36 months were associated with significantly smaller TV compared to WT and only 2/21 with more than 500 mL (Table 2).

3.1.2 | Age group 36–84 months and 84–120 months

WT was present in approximately 94% of patients diagnosed between 36–84 and 84–120 months. Accordingly, non-WT were rare in these age groups. MRTK and RCC were present in less than 1% of cases. However, compared to WT, RCC occurred significantly more frequently in small tumours <100 mL in the 84–120 months age group than in<84 months ($p < .001$). MRTK did not occur in patients older than 84 months (Table 2).

3.1.3 | Age group >120 months

In this age group, RCC (23.6%) was the second most common tumour and occurred in a significantly higher proportion compared to earlier age ranges. CCSK was rare (3.8%) and RCC showed significant smaller TV at diagnosis than WT (Figure 1, Table 2).

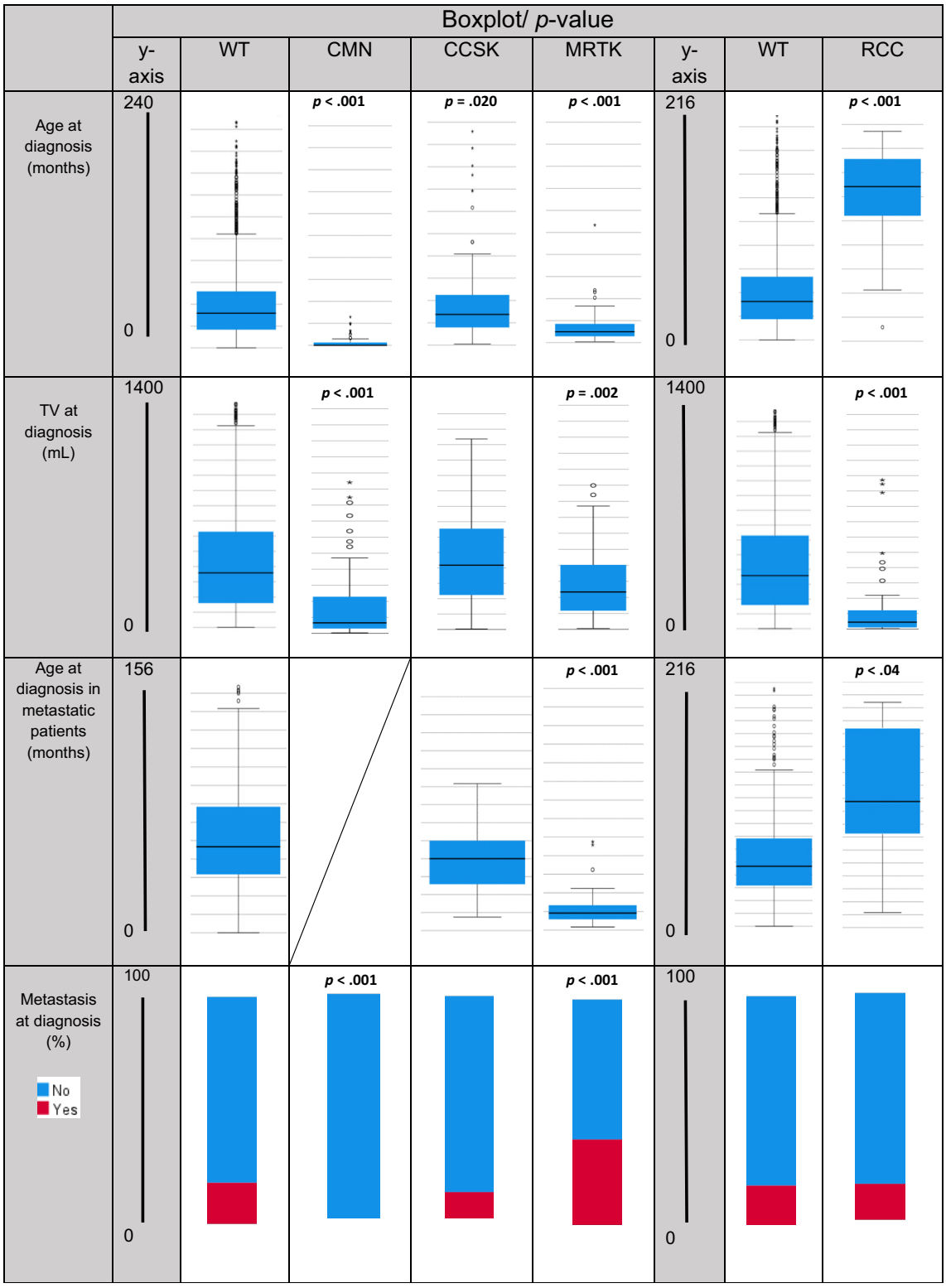


FIGURE 1 Comparative analysis of relevant clinical and tumour related parameters; $N = 3052$ patients with unilateral paediatric kidney tumours, statistical tests: Mann–Whitney-*U*, chi^2-test.

3.2 | Metastatic unilateral kidney tumours

The distribution of histologies among the 431 patients who presented with metastatic disease at diagnosis was WT 395 (91.6%), MRTK 17 (4.0%), CCSK 15 (3.5%), and RCC 4 (1.0%). Metastatic WT was larger, and patients were older than localized WT, whereas metastatic RCC had smaller TV and patients were younger than localized RCC. In contrast such correlations were not

TABLE 1 Characteristic of the five most common paediatric kidney tumours.

	Frequency *N* (%)	Age at diagnosis (months) Median [CI] (mean)	TV at diagnosis (mL) Median [CI] (mean)	Metastasis at diagnosis *N* (%)	Age at diagnosis of metastasis Median [CI] (mean)	CPS *N* (%)	Bilaterality *N* (%)
WT	2927 (88.5)	38.0 [47.3; 51.1]	361.1 [434.5; 464.7]	529 (18.1)	54.5 [63.3; 73.1]	171 (5.8)	253 (8.6)
CMN	138 (4.2)	0.0[a] [1.5; 3.2]	67.2 [122.9; 193.8]	0 (0.0)	n.a.	3 (2.2)	0 (0.0)
CCSK	126 (3.8)	33.0 [36.5; 51.7]	418.0 [422.1; 582.3]	16 (12.7)	48.0 [33.2; 72.5]	3 (2.4)	1 (0.8)
MRTK	58 (1.8)	12.0 [12.6; 23.6]	234.0 [220.1; 344.1]	22 (37.9)	11.0 [9.4; 23.6]	1 (1.7)	0 (0.0)
RCC	57 (1.7)	154.0 [133.5; 159.4]	44.6 [68.6; 201.1]	9 (15.8)	117.0 [45.6; 197.4]	1 (1.8)	0 (0.0)
All	3306 (100)	36.0 [46.2; 49.8]	345.0 [418.2; 446.4]	577 (17.4)	54.0 [61.6; 71.0]	179 (5.4)	254 (7.7)

Note: $N = 3306$ patients with paediatric kidney tumours.
Abbreviation: CPS, congenital predisposition syndrome.
[a]Prenatal diagnosis in 20 patients.

seen in MRTK and CCSK. (Supplemental Table 1, Supplemental Figure 1).

3.2.1 | Patients <18 and 18–36 months

MRTK was the most common metastatic tumour in patients younger than 18 months (48.0%), followed by WT (44.0%), CCSK, and RCC (14.0% each) (Table 3, Supplemental Figure 2). More than 80% of MRTK patients had TV <500 mL at diagnosis (Table 3). At 18–36 months WT was present in 91.0% of patients. Despite the high proportion of WT in this age group, CCSK must be considered in TV between 500 and 1000 mL, and over 1000 mL, where it occurred in 7.7% and 15.4%, respectively (Table 3).

3.2.2 | Patients >36 months at diagnosis

WT was associated with the largest TV gradually increasing with age followed by CCSK, MRTK, and RCC (Supplemental Table 1, Supplemental Table 3). In contrast to metastatic RCC in whom three out of four patients had TV <100 mL, no metastatic CCSK patient was diagnosed with TV <100 mL. No metastatic MRTK patient was older than 84 months and only one RCC patient younger than 84 months (Table 3).

3.3 | ROC for age and TV

The separate ROC analysis for age and TV at diagnosis yielded outstanding AUC values for discrimination between WT and CMN or RCC by age and clearly helpful values for discrimination by TV with cut-off values for age and TV of 8.5 months and 123.5 mL (WT vs. CMN) or 86.5 months and 128.5 mL (WT vs. RCC) (Figure 2). In binary logistic regression these results were confirmed as highly statistically significant (Supplemental Table 4). WT and MRTK could be differentiated from each other by age but not by TV (AUC value <0.7, Figure 2). No discrimination was possible for WT and CCSK (AUC values <0.7, Supplemental Table 3). Combining the age and volume in a multiple logistic regression for WT versus CMN, RCC, and MRTK, the subsequent ROC analyses, based on the predicted probabilities determined in the regression analyses, yielded higher AUC values of >0.9 for WT versus CMN or RCC and >0.8 for WT versus MRTK, compared with the ROC analysis of the volume parameter alone and, for WT versus MRTK, even for the age parameter alone (Figure 2).

4 | DISCUSSION

In this retrospective study, we aimed to identify in addition to imaging, clinical and tumour-related parameters that may increase the accuracy of initial diagnosis of paediatric kidney tumours. Such non-invasive attempts have been described already.[8] However, to the best of our knowledge, this is the first and largest cohort to systematically classify paediatric kidney tumours by age, TV, metastasis and bilaterality at diagnosis.

4.1 | Incidence, bilaterality and metastasis

Our results of 11.5% non-WT (Table 1) confirm those from the Surveillance, Epidemiology, and End Results Program (SEER) in the United States, where non-WT occurred in 12.2%.[13] But comparing the SEER data with data from the Nationwide Registry for Childhood Haematological Malignancies and Solid Tumors (NARCHEM-ST) in Greece, Doganis found more non-WT (22.6% of paediatric kidney tumours) attributed to different registration and coding practices and healthcare systems.[13] Frequencies of 3.5%, 2%–5%, 2%–4%, and 1.5% for CMN, CCSK, RCC, and MRTK respectively[5,14–16] are similar with those in our study.

Bilateral paediatric kidney tumours are highly suspicious for WT. Of a total of 254 patients in our series with bilateral tumours, 253 were WT and only one patient had CCSK. In the literature, bilateral CCSK has been reported in only three cases with widely

TABLE 2 Classification regarding age and at TV diagnosis for unilateral, localized, non-CPS associated paediatric kidney tumours, n.a. not applicable, grey if frequency <5%.

Age [months]	TV at diagnosis [mL]	CMN		WT		CCSK		MRTK		RCC		Total	
		N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
<36	<100	53	25.2	144	68.6	5	2.4	8	3.8	0	0.0	210	100
	100–499	35	6.5	457	85.3	33	6.2	11	2.1	0	0.0	536	100
	500–999	7	3.3	189	89.2	14	6.6	2	0.9	0	0.0	212	100
	≥1000	0	0.0	29	87.9	4	12.1	0	0.0	0	0.0	33	100
	All volumes	95	9.6	819	82.6	56	5.7	21	2.1	0	0.0	991	100
	Median	70.0		313.0		354.0		140.0		n.a.		290.0	
	95% CI (mean)	[131.7; 215.9]		[348.7; 391.2]		[336.1; 547.8]		[125.4; 319.6]		n.a.		[332.7; 371.5]	
36–84	<100 mL	0	0.0	96	98.0	1	1.0	0	0.0	1	1.0	98	100
	100–499	0	0.0	320	93.0	18	5.2	5	1.5	1	0.3	344	100
	500–999	0	0.0	197	96.6	7	3.4	0	0.0	0	0.0	204	100
	≥1000	0	0.0	60	93.8	4	6.3	0	0.0	0	0.0	64	100
	All volumes	0	0.0	673	94.8	30	4.2	5	0.7	2	0.3	710	100
	Median	n.a.		377.0		417.5		226.0		223.7		379.5	
	95% CI (mean)	n.a		[437.9; 494.3]		[382.6; 794.6]		[109.9; 467.7]		[−2461.8; 2909.1]		[441.2; 497.5]	
84–120	<100	0	0.0	18	85.7	0	0.0	0	0.0	3	14.3	21	100
	100–499	0	0.0	49	96.0	1	2.0	0	0.0	1	2.0	51	100
	500–999	0	0.0	39	95.1	2	4.9	0	0.0	0	0.0	41	100
	≥1000	0	0.0	14	93.3	1	6.6	0	0.0	0	0.0	15	100
	All volumes	0	0.0	120	93.8	4	3.1	0	0.0	4	3.1	128	100
	Median	n.a.		411.5		649.5		n.a.		42.3		376.5	
	95% CI (mean)	n.a		[424.6; 567.0]		[2.4; 1257.6]		n.a.		[−12.4; 113.9]		[417.0; 555.1]	
>120	<100	0	0.0	18	51.4	1	2.9	0	0.0	16	45.7	35	100
	100–499	0	0.0	28	80.0	1	2.9	0	0.0	6	17.1	35	100
	500–999	0	0.0	15	83.3	0	0.0	0	0.0	3	16.7	18	100
	≥1000	0	0.0	16	88.9	2	11.1	0	0.0	0	0.0	18	100
	Total	0	0.0	77	72.6	4	3.8	0	0.0	25	23.6	106	100
	Median	n.a.		396.0		751.0		n.a.		75.9		271.0	
	95% CI (mean)	n.a.		[464.8; 742.1]		[−315.3; 1677.8]		n.a.		[65.2; 307.2]		[396.8; 619.2]	
All ages	All volumes	95	4.9	1689	87.3	94	4.9	26	1.3	31	1.6	1935	100
	Median	70.0		344.0		402.5		205.0		65.0		328.0	
	95% CI (mean)	[131.7; 215.9]		[410.4; 445.3]		[412.7; 601.2]		[154.0; 316.5]		[71.3; 271.1]		[369.1; 428.9]	

disseminated disease.[17] The high proportion of WT is consistent with a previous study in which bilateral tumours occurred only in WT and MRTK (92% and 8%, respectively) in patients aged less than 7 months at diagnosis.[18] Such rare cases of bilateral MRTK are also reported in other studies.[16,18] In addition, we could not confirm the risk of bilaterality of RCC as reported previously.[14,16,19]

As patients with bilateral tumours are at higher risk of an underlying cancer predisposition syndrome (CPS)[20] we found significantly more CPS (not including MRTK predisposition syndrome) in WT than in non-WT.

We confirm the highest risk of metastasis in MRTK (38% in our series), ranging from 22% to 50% despite their young age.[21] Particularly in young children with metastasis and TV <500 mL, MRTK must be considered. 15.8% of RCC patients presented with metastasis at diagnosis which is in accordance with previous studies that reported from 18% to 25%.[5,14] No CMN patient of our cohort had metastasis, confirming the very low metastatic risk of this tumour.[18] Nevertheless, CMN with distant metastases has been reported in rare cases, mainly in association with the cellular subtype.[22–24] Compared to previous studies, we found a higher risk of distant metastasis for CCSK (13% vs. 4%–7%).[15,17] The association of older age, larger TV and more advanced tumour stage in our series of WT was recently also reported in a large SEER cohort of 3463 patients[25] (Supplemental Table 3).

TABLE 3 Classification regarding age and at TV diagnosis for unilateral, metastatic, non-CPS associated paediatric kidney tumour; grey if frequency <5%.

Age [months]	TV at diagnosis [mL]	WT N	WT %	CCSK N	CCSK %	MRTK N	MRTK %	RCC N	RCC %	Total N	Total %
<18	<100	1	50.0	0	0.0	1	50.0	0	0.0	2	100
	100–500	5	33.3	0	0.0	9	60.0	1	6.7	15	100
	500–1000	4	57.1	1	14.3	2	28.6	0	0.0	7	100
	>1000	1	100	0	0.0	0	0.0	0	0.0	1	100
	Total	11	44.0	1	4.0	12	48.0	1	4.0	25	100
	Median [mL]	470		n.a.		291.5		n.a.		397.0	
	95% CI [mL]	[293.5; 692.3]		n.a.		[201.6; 454.4]		n.a.		[304.5; 521.0]	
18–36	<100	1	100	0	0.0	0	0.0	0	0.0	1	100
	100–500	35	92.1	1	2.6	2	5.3	0	0.0	38	100
	500–1000	24	92.3	2	7.7	0	0.0	0	0.0	26	100
	>1000	11	84.6	2	15.4	0	0.0	0	0.0	13	100
	Total	71	91.0	5	6.4	2	2.6	0	0.0	78	100
	Median [mL]	499.0		827.0		211		n.a.		499.5	
	95% CI [mL]	[596.1; 74.4]		[165.2, 1452.8]		[−335.4, 757.4]		n.a.		[539.2; 739.1]	
36–84	<100	8	100	0	0.0	0	0.0	0	0.0	8	100
	100–500	96	92.3	6	5.8	2	1.9	0	0.0	104	100
	500–1000	89	97.8	1	1.1	1	1.1	0	0.0	91	100
	>1000	35	100	0	0.0	0	0.0	0	0.0	35	100
	Total	228	95.8	7	2.9	3	1.3	0	0.0	238	100
	Median [mL]	535.0		423.0		403.0		n.a.		524.0	
	95% CI [mL]	[552.2; 662.2]		[283.6; 490.1]		[−386.1; 1230.7]		n.a.		[545.3; 651.5]	
84–120	<100	5	71.4	0	0.0	0	0.0	2	28.6	7	100
	100–500	14	100	0	0.0	0	0.0	0	0.0	14	100
	500–1000	21	95.5	1	4.5	0	0.0	0	0.0	22	100
	>1000	11	100	0	0.0	0	0.0	0	0.0	11	100
	Total	51	94.4	1	1.9	0	0.0	2	3.7	54	100
	Median [mL]	674.0		n.a.		n.a.		7.7		672.5	
	95% CI [mL]	[575.1; 819.4]		n.a.		n.a.		[−9.09; 24.5]		[551.8; 793.1]	
>120	< 100	0	0.0	0	0.0	0	0.0	1	100	1	100
	100–500	4	80.0	1	20.0	0	0.0	0	0.0	5	100
	500–1000	9	100	0	0.0	0	0.0	0	0.0	9	100
	>1000	21	100	0	0.0	0	0.0	0	0.0	21	100
	Total	34	94.4	1	2.8	0	0.0	1	2.8	36	100
	Median [mL]	1140.0		n.a.		n.a.		n.a.		1112.0	
	95% CI [mL]	[996.8; 1514.5]		n.a.		n.a.		n.a.		[935.7; 1453.2]	
All ages	All volumes	395	91.6	15	3.5	17	4.0	4	1.0	431	100
	Median [mL]	573.0		483.0		254.0		51.6		543.0	
	95% CI [mL]	[628.6; 725.9]		[362.9; 767.4]		[223.0; 438.8]		[−63.9; 214.1]		[608.1; 700.0]	

4.2 | Age, volume and ROC curves

Age at diagnosis showed the highest discriminatory potential, which is reflected in the AUC values of the ROC analysis, indicating that age is the best parameter to discriminate between entities. However, when the parameters TV and age at diagnosis are combined in the ROC analysis for WT versus CMN or RCC, AUC values are improved compared to the volume parameter but not to the age parameter alone. Especially, for MRTK, it is recommended to consider both parameters, as the AUC value for the combined ROC analysis was even higher than for the age parameter alone.

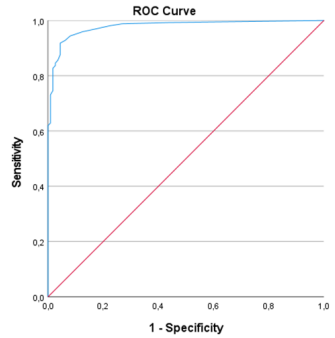
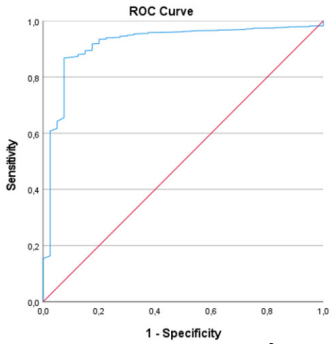
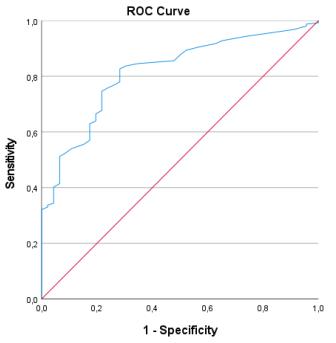
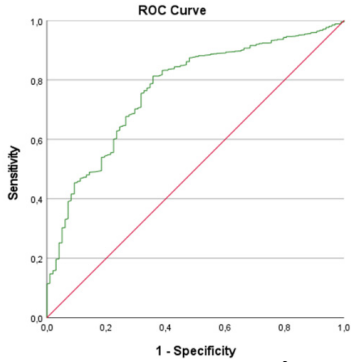
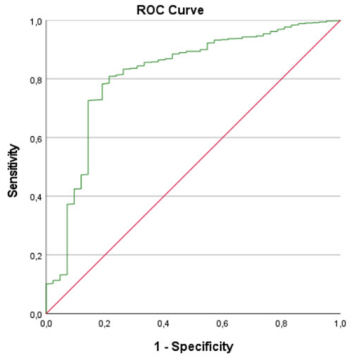
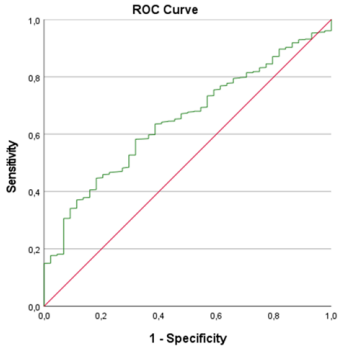
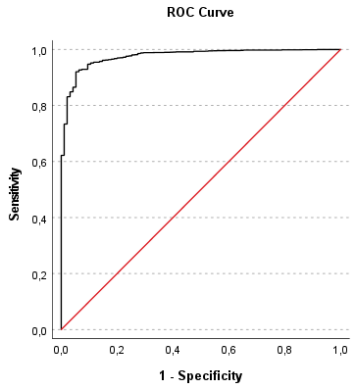
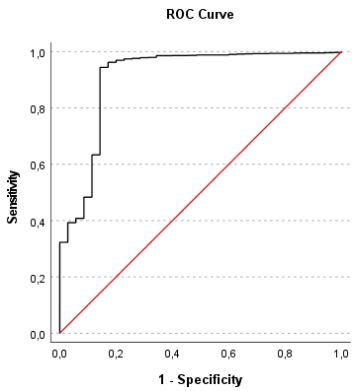
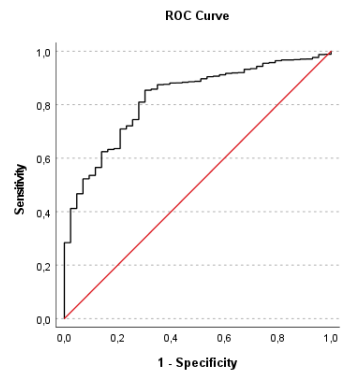
Age at diagnosis		
CMN (*N* = 112) vs. WT (*N* = 2223)	**RCC (*N* = 40) vs. WT (*N* = 2223)**	**MRTK (*N* = 46) vs. WT (*N* = 2223)**
		
AUC = 0.978; SE = 0.005; $p < 10^{-3}$; **Cut-off:** Age[months] = **8.5** ; **Youden-Index** = 0.873	**AUC = 0.918;** SE = 0.023; $p < 10^{-3}$; **Cut-off:** Age[months] = **86.5**; **Youden-Index** = 0.793	**AUC = 0.816;** SE = 0.027; $p < 10^{-3}$; **Cut-off:** Age[months] = **15.5, Youden-Index** = 0.544
TV at diagnosis		
CMN (*N* = 98) vs. WT (*N* = 2150)	**RCC (*N* = 42) vs. WT (*N* = 2150)**	**MRTK (*N* = 44) vs. WT (*N* = 2150)**
		
AUC = 0.767; SE = 0.023; $p < 10^{-3}$; **Cut-off:** TV[ml] = **123.5; Youden-Index** = 0.456	**AUC = 0.814;** SE = 0.037; $p < 10^{-3}$; **Cut-off:** TV[ml] = **128.5; Youden-Index** = 0.594	**AUC = 0.648**; SE = 0.035; p = .002; **Cut-off:** TV[ml] = **414.5; Youden-Index** = 0.265
Combination of age and TV at diagnosis in logistic regression		
CMN (*N* = 95) vs. WT (*N* = 2084)	**RCC (*N* = 35) vs. WT (*N* = 2084)**	**MRTK (*N* = 43) vs. WT (*N* = 2084)**
		
AUC = 0.976; SE = 0.006; $p < 10^{-3}$; **Cut-off:** Predicted Probability = **92.9%; Youden-Index** = 0.868	**AUC = 0.909**; SE = 0.033; $p < 10^{-3}$; **Cut-off:** Predicted Probability = **95·8%**; **Youden-Index** = 0.801	**AUC = 0.823**; SE = 0.027; $p < 10^{-3}$; **Cut-off:** Predicted Probability = **95.6%**; **Youden-Index** = 0.552

FIGURE 2 Receiver operating characteristic analyses for unilateral, non-syndromic WT versus CMN, RCC and MRTK regarding age- and TV at diagnosis.

Consistent with previous work, we identified CMN as the most common kidney tumour up to 3 months of age.[13] Thereafter the frequency decreases significantly as reported by others.[18] No other localized tumour than CMN and WT was diagnosed within the first 3 months of life (Supplemental Table 2). The significantly older age at diagnosis, the higher proportion of RCC diagnosed after 120 months of age, and the smaller TV at diagnosis compared to WT (Figure 1), are consistent with literature.[1,5,17,26]

Despite the significantly younger age at diagnosis of unilateral CCSK compared with unilateral WT in our series, the median ages (33 and 38 months, respectively) are close and CCSK cannot be reliably distinguished from WT based on age or TV.[13,15,17] This is confirmed in our ROC analysis. In addition, WT and CCSK are associated with significantly larger TV at diagnosis compared to all other entities.[27]

In accordance with the known young age of MRTK patients,[16] our ROC analysis can discriminate MRTK from WT for age but not for TV alone. Nevertheless, MRTK was associated with significantly smaller TV compared to WT in our cohort, especially in metastatic tumours.

4.3 | Biopsy recommendations

A recent review made biopsy recommendations for kidney tumours based on various factors such as imaging, age, TV, metastases, and biochemical features.[28] For the parameters examined here, we propose to discuss adjustments to biopsy recommendations based on the frequency profiles established for the respective subgroups. It is important to note that our results are from a retrospective analysis and therefore prospective validation using an independent data set is required. Our approach to biopsy recommendations is shown in Table 4. In a French cohort of 317 patients with kidney tumours (265 WT, 44 non-WT [13.9%]), treated according to SIOP 93-01 and 2001 protocols, a biopsy was performed in 35% of patients.[27] In our series 11.5% of patients had a non-WT. With our parameters we can distinguish WT from non-WT in up to 90% to get a precise diagnosis. We have defined subgroups of kidney tumours that need a histological proven tumour diagnosis to be safe starting pre-operative chemotherapy. According to our approach, upfront histology will be necessary in 14.6% of patients with unilateral, localized and in 7.7% with unilateral, metastatic tumours only (Table 4). In addition to our recommendations, imaging parameters and, in the future, radiomics and liquid biopsies can help to decide whether a biopsy is necessary.[2,28]

4.3.1 | Unilateral, localized tumours

We recommend a tru-cut biopsy in patients with small and localized, unilateral kidney tumours who are older than 120 months (Table 4) as the intraoperative rupture rate is independent of TV and will be reduced by pre-operative chemotherapy[29] By giving pre-operative chemotherapy in case of WT these patients may also qualify for NSS. In the group of patients older than 84 months with a TV <100 mL, primary resection can be discussed, as the relative frequency of RCC increases significantly in this group compared to WT (Table 2). This decision needs to be made by an experienced surgeon. In the literature, a cut-off value of TV <70 mL is given for biopsy, especially in patients older than 120 months of age.[28,30] Patients who are younger than 6 months of age should be operated primarily according to SIOP.[3] However, because WT is the most common tumour in patients between 3 and 6 months, a tru-cut biopsy not upstaging a tumour should be considered in this age group, at least if WT is suspected on imaging, in order to reduce the risk of stage III by giving pre-operative chemotherapy.[2,28,30]

4.3.2 | Unilateral, metastatic tumours

Currently, a tru-cut biopsy is recommended in metastatic kidney tumours <2 years.[2,28,30] In a recent study, one-third of biopsied metastatic patients <2 years had MRTK.[27] However, in our series, MRTK was the most common tumour only below the age of 18 months. Between 18 and 36 months MRTK occurred only in 2.6%. Therefore, we suggest a tru-cut biopsy only in metastatic patients who are younger than 18 months (Table 4). In addition, our analysis revealed that 37.5% of patients older than 7 years at diagnosis with small tumours of less than 100 mL had RCC. Hence, we would further recommend a tru-cut biopsy in this subgroup. However, it should be mentioned that only eight patients met these criteria (Table 4).

4.4 | Imaging, radiomics and biomarker

MRI, including diffusion-weighted imaging (DWI), demonstrates increasing non-invasive differentiation potential of paediatric renal tumours through the identification of characteristic imaging features for each entity. CCSK, for example, shows a typical band-like enhancement pattern on contrast-enhanced TW1 imaging and relatively high ADC values on DWI.[11] MRTK has been described in previous studies to be associated with subcapsular fluid collection and multiple tumour lobules on MRI, but this is not confirmed in the current literature, which focuses more on the aggressive growth pattern of MRTK.[11,31] In contrast to WT, CMN and in particular the classic subtype is typically characterized by the absence of the T2-hypointense tumour capsule,[32] whereas RCC shows a T2 hypointensity on MRI, which, in combination with the significantly higher age at diagnosis and the smaller TV, is an important differentiating parameter from WT.[10]

However, not all of the imaging features described above are specific to the respective non-WT and WT may also exhibit some of these features.[8] Further improvements in non-invasive diagnosis of childhood kidney tumours can be expected by the addition of interpretation of MRI images including radiomics. First results are already available, showing that different MRI modalities (T1, T1 plus contrast enhancement, T2, DWI) as well as radiomic parameters might be beneficial in such a setting.[4,6,8,10,26,33,34] Postprocessing techniques of

TABLE 4 Biopsy recommendations, [1]PE = primary excision, [2]primary excision if imaging indicative for CMN, tru-cut biopsy if imaging is suggestive for WT and surgery is deemed difficult, [3]NSS = nephron sparing surgery, [4] sum of the patients in the white columns.

Unilateral, localized kidney tumours (*N* = 1935)															
Age (months)		0–3		3–6		6–84		84–120				> 120			
TV (mL)								>100		<100		< 1000		>1000	
Approach		PE[1]		PE vs. tru-cut [2]		Preop. Chemo		Preop. Chemo		NSS[3]		tru-cut/ NSS		Preop. Chemo	
N%	Total	95	100.0	79	100.0	1527	100.0	107	100.0	21	100.0	88	100.0	18	100.0
	WT	25	26.3	61	77.2	1407	92.1	102	95.3	18	85.7	61	69.3	16	88.9
	Non-WT	70	73.7	18	22.8	121	7.9	5	4.7	3	14.3	27	30.7	2	11.1
N%	CMN	68	71.6	14	17.7	13	0.9	0	0.0	0	0.0	0	0.0	0	0.0
	CCSK	1	1.1	1	1.3	84	5.5	4	3.7	0	0.0	2	2.3	2	11.1
	MRTK	1	1.1	3	3.8	22	1.4	0	0.0	0	0.0	0	0.0	0	0.0
	RCC	0	0.0	0	0.0	2	0.1	1	0.9	3	14.3	25	28.4	0	0.0
Indication for upfront histology[4] in 283/1935 (14·6%)															
Unilateral, metastatic kidney tumours (*N* = 431)															
Age (months)		<18		18–36		36–84		> 84							
TV (mL)										>100		<100			
Approach		tru-cut		Preop. Chemo		Preop. Chemo		Preop. Chemo				tru-cut/ NSS			
N (%)	Total	25	100.0	78	100.0	238	100.0	82	100.0			8	100.0		
	WT	11	44.0	71	91.0	228	95.8	80	97.6			5	62.5		
	non- WT	14	56.0	7	9.0	10	4.2	2	2 .4			3	37.5		
N (%)	CMN	0	0.0	0	0.0	0	0.0	0	0.0			0	0.0		
	CCSK	1	4.0	5	6.4	7	2.9	2	2.4			0	0.0		
	MRTK	12	48.0	2	2.6	3	1.3	0	0.0			0	0.0		
	RCC	1	4.0	0	0.0	0	0.0	0	0.0			3	37.5		
Indication for upfront histology[4] in 33/431 (7·7%)															

DWI can be helpful in discriminating WT subtypes.[33] Littooij et al. demonstrated a strong inverse linear relationship between the percentages of stromal- and blastemal histopathology with ADC parameters, if necrosis, haemorrhage or cystic lesions were excluded.[35]

In addition, liquid biopsy analysis of specific tumour markers will be of help in the future. The broad spectrum of Wilms tumour driver genes would still require whole exome or genome sequencing to identify culprits, but this is different for non-WT cases.[36] The highly specific internal tandem duplications of BCOR in CCSK are amenable to direct PCR testing.[37] In addition, the frequent ETV6-NTRK3 translocations, EGFR internal tandem duplications and BRAF alterations in CMN are targetable in liquid biopsy samples.[38] For RCC, translocations involving TFE3 are likewise frequent, while SMARCB1 inactivation in MRTK may require deep sequencing to identify causative mutations.[38] All these tools will require well-established analytic pipelines to enable rapid assessment in this time-critical period prior to initiation of neoadjuvant chemotherapy.

4.5 | Pre-operative treatment optimization and its possible beneficial effects

Our approach allows us to treat as many patients as possible with neoadjuvant treatment with the lowest risk of inadequate pre-operative treatment allowing a better stage distribution and taking into consideration the response to pre-operative chemotherapy post-operatively. In this way, treatment intensity could be significantly reduced or even personalized in the future. The higher number of stage I, the lower number of stage III and the achievement of complete remission of metastasis in patients with stage IV after pre-operative chemotherapy may result in less post-operative anthracyclines, shorter duration of treatment and less radiotherapy.[3] The reduction of treatment intensity is correlated with fewer late effects. Even the number of NSS will be likely increased after pre-operative chemotherapy compared to primary surgery.[39]

4.6 | Limitations

Our analysis has some limitations. These include the retrospective design of the statistical analysis. Therefore, a prospective analysis or validation in an independent cohort is required to validate the proposed biopsy recommendations. In addition, bias in the measurement of tumour volume cannot be excluded regarding the use of different imaging modalities over the long study period. Similarly, the frequency of metastases is dependent on the underlying imaging modality. In all three SIOP/GPOH studies 9, 93-01 and 2001, lung metastases were diagnosed by chest x-ray as standard, but a bias with regard to CT cannot be ruled out in the more recent study period, especially as in SIOP/GPOH 2001 more lung CTs were performed that is now standard in the current UMBRELLA protocol of SIOP/RTSG.

4.7 | Conclusions

We identified age and TV at diagnosis as reliable parameters for the differentiation between WT and CMN or RCC. MRTK must be considered for metastatic tumours in patients younger than 18 months of age. Non-invasive differentiation between WT and CCSK remains a challenge.

According to our results, tumours with specific parameters of age, TV, non-bilaterality and/or metastases should be confirmed by a tru-cut biopsy. If RCC or CMN is suspected, primary surgery must be considered instead of a tru-cut biopsy. Overall, upfront histology is required in about 13% of patients with unilateral kidney tumours as given in our cohort. These recommendations are waiting for prospective confirmation. With the help of further parameters (e.g., recently described MRI characteristics of non-WT including DWI and in future AI-based texture analysis of MRI images of different modalities and liquid biopsies) a better discrimination can be expected.

AUTHOR CONTRIBUTIONS

The work reported in the paper has been performed by the authors, unless clearly specified in the text. *Investigation*: N.W., G.M., R.F., N.G., J-P.S. *Conceptualization*: N.W., N.G., J-P.S. *Data curation*: N.W., G.M., J-P.S., N.G. *Visualization*: N.W., N.G., J-P.S. *Formal analysis*: N.W., S.W., N.G., J-P.S. *Wiring-original draft*: N.W. *Writing-review and editing*: R.F., A.B., M.M., L.K., C.V., S.W.W., J.F., C-M.M., P.M., M.G., S.W., J-P.S., N.G. *Methodology*: N.W., R.F., M.G., S.W., N.G., J-P.S. *Project administration*: N.W., N.G. *Supervision*: R.F., J-P.S., N.G. *Validation*: R.F., A.B., M.M., L.K., C.V., S.W.W., J.F., C-M.M., P.M., M.G., S.W., J-P.S., N.G. *Management and coordination responsibility for the research activity planning/execution*: N.W., N.G. *Funding acquisition*: N.G. *Resources*: S.W.W, J.F., M.G., P.M., J-P.S., R.F., N.G.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data presented in this study is available on request from the corresponding author. The data of all patients was pseudonymized and stored in a central and encrypted SQL database.

ETHICS STATEMENT

Ethical approval for these trials was obtained from the Ärztekammer des Saarlandes (No: 136/01, 09/20/2002, and 248/13, 01/13/2014). All parents or guardians gave informed consent for study participation.

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SUPPORTING INFORMATION

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

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