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Pediatric Small Renal Masses: Can Tumor Size Predict Histology and the Potential for Nephron-sparing Surgery?

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Study Need and Importance: Radical nephrectomy (RN) is the standard of care for surgical resection in children with nonsyndromic unilateral renal masses (uRMs) suspicious for malignancy. Nephron-sparing surgery (NSS) in children is generally reserved for those with bilateral Wilms tumor (WT), predisposition syndromes, a solitary kidney, or select non-WT histologies.

In this study, we evaluated the utility of preoperative radiographic tumor size as a clinical factor to determine the probability of finding WT on final pathology for children with uRMs. We hypothesized that pediatric small renal masses, defined as tumors <4 cm, are more likely to have benign/intermediate or other non-WT histologies that may be potentially appropriate for NSS.

What We Found: In the SEER (Surveillance, Epidemiology, and End Results) database analysis, tumors ≥4 cm had higher odds of being WT compared to tumors <4 cm. After age stratification, it was observed that this predictive relationship was driven by patients 5-9 years of age. In the institutional analysis, tumors ≥4 cm had higher odds of being WT (vs non-WT), malignant (vs benign), and of having RN appropriate histology (vs NSS appropriate histology; see Table).

Limitations: Limitations included the study's retrospective nature and single-institution origin of the institutional data. Additionally, there was a relatively low number of patients in the institutional data with a unilateral renal mass <4 cm. Finally, there are well-known limitations of SEER-based research, including: variability in data reporting, limited information on treatment and tumor characteristics, and error-rates of clinical research databases

Interpretation for Patient Care: A pediatric renal tumor size cut point of 4 cm was helpful in predicting WT, malignancy, and RN-appropriate histology. Renal tumor size should be considered as an additional factor during clinical decision-making for the surgical management of pediatric uRMs.

Table. *Institutional Analysis: Logistic Regression Models for Outcomes of Interest*

Variable	Wilms tumor status Odds ratio (*P* value; 95% CI)	Malignant vs benign Odds ratio (*P* value; 95% CI)	Radical nephrectomy vs nephron-sparing surgery appropriateness Odds ratio (*P* value; 95% CI)
Tumor size			
<4 cm (reference)	-	-	-
≥4 cm	30.85 (.001; 3.75, 254.1)	6.75 (.005; 1.76, 25.93)	46.79 (< .001; 5.61, 390.1)

Abbreviation: CI, confidence interval.

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Pediatric Small Renal Masses: Can Tumor Size Predict Histology and the Potential for Nephron-sparing Surgery?

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Purpose: The majority of children with unilateral renal masses suspicious for malignancy undergo radical nephrectomy, while nephron-sparing surgery is reserved for select cases. We investigated the impact of tumor size on the probability of histology. We hypothesized that pediatric small renal masses are more likely benign or non-Wilms tumor, thus potentially appropriate for nephron-sparing surgery.

Materials and Methods: The SEER (Surveillance, Epidemiology, and End Results) database was analyzed for patients aged 0-18 years diagnosed with a unilateral renal mass from 2000-2016. Statistical analysis was performed to help determine a tumor size cut point to predict Wilms tumor and assess the predictive value of tumor size on Wilms tumor histology. Additionally, a retrospective review was performed of patients 0-18 years old who underwent surgery for a unilateral renal mass at a single institution from 2005-2019. Statistical analysis was performed to assess the predictive value of tumor size on final histology.

Results: From the SEER analysis, 2,016 patients were included. A total of 1,672 tumors (82.9%) were Wilms tumor. Analysis revealed 4 cm to be a suitable cut point to distinguish non-Wilms tumor. Tumors $\geq$4 cm were more likely Wilms tumor (OR 2.67, $P \leq .001$), but this was driven by the statistical significance in children 5-9 years old. From the institutional analysis, 134 patients were included. Ninety-seven tumors (72.3%) were Wilms tumor. Tumors $\geq$4 cm had higher odds of being Wilms tumor (OR 30.85, $P = .001$), malignant (OR 6.75, $P = .005$), and having radical nephrectomy-appropriate histology (OR 46.79, $P < .001$).

Conclusions: The probability that a pediatric unilateral renal mass is Wilms tumor increases with tumor size. Four centimeters is a logical cut point to start the conversation around defining pediatric small renal masses and may help predict nephron-sparing surgery-appropriate histology.

Key Words: Wilms tumor; carcinoma, renal cell; nephrectomy; surgical oncology; medical oncology

PRIMARY renal malignancies account for approximately 7% of pediatric cancers, the most common of which is Wilms tumor (WT).[1] The standard of care for children with nonsyndromic, unilateral renal masses (uRMs)

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Conflict of Interest: AFS: Ethicon. The remaining Authors have no conflicts of interest to disclose.

Ethics Statement: This study received Institutional Review Board approval (IRB No. 14-1758).

Author Contributions: Acquisition of the data: DSH, JPW, PB, SLH, NGC; analysis of the data: DSH, JPW, AN, PB, NVH, MT, SLH, AS, ME, MGC, NGC; critical revision of the work: DSH, JPW, AN, NVH, MT, SLH, AS, ME, MGC, JPR, AFS, NGC; design of the work: DSH, JPW, SLH, JPR, AFS, NGC; drafting of the work: DSH, JPW, AN, PB, NGC; interpretation of data: DSH, JPW, AN, NVH, MT, SLH, AS, ME, MGC, NGC. All Authors approve of the final version to be published and agree to be accountable for all aspects of the work.

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See Editorial on page 464.

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suspicious for malignancy is to undergo a radical nephrectomy (RN). Nephron-sparing surgery (NSS) is generally reserved for children with bilateral WT, predisposition syndromes, a solitary kidney, or select non-WT histologies. While most often part of curative multimodal therapy, RN can have significant long-term health consequences in children, including chronic kidney disease (CKD) and hypertension.[2]

The definition of a small renal mass (SRM) is well-established in the adult urology literature.[3,4] SRMs are defined as clinically localized renal masses $\leq$4 cm in largest diameter. While RN was historically considered the treatment of choice in all localized renal malignancies, the current AUA Guideline for Renal Mass and Localized Renal Cancer advocates prioritizing NSS for adult SRMs when intervention is indicated because NSS minimizes the risk of CKD compared to RN without compromising oncologic outcomes.[5,6]

It is well known that many oncologic staging systems use radiographic primary tumor size (TS) as criteria for clinical staging. However, there have been studies that have analyzed whether TS can have additional utility to also help predict histology and guide the selection of surgical treatment. Multiple studies have shown that increased radiographic renal TS is associated with an increased risk of malignant histology in adults.[7,8] TS has also been advocated as a factor to help guide surgical approach in other genitourinary tumors, such as determining whether to attempt partial orchiectomy for small testicular tumors due to the likelihood of benign histology in smaller tumors.[9,10]

In this study, we investigated how TS impacted the probability of finding WT on final pathology for children with uRM. This was done via 2 approaches. First, we utilized the SEER (Surveillance, Epidemiology, and End Results) database to help determine an optimal size cut point to predict WT. Second, in order to capture data on benign renal masses, which are not reported in SEER, we utilized institutional level data to validate the predictive value of the determined cut point to predict tumor histology. We hypothesized that pediatric small renal masses (pSRMs) are more likely to have benign/intermediate or specific non-WT histologies that may be potentially appropriate for NSS.

METHODS

Institutional Review Board approval was obtained for the portion of the study utilizing institutional data (IRB No. 14-1758). The SEER database portion of the study was deemed exempt from Institutional Review Board review.

SEER Analysis

The SEER database was retrospectively analyzed for patients 0-18 years of age who were diagnosed with a unilateral renal malignancy from 2000-2016 (supplemental Figure 1, https://www.jurology.com). The included histology codes are listed in supplemental Table 1 (https://www.jurology.com). Exclusion criteria consisted of unknown histology, prior history of renal tumors, no surgery or unknown if surgery was performed, receipt of neoadjuvant chemotherapy/radiotherapy, missing TS, and size >65 cm, as it was assumed these were errors in sizing. Patients were stratified by histology in a binary fashion—WT vs non-WT. A calibration plot was created to visualize the relationship between TS and probability of WT. This analysis supported the use of a cut point of 4 cm for a SRM as used in the adult population. Multivariable complete case logistic regression analysis was performed to determine the predictive characteristics of pathological TS (<4 cm vs $\geq$4 cm) on WT histology. Subgroup analysis was performed based on age.

Institutional Analysis

A retrospective review was performed from the hospital electronic medical record of children 0-18 years of age who underwent surgical resection (RN or NSS) for a uRM at a single tertiary children's hospital from 2005-2019. Patients with unknown final histology were excluded. We also excluded patients who received neoadjuvant chemotherapy due to the inability to correlate radiographic TS with pathological TS because of cytoreduction from treatment. Except for year of surgery, the same exclusion/inclusion criteria were utilized for both cohorts.

Informed by the SEER analysis and the adult definition of a SRM, we utilized 4 cm on preoperative imaging (CT abdomen with contrast or MRI abdomen with contrast), as an optimal size cut point to predict WT. Sizing was determined based on the largest single dimension measured in the uRM on either the anterior-posterior, cranio-caudal, or transverse planes. Patients were stratified based on whether preoperative TS was <4 cm or $\geq$4 cm, similar to the SEER data analysis. Primary outcome was histology based on pathological analysis after surgical resection. Patients were substratified according to appropriateness of surgical approach (RN vs NSS) based on final histology to determine if TS could help predict NSS-appropriate vs RN-appropriate histology. A priori, histologies deemed appropriate for RN were: WT, clear cell sarcoma of the kidney (CCSK), rhabdoid tumor of the kidney, and other primary renal sarcomas. Those deemed as potentially appropriate for NSS were: benign histology, renal cell carcinoma (RCC), or intermediate histology, which consisted of cystic nephroma, congenital mesoblastic nephroma, or cystic partially differentiated nephroblastoma. We hypothesized that larger tumors would be more likely to have RN-appropriate histology. Finally, since the SEER database solely utilizes pathological TS, we analyzed how radiographic TS correlated with pathological TS.

Statistical analysis was performed to explore the relationship of radiographic TS with final histology and whether histology was RN appropriate or NSS appropriate. The Wilcoxon rank-sum test was used for continuous variables. The χ^2 test was used for categorical variables, with the Fisher's exact test utilized in situations with low counts. Spearman's rank correlation coefficient was utilized to determine the correlation between

Table 1. *SEER Analysis: Overall Patient Demographics by Histological Category*

Variables	Wilms tumor status					
	Non-Wilms tumor (n = 344)		Wilms tumor (n = 1,672)		Overall (N = 2,016)	
Demographics						
Gender, No. (%)						
Female	170	(49.42)	892	(53.35)	1,062	(52.68)
Male	174	(50.58)	780	(46.65)	954	(47.32)
Age range, No. (%), y						
<1	48	(13.95)	194	(11.6)	242	(12)
1-4	93	(27)	1,039	(62.1)	1,132	(56.2)
5-9	42	(12.2)	370	(22.1)	412	(20.4)
10-14	61	(17.7)	51	(3.1)	112	(5.6)
15-18	100	(29.1)	18	(1.1)	118	(5.9)
Median age (IQR), y	8.0 (1.0-15.0)		3.0 (1.0-5.0)		3.0 (1.0-5.0)	
Clinical measures						
SEER stage						
Unknown	1	(0.29)	18	(1.08)	19	(0.94)
Localized	174	(50.58)	791	(47.31)	965	(47.87)
Regional	118	(34.30)	568	(33.97)	686	(34.03)
Distant	51	(14.83)	295	(17.64)	346	(17.16)
Metastatic						
Unknown	18	(5.23)	128	(7.66)	146	(7.24)
Nonmetastatic	278	(80.81)	1,307	(78.17)	1,585	(78.62)
Metastatic	48	(13.95)	237	(14.17)	285	(14.14)
Nodal status[a]	125	(36.34)	1,149	(68.72)	1,274	(63.19)
N0	95	(27.62)	291	(17.40)	386	(19.15)
N1	124	(36.05)	232	(13.88)	356	(17.66)
Nx						
Median tumor size (IQR), cm	7.8 (4.3-11.5)		10.5 (8.0-13.0)		10.10 (7.2-13.0)	

Abbreviations: IQR, interquartile range; SEER, Surveillance, Epidemiology, and End Results.
[a] Nodal status: N0 = no nodes positive, N1 = any nodes positive, Nx = unknown.

radiographic TS and pathological TS in our institutional data set.

Least absolute shrinkage and selection operator (LASSO) logistic regression was performed to explore the predictive characteristics of radiographic TS and control for potential confounders amongst a subset of demographic variables prespecified as being clinically relevant to tumor histology. LASSO was utilized to perform feature selection. Models were built applying a penalty factor of 0 to the TS cut point. The optimal models were chosen by utilizing the values of λ that minimized error in 10-fold cross-validation. *P* values were calculated based on a null hypothesis of no effect against a 2-sided alternative at a significance threshold of 0.05. Analyses were performed using SAS 9.4.

RESULTS

From the SEER analysis, a total of 2,016 patients were identified for inclusion. Table 1 shows overall data broken down by histological category. Median age was 3 years (IQR 1.0-5.0). A total of 344 tumors (17.06%) were non-WT. Supplemental Table 1 (https://www.jurology.com) lists data broken down by individual histology codes and stratified by age. Visual assessment of the calibration plot demonstrated that 4 cm was a potential candidate for size cut point to predict WT, affirming our disposition to explore the adult definition of SRM in a pediatric population (see Figure). Multivariable complete case logistic regression analysis revealed that tumors ≥4 cm had higher odds of being WT compared to tumors <4 cm (OR 2.67, 95% CI 1.77-4.04; $P \leq .001$; Table 2). After age stratification, it was observed that this predictive relationship was driven by patients 5-9 years of age (OR 11.06, 95% CI 4.82-25.36; $P < .001$). The predictive capacity of a 4 cm cut point was not statistically significant in patients 0-4 years (OR 0.97; 95% CI 0.47-1.99; $P = .9$) or 10-18 years of age (OR 2.55; 95% CI 0.87-7.50; $P = .09$; supplemental Table 2, https://www.jurology.com).

From the institutional analysis, there were 137 patients with a uRM who underwent surgical resection without receiving neoadjuvant chemotherapy. Of these, 134 patients met inclusion criteria due to 3 patients having unknown final histology. Table 3 details demographic, clinical, and histological data based on renal size cutoff. There were 97 (72.39%) tumors with WT histology. Of all patients with WT, 96 (98.97%) tumors were ≥4 cm in size. There were 29 patients with histology appropriate for NSS—7 benign tumors, 14 tumors with intermediate histology, and 8 RCC. Histologies included under "benign other" were: calcified nodule, renal cyst, cystic metanephric adenoma, angiomyolipoma, segmental renal dysplasia, juxtaglomerular cell tumor, and IgG4 lymphoplasmacytic infiltrate. The histology included under "malignant other" was high-grade pleomorphic undifferentiated sarcoma.

There were 10 tumors <4 cm in size; of these, 1 was WT. None of the tumors <4 cm had distant

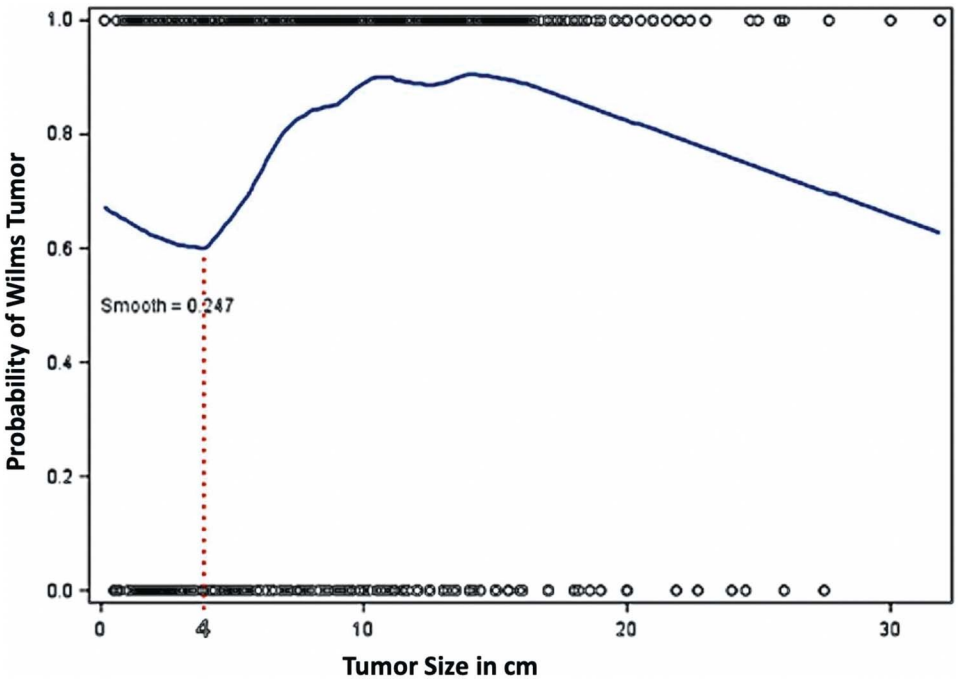

Figure. SEER analysis: logistic regression analysis representing the probability of a renal mass being Wilms tumor based on size.

metastatic disease. There was 1 patient with a tumor <4 cm who had stage III disease-pathology was pT3a RCC with renal sinus fat invasion. Out of the 124 tumors ≥4 cm, 104 (83.87%) had histology appropriate for RN.

For each outcome, the LASSO model that resulted in the smallest cross-validation error only included tumor cut point. No additional variables were found to be important features in addition to TS in the institutional data set. Tumors ≥4 cm had higher odds of being WT vs non-WT (OR 30.85, 95% CI 3.75-254.1; $P = .001$), of being malignant vs benign (OR 6.75, 95% CI 1.76-25.93; $P = .005$), and of having RN-appropriate histology vs NSS-appropriate histology (OR 46.79, 95% CI 5.61-390.1; $P < .001$; Table 4). There was a strong positive Spearman correlation of 0.87 ($P < .0001$) between preoperative TS on imaging and postoperative TS on pathology.

DISCUSSION

RN is the standard of care for surgical resection of most nonsyndromic pediatric uRM, as the majority are WT or other malignant histology which warrants aggressive surgical resection.[11] The Children's Oncology Group protocols support RN as the standard of care for definitive surgical treatment for unilateral WT in children. There is, however, a well-known distribution of tumor histology by age among nonsyndromic children presenting with a uRM. At younger ages, WT is more likely than other histologies and in adolescence, RCC becomes more likely. Therefore, the age of a child presenting with a uRM is one factor, among others, that can be used to clinically determine the probability of histology and thus affect surgical management if there is suspicion that a uRM is not WT.

Our study suggests that the size of a uRM on preoperative imaging is another clinical factor which may be utilized to determine the probability of a histological diagnosis. There have been other studies which have corroborated our results where WT appears to typically present with large

Table 2. *SEER Analysis: Logistic Regression Predicting Wilms Tumor*

Variable	Level	OR (95% CI)
Year of diagnosis	Continuous	0.99 (0.96, 1.02)
Age category, y	1-4 (reference)	-
	10-14	0.08 (0.05, 0.12)
	15-18	0.02 (0.01, 0.03)
	5-9	0.77 (0.52, 1.14)
	<1	0.34 (0.23, 0.51)
Sex	Male (reference)	-
	Female	1.56 (1.18, 2.08)
Race/ethnicity	White NH (reference)	-
	Black NH	0.88 (0.59, 1.29)
	Hispanic	0.83 (0.60, 1.17)
	Other	0.71 (0.41, 1.26)
Laterality	Right (reference)	-
	Left	1.22 (0.92, 1.62)
SEER summary stage	Localized (reference)	-
	Distant	0.96 (0.64, 1.45)
	Regional	0.75 (0.55, 1.03)
Tumor size	Less than 4 cm (reference)	-
	4 cm or larger	2.67 (1.77, 4.04)

Abbreviations: CI, confidence interval; NH, non-Hispanic, OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results.

Table 3. *Institutional Analysis: Demographic, Clinical, Histological Data by Renal Mass Cutoff*

Variables	Renal mass cutoff						Overall (N = 134)	
	<4 cm (n = 10)		≥4 cm (n = 124)		*P* value			
Demographics								
Gender, No. (%)					.9609[a]			
Male	5	(50)	61	(49.2)			66	(49.25)
Female	5	(50)	63	(50.8)			68	(50.75)
Race, No. (%)					.349[b]			
White (non-Hispanic)	5	(50)	84	(67.7)			89	(67.94)
Black (non-Hispanic)	0	(0)	8	(6.5)			8	(6.11)
Hispanic	4	(40)	23	(18.5)			27	(20.61)
Other	1	(10)	7	(5.6)			7	(5.34)
Age at surgery, median (IQR), mo	69.12	(53.68, 175.46)	34.41	(17.12, 55.6)	.0042[c]		36.65	(17.74, 62.35)
Clinical measures								
Laterality, No. (%)					.1025[b]			
Left	2	(20)	61	(49.2)			63	(47.01)
Right	8	(80)	63	(50.8)			71	(52.99)
Tumor thrombus, No. (%)					1[b]			
No	10	(100)	116	(93.5)			126	(94.03)
Yes	0	(0)	8	(6.5)			8	(5.97)
Overall disease stage (malignant and CMN only), No. (%)					.6151[b]			
1	2	(40)	24	(20.9)			26	(21.67)
2	2	(40)	34	(29.6)			36	(30)
3	1	(20)	39	(33.9)			40	(33.33)
4	0	(0)	18	(15.7)			18	(15)
Nephrectomy type, No. (%)					< .0001[b]			
Partial	10	(100)	12	(54.55)			22	(16.42)
Radical	0	(0)	112	(100)			112	(83.58)
Histology, No. (%)					< .0001[b]			
Wilms	1	(10)	96	(77.4)			97	(72.39)
RCC	4	(40)	4	(3.2)			8	(5.97)
CMN	0	(0)	7	(5.6)			7	(5.22)
CCSK	0	(0)	4	(3.2)			4	(2.99)
RTK	0	(0)	3	(2.4)			3	(2.24)
MLCN	1	(10)	4	(3.2)			5	(3.73)
CPDN	0	(0)	2	(1.6)			2	(1.5)
Benign other	4	(40)	3	(2.4)			7	(5.2)
Malignant other	0	(0)	1	(0.8)			1	(0.75)
Favorable histology, No. (%)					1[b]			
No	0	(0)	4	(4.2)			4	(4.12)
Yes	1	(100)	92	(95.8)			93	(95.88)
Lymph nodes sampled, No. (%)					.0002[b]			
No	5	(50)	5	(4.0)			10	(7.46)
Yes	5	(50)	119	(95.97)			124	(92.54)
Lymph node status, No. (%)					.5899[b]			
Negative	5	(100)	90	(75.6)			95	(76.6)
Positive	0	(0)	29	(23.4)			29	(23.4)
Patient alive at last follow-up?, No. (%)					1[b]			
No	0	(0)	3	(2.4)			3	(2.24)
Yes	10	(100)	121	(97.6)			131	(97.76)
Length of stay, median (IQR), d	4	(2, 7)	5	(4, 6)	.3279[c]		5	(4, 6)
Length of follow-up, median (IQR), mo	36.01	(12.52, 66.82)	36.09	(9.41, 73.83)	.9831[c]		36.01	(9.43, 73.16)
Preoperative tumor size, median (IQR), cm	2.15	(1.3, 2.9)	10.5	(8.35, 13)	< .0001[c]		10	(7.5, 12.8)
Postoperative (pathology) tumor size, median (IQR), cm	2.75	(1, 3)	10.5	(7.5, 12.5)	< .0001[c]		10	(6.5, 12.4)

Abbreviations: CCSK, clear cell sarcoma of the kidney; CMN, congenital mesoblastic nephroma; CPDN, cystic partially differentiated nephroblastoma; IQR, interquartile range; MLCN, multilocular cystic nephroma; RCC, renal cell carcinoma; RTK, rhabdoid tumor of kidney.
[a] Based on χ^2 test.
[b] Based on Fisher's exact test.
[c] Based on Wilcoxon rank-sum test.

tumors.[12,13] In a European study analyzing renal tumor biopsy results under the International Society of Paediatric Oncology protocol, la Monneraye et al found that tumor volumes were higher in those with CCSK and WT, while RCC had lower tumor volumes, even after adjusting for age.[14] Additionally, in a retrospective review of 248 WT cases treated in France in the 1950-1960s, Lemerle et al found that 82% of 102 WT cases with known tumor dimensions had TS greater than 5 cm.[15] Although the definition of an SRM in adults is widely accepted as a renal tumor ≤4 cm in size, our study suggests that this same concept may also be clinically useful in children.

The use of organ-sparing techniques for surgical treatment of malignancies has been increasingly

Table 4. *Institutional Analysis: Logistic Regression Models for Outcomes of Interest*

Variable	Wilms tumor status Odds ratio (*P* value; 95% CI)	Malignant vs benign Odds ratio (*P* value; 95% CI)	Radical nephrectomy vs nephron-sparing surgery appropriateness Odds ratio (*P* value; 95% CI)
Tumor size			
<4 cm (reference)	-	-	-
≥4 cm	30.85 (.001; 3.75, 254.1)	6.75 (.005; 1.76, 25.93)	46.79 (< .001; 5.61, 390.1)

Abbreviation: CI, confidence interval.

utilized, with the simultaneous goals of providing appropriate oncologic control while avoiding overtreatment and preserving organ function. The goals of cancer treatment do not only include cure, but also the preservation of long-term health and quality of life. A remnant solitary kidney after RN may be subject to hyperfiltration injury which can lead to renovascular hypertension, proteinuria, and CKD.[16-18] Long-term data have shown that adult survivors of childhood renal tumors in their fourth and fifth decades of life who underwent RN during childhood have worse renal function than expected with physiological renal decline from aging.[19] Additionally, patients after RN have greater resultant decreases in glomerular filtration rate and higher blood pressures compared to NSS for the treatment of nonsyndromic childhood uRM.[20] Finally, in a long-term study of over 25,000 childhood cancer survivors, Dieffenbach et al reported a 1.7% 35-year cumulative incidence of late-onset kidney failure, with RN being independently associated with an elevated risk of late-onset kidney failure.[21] Thus, if an organ-sparing approach is feasible from an oncologic perspective, this may mitigate the health risks from having an acquired solitary kidney due to RN.

If there is sufficient suspicion that a pSRM is of NSS-appropriate histology, it is reasonable to attempt to verify histology during the time of surgical resection as the treating team may convert to a completion nephrectomy depending on the histology. The use of intraoperative frozen section (IFS) plays an important role in these scenarios. Carrasco et al showed that IFS on a nephrectomy specimen is a reliable method to determine final pathology for the diagnosis of renal tumors at the time of resection, with a sensitivity and specificity for correct identification of tumor histology of 0.92 and 1, respectively.[22] Additionally, they reported that IFS correctly distinguished between WT and non-WT cases in 94% of cases. Thus, IFS could help in "real time" by analyzing the NSS resection specimen after excision to determine if a small tumor is WT or other RN-appropriate histology.

A key finding in the SEER analysis was the fact that the 4 cm cut point was driven by patients 5-9 years of age, and was not significant for those 0-4 and 10-18 years of age. In the 0-4 age range, the 2 most common histologies after WT were rhabdoid tumor of the kidney and CCSK, which are known to be aggressive tumor histologies with poor prognoses, and the majority of these tumors were >4 cm. Furthermore, in the 10-18 age range, the majority of tumors that were RCC in this age range was >4 cm. It is known that children with RCC present with higher stage and grade compared to adults.[23-25] Thus, it appears that in the 0-4 and 10-18 year age ranges, the cut point may not be as useful where there are common non-WT histologies that may present with larger tumors and may ultimately require RN regardless.

Limitations of this study include the retrospective nature and single-institution origin of the institutional data. Additionally, there were a relatively low number of patients who had a uRM <4 cm causing instability in point estimates surrounding the cut point analyses. While there were indications of its utility in a predictive model amongst this population, a more balanced sample would be necessary to increase parameter precision. Another limitation in our institutional study is the selection bias of a tertiary referral center treating a high volume of patients with renal tumors. We also do not have IFS data on all these patients so conclusions on the feasibility of IFS to help determine potential NSS-appropriate histology must be tempered. There are also well-known limitations of SEER-based research, which include: variability in data reporting, limited information on treatment and tumor characteristics, and error-rates of clinical research databases.[26,27] Furthermore, the SEER database does not include benign tumors and thus, there is a bias toward overrepresenting malignant tumors. Finally, the authors want to be clear that our aim is not to argue that NSS is universally appropriate for small WT. Rather, we want to emphasize that there are certain pediatric renal tumor histologies that could be appropriately treated with NSS, and TS is a factor that can help identify these tumors preoperatively. Further studies are needed with greater patient numbers to validate our results.

CONCLUSIONS

We observed that a pediatric renal TS cut point of 4 cm was helpful in the clinical assessment of which tumors were of WT histology, malignant histology,

and having RN-appropriate histology. Renal TS should be considered as an additional factor during clinical decision-making for the surgical management of pediatric uRMs. Future multi-institutional prospective studies will be helpful to determine the clinical utility of defining the pSRM.

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EDITORIAL COMMENT

The authors have made an immense effort to provide insight into whether renal tumor size in children can be predictive of a wide range of pathological subtypes, clarifying who is best served with nephron-sparing surgery. In their SEER (Surveillance, Epidemiology, and End Results) analysis, there does appear to be a loose association between Wilms tumor histology and tumor size greater than 4 cm (OR=2.67). However, some caution in interpretation should be taken here; the lower bound of the IQR in the Wilms (8.0 cm) and non-Wilms (4.3 cm) groups exceeded 4 cm, indicating that 75% of the population was over 4 cm regardless of pathology. Additionally, a substantial portion of the association between tumors >4 cm and Wilms was driven by the age group 5-9 years

despite age being controlled for in the analysis. Is age, then, colinear with tumor size? If so, this would infringe on the assumptions of a logistic regression model. As the authors indicate, their non-Wilms group does include malignant pathology such as rhabdoid tumors and sarcoma. SEER excludes benign tumor data, but that alone doesn't justify anchoring the narrative to Wilms vs non-Wilms. Malignant vs benign would seem more relevant, supporting their proposal regarding surgical approach of radical nephrectomy-appropriate vs potentially partial nephrectomy-appropriate histology as a better comparison. Indeed, the authors attempt to answer this question with their institutional analysis. Tumors greater than 4 cm have 7 times higher odds of being malignant and 47 times higher odds of being appropriate for radical nephrectomy. This finding is a "logical starting point," and advocating for a more judicious use of radical nephrectomy in the pediatric population is a principled message in this paper. However, other than tumor size, much more remains to be discovered to help us better balance the challenge of oncologic efficacy and the risk of chronic kidney disease when choosing nephron-sparing surgery vs radical nephrectomy. Further advancements in the diagnostic performance of MRI[1] and expansion of the Cancer Genome Atlas[2] will improve our predictive models for treating pediatric renal tumors.

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REPLY BY AUTHORS

We appreciate the insightful comments regarding our manuscript. We agree with most of the points and have the following responses: (1) We did check to make sure there was no collinearity in our institutional analysis. With regard to the SEER (Surveillance, Epidemiology, and End Results) analysis, the possibility of collinearity between age and tumor size was addressed by doing the stratified analysis by age. Within each age subgroup analysis, age was not included as an independent variable, and therefore there would not be a collinearity effect of age on tumor size in the model. (2) We would also like to clarify that we are not advocating for a more judicious use of radical nephrectomy in children with renal tumors per se. Rather, we hope that utilizing tumor size would allow clinicians to better identify patients who may potentially be appropriately treated with nephron-sparing surgery.

We hope our study can be a starting point for further studies that explore the utility of tumor size for clinical decision-making in the management of pediatric renal tumors.