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Evaluation of Diagnostic Performance of CT for Detection of Tumor Thrombus in Children with Wilms Tumor: A Report from the Children's Oncology Group

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Abstract

Background—Pre-operative assessment of intravascular extension of Wilms tumor is essential to guide management. Our aim is to evaluate the diagnostic performance of multidetector CT in detection of tumor thrombus in Wilms tumor.

Procedure—The study population was drawn from the first 1015 cases in the AREN03B2 study of the Children's Oncology Group. CT scans of children with (n=62) and without (n=111) tumor thrombus at nephrectomy were independently reviewed by two radiologists, blinded to patient information. Doppler sonography results were obtained from institutional radiology reports, as Doppler requires real-time evaluation. The diagnostic performance of CT and Doppler for detection of tumor thrombus was determined using nephrectomy findings as reference standard.

Results—In the primary nephrectomy group, tumor thrombus detection sensitivity, specificity of CT was 65.6%, 84.8%, and Doppler was 45.8%, 95.7%, respectively. In this group, sensitivity of CT, Doppler for detection of cavoatrial thrombus was 84.6% and 70.0%, respectively. In the secondary nephrectomy group, tumor thrombus detection sensitivity, specificity of CT was 86.7%, 90.6%, and Doppler was 66.7%, 100.0%, respectively. In this group, sensitivity of CT, Doppler for detection of cavoatrial thrombus was 96.0% and 68.8%, respectively. Pre-operative Doppler evaluation performed in 108/173 cases, detected 3 cases with intravenous extension (2 in renal vein, 1 in IVC at renal vein level) that were missed at CT.

Conclusions—CT can accurately identify cavoatrial tumor thrombus that will impact surgical approach. Routine Doppler evaluation, after CT has already been performed, is not required in Wilms tumor.

Keywords

Wilms tumor; tumor thrombus; CT; Doppler

Introduction

Intravenous tumor thrombus has been reported in up to 11.3% of Wilms tumor cases, with tumor thrombus extending into the inferior vena cava (IVC) or right atrium in up to 8.1% of cases [1-4]. The presence of cavoatrial tumor thrombus can lead to differences in management with some patients undergoing attempt at surgical resection (primary nephrectomy) while others receive neoadjuvant chemotherapy followed by surgery (secondary nephrectomy). In either instance, the tumor thrombus poses an increased surgical risk [1]. The current recommendation is for selective management of patients with tumor thrombus based on the distal most location of the thrombus [2,4]. This decision making is based on adequate diagnostic imaging that will allow identification of the presence of the tumor thrombus and adequate detail as to determine the distal most extent of the thrombus. Pre-operative knowledge of tumor thrombus has been shown to decrease the rate of perioperative complications [5].

There is limited information regarding the diagnostic performance of individual imaging modalities for detection of tumor thrombus. In the third National Wilms Tumor Study (NWTs-3), ultrasound was shown to have a sensitivity of 59% in detection of cavoatrial tumor thrombus, as compared to 42% for computed tomography [3]. However, this study had important limitations: it was a retrospective review of a small cohort, lacked central review of imaging, and reported upon now outdated CT technology. Diagnostic performance of individual imaging modalities was not evaluated in NWTs-4 [2]. The current recommendation in the radiology, pediatric, and surgical literature is that ultrasound with color Doppler sonography should be performed for preoperative evaluation of Wilms tumor to evaluate for tumor thrombus [6-8]. In North America, local staging of Wilms tumor is performed with CT or MRI of the abdomen and pelvis. Doppler sonography is frequently requested by treating physicians after local staging of the renal mass has been performed with CT. Significant advances have been made in CT technology over the last two decades with widespread availability of multidetector CTs. In this study, we sought to evaluate the diagnostic performance of current CT technology for detection of tumor thrombus in children with Wilms tumor. In this era of rising healthcare costs, we sought to determine whether we can do away with an additional sonographic evaluation, after a CT has already been performed.

Materials and Methods

The study population was drawn from the first 1015 cases enrolled in the ongoing renal tumors classification, biology and banking study of the Children's Oncology Group (AREN03B2). Cases were enrolled from 177 institutions over the time period March 2006 to September 2008. All institutions had obtained approval from their institutional review boards. Per the study protocol, all children with a first time occurrence of a renal mass are eligible for the study. At the time of enrollment CT studies of the chest, abdomen, and pelvis performed at the local institution are submitted to the Quality Assurance Review Center (QARC) based in Providence, RI. Performance of ultrasound with Doppler evaluation is not mandatory in the study protocol and is at the discretion of the treating institution. Local institutions have to submit operative notes and pathology slides from biopsy and/or nephrectomy for central review. As per the guidelines of the study, initial nephrectomy is recommended for all renal masses with the exception of patients presenting with bilateral disease, renal tumor that is judged to be unresectable or tumor thrombus that extends into the inferior vena cava above the hepatic vein level or into the right atrium. The surgical guidelines ask the local surgeon to palpate the renal vein and IVC for tumor thrombus and document this in the surgical notes.

For the purpose of this study, we identified all children with a pathologically proven diagnosis of Wilms tumor, who had been found to have tumor thrombus at the time of nephrectomy. This resulted in 62 cases. CT scans of these children were mixed with a random sample of 114 children with Wilms tumor who had been determined to not have tumor thrombus at the time of surgery. CT scans had not been submitted for central review in 3 out of these 176 cases and so these were excluded from review. Therefore, the radiology review consisted of 173 CT scans that were independently reviewed by two board certified radiologists with 35 and 10 years of experience. The radiology reviewers had IRB approval from their institutions to perform central imaging review. The reviewers were blinded to all patient information including the report of the local radiologist and the surgical/pathologic findings. If there was a discrepancy between the two radiologists, this was resolved by consensus review. Criterion for determination of tumor thrombus included presence of an intraluminal filling defect within the renal vein, IVC, or right atrium. If the vessel lumen was obliterated due to mass effect from the primary mass or retroperitoneal lymph nodes, tumor thrombus was considered absent. The distal most extent of tumor thrombus was categorized as renal vein, inferior vena cava, or atrium. In the study protocol, all institutions are advised to perform contrast enhanced CT scans of the abdomen and pelvis during the portal venous phase of contrast injection. All exams had been performed with intravenous contrast administration, and 134/173 cases had received gastrointestinal contrast also. Portal venous phase images were available for review in all 173 cases, and multiphase (arterial/delayed) imaging had also been performed in 50 cases. Only the portal venous phase images were evaluated in this study to determine the intravascular extension of Wilms tumor. The slice thickness of the images available for central review was 2.5-5mm in 166 cases, <2.5mm in 6 cases, and 7mm in 1 case. Axial and multiplanar images (sagittal and coronal) were available for review in 120 cases, while only axial images were available in 53 cases. We did not evaluate the accuracy of the institutional CT readings, as we determined that the local radiologists may not have been blinded to the findings of additional imaging studies such as ultrasound with Doppler.

Central review of Doppler imaging was not a part of this study, as it is a real-time and operator dependent technique. However, the ultrasound reports were available and were reviewed to determine the reason for the ultrasound, and whether specific evaluation for vascular invasion had been performed during sonographic evaluation. In the primary nephrectomy group sonography had been performed in 84 cases- 47 cases had undergone an additional ultrasound exam with Doppler specifically to assess for vascular invasion, after local staging had already been performed with another cross-sectional modality (36 cases prior CT, 4 cases prior ultrasound, and 7 cases prior imaging unclear from Doppler report). Twenty four cases had undergone Doppler evaluation to evaluate for vascular invasion at the time of identification of renal mass at screening ultrasound, while in 13 cases only a screening abdominal ultrasound had been performed without attention to the status of the vessels. In the secondary nephrectomy group, sonography had been performed in 44 cases – 31 had undergone Doppler evaluation for the specific purpose of evaluating vascular invasion after prior imaging identified a renal mass (prior CT 29 cases, prior imaging unknown 2 cases), 6 cases had undergone Doppler evaluation to evaluate vascular invasion at the time of the screening ultrasound, while 7 cases had undergone a screening ultrasound only without specific mention of the status of the renal vasculature or IVC. The cases where ultrasound was performed without specific evaluation for vascular invasion were excluded from the analysis.

Results

The age range of the 62 cases with tumor thrombus was 0-23 years (median 4 years). There were 28 males and 34 females in this group. The age range of the 111 cases without tumor

thrombus was 0-19 years (median 3 years) with 56 females and 55 males. Primary nephrectomy had been performed in 111 cases, while 62 had undergone secondary nephrectomy after 6 weeks of chemotherapy. The demographics of the two groups are listed in Table I. The results of the two groups are presented separately below.

In the primary nephrectomy group tumor thrombus was present in 32 out of the 111 cases. The location of the distal most extent of the tumor thrombus, as determined at surgical evaluation was as follows: renal vein (n=19), inferior vena cava (n=12), and atrium (n=1). In this group CT had an overall sensitivity of 65.6% and specificity of 84.8% for detection of tumor thrombus (Table II). Doppler sonography in the primary nephrectomy group had an overall sensitivity of 45.8% and specificity of 95.7% for detection of tumor thrombus (Table II). When limiting evaluation to cases with tumor thrombus extending into the IVC or atrium, CT accurately identified presence of cavoatrial tumor thrombus in 11 out of 13 cases; while Doppler accurately identified presence of cavoatrial tumor thrombus in 7 out of 10 cases (3 cases had not undergone Doppler evaluation). In the two cases where CT did not detect cavoatrial tumor thrombus, the thrombus was limited to the IVC at the level of the renal vein. Institutional Doppler ultrasound had detected tumor thrombus in one case but was false negative for tumor thrombus in the other case. In the primary group preoperative Doppler evaluation had been performed by the local institution in 71/111 cases, and led to the detection of 2 additional cases of intravenous extension that were missed by CT – one in the renal vein and one in the inferior vena cava at the level of the renal vein.

In the secondary nephrectomy group, tumor thrombus was present in 30 out of the 62 cases. The location of the distal most extent of tumor thrombus, as determined by findings at secondary nephrectomy, was as follows: renal vein (n= 5), inferior vena cava (n=20), and atrium (n=5). In this group CT had a sensitivity of 86.7%, and specificity of 90.6% for detection of any level of tumor thrombus (Table III). Doppler sonography had a sensitivity of 66.7%, and specificity of 100.0% for detection of any level of tumor thrombus (Table III). CT accurately identified presence of tumor thrombus in 24 out of the 25 cases with tumor thrombus extending into the IVC or atrium. Doppler sonography had been performed in 16 cases with tumor thrombus in the IVC or atrium, and detected tumor thrombus in 11/16 cases. In the one case where CT did not detect cavoatrial tumor thrombus, the institutional Doppler evaluation for tumor thrombus had been false negative as well. In the secondary nephrectomy group routine preoperative Doppler evaluation had been performed in 37/62 cases, and led to the additional detection of 1 case of intravenous extension into the renal vein missed at CT.

In cases where tumor thrombus was detected preoperatively by CT the distal most extension of tumor thrombus was accurately predicted in 17/21 (80.9%) cases in the primary nephrectomy group (Table IV), and 23/26 (88.5%) cases in the secondary nephrectomy group (Table V).

Discussion

Wilms tumor can extend into its venous drainage resulting in tumor thrombus. The prevalence of tumor thrombus in the renal vein has been reported at 11.3%, while extension into the IVC or atrium has been reported in 4.1-8.1% of cases [2-4]. The presence of tumor thrombus can alter clinical management with some cases receiving preoperative chemotherapy followed by delayed surgery. Those patients with tumor thrombus tip located in the infrahepatic IVC are amenable to upfront resection. Those located in the retrohepatic IVC may be approachable with suprahepatic IVC control. But those located above the liver will usually require cardiopulmonary bypass and are usually approached with neoadjuvant chemotherapy. Also, the presence of tumor thrombus increases the difficulty of resection as

securing the tumor thrombus poses technical challenges. In NWTS-4, complications arising from nephrectomy and tumor thrombectomy occurred in 17.2% of cases with IVC extension and 36.7% of cases with atrial extension of tumor thrombus [2]. As the detection of tumor thrombus and the exact delineation of its distal most extent are paramount in guidance of management, a review of current CT technology was undertaken.

The accuracy of various imaging modalities in detection of tumor thrombus in children with Wilms tumor has not been defined. Data available from NWTS-3 is based upon outdated technology with single detector CT scanners which had limited spatial and temporal resolution and lacked multiplanar ability. In NWTS-3, renal vein involvement was reported at 11.3%, however the correct imaging diagnosis of renal vein thrombus was made in only 2% (5/211) of cases [1]. For the detection of cavoatrial thrombus, ultrasound was shown to have a sensitivity of 59% as compared to 42% for CT [3]. In NWTS-4 various imaging studies were used to detect tumor thrombus including CT, ultrasound, MRI, echocardiography, and venography. Diagnostic performance of individual studies could not be determined as they were neither uniformly obtained nor centrally reviewed. In a single institutional study of 12 patients with cavoatrial thrombus, the positive predictive value of Doppler ultrasound at detecting tumor thrombus was reported at 73.4% [9]. In this study, 22% of scans were non-diagnostic due to compression or non-visualisation of the inferior vena cava secondary to mass effect from the tumor. The current recommendation in the pediatric radiology literature is that ultrasound with color Doppler evaluation is the best imaging modality to determine the patency of the IVC [6-8]. Doppler ultrasound is often performed in children with Wilms tumor, even if the CT findings for presence/absence of Wilms tumor are unequivocal. This is supported by the fact that 65/173 cases in this study underwent a Doppler evaluation after a CT had already been performed, even though it was not a requirement in the study protocol. A commonly encountered clinical scenario is where a child is found to have a renal mass on clinical exam or imaging performed at a community hospital. The child gets referred to the treating institution where a staging CT is performed. The treating oncologist or surgeon then requests an ultrasound with Doppler to evaluate for vascular patency. The question we are asking is whether another diagnostic test, namely Doppler sonography, is still required after a staging CT has been performed.

Assessment of vascular patency can be performed with magnetic resonance imaging (MRI). The advantages of MRI include the lack of ionizing radiation, multiplanar ability, and the ability to evaluate vascular anatomy without contrast administration. In two single institutional studies of 2 and 4 patients with intravenous extension of Wilms tumor, MRI and sonography were noted to have comparable accuracy in detection of tumor thrombus [10,11]. However, the primary limitations of MRI are expense, longer duration of exams resulting in greater need for sedation/anesthesia, and poor sensitivity for lung metastases which is essential for staging of children with Wilms tumor.

Significant advances have been made in CT technology over the last decade. Multidetector CT technology allows acquisition of sub millimeter data sets. This allows for reformatting of images in any plane, with spatial resolution identical to the original scanning plane (isotropic imaging). Several recent studies in adults with renal cell carcinoma have shown that CT has high diagnostic accuracy in detection of tumor thrombus [12-14]. However, there is no information on the accuracy of current CT technology in detection of tumor thrombus in children with Wilms tumor. Central submission and archiving of CT scans in the ongoing renal tumors classification, banking, and biology study of the Children's Oncology Group gave us unprecedented opportunity to centrally review these exams. This made it feasible for us to evaluate the diagnostic performance of CT for detection of tumor thrombus in Wilms tumor using surgical findings at nephrectomy as the gold standard. The concordance rate between CT and surgical findings in this study was 82.7%. Awareness of

thrombus extension into the IVC or atrium is critical for planning the need for preoperative chemotherapy, the surgical approach, and the need for cardiopulmonary bypass. CT accurately identified the presence of cavoatrial thrombus in 35 out of 38 cases. In the three cases in which CT did not identify the cavoatrial thrombus, only one was identified by Doppler ultrasonography. In the cases where CT correctly identified the presence of tumor thrombus, it accurately predicted the level of tumor thrombus in 85.1% of cases. Review of all cases where an error in detection of tumor thrombus was made on CT images revealed that the most common cause of error was a large mass that caused distortion of normal anatomical planes. This was followed by cases with mass protruding at the hilum and cases with large hilar nodes that distorted adjacent vessels and limited evaluation of the renal vein at the hilum. These have been noted as limitations by other authors as well, irrespective of the imaging modality used [9]. Routine Doppler evaluation, performed in 108/173 cases in this study, identified only 3 additional cases of tumor thrombus, 2 in the renal vein and 1 in the IVC at the level of renal vein that were missed by CT. The location of the tumor thrombus in these cases would not have led to a change in the surgical approach. Based on these results we recommend that routine Doppler evaluation for tumor thrombus is not required in Wilms tumor cases where CT findings are unequivocal for presence/absence of tumor thrombus. However, we reinforce that sonography is the recommended first line imaging modality for the initial evaluation of a suspected abdominal mass in a child, irrespective of the organ of origin. Once a renal mass is identified at screening ultrasound, it is essential that the sonographer evaluate the status of the renal vein, and IVC using both gray scale and Doppler evaluation to determine if there is tumor thrombus as this affects surgical management. In North America, a CT or MRI of the abdomen/pelvis is essential for local staging of the Wilms tumor prior to surgery. We have shown that intravascular extension of Wilms tumor can be assessed at CT, so the interpreting radiologist should evaluate the status of the renal vein and IVC on CT. In this era of rising healthcare costs, an additional Doppler ultrasound after a staging CT has already been performed is not required on a routine basis, but can be limited to cases where the CT findings are equivocal.

We recognize that this study has several limitations. First, the CT scans were evaluated by two radiologists with expertise in pediatric oncologic imaging. We did not evaluate the accuracy of local interpretation of CT scans, as the interpreting radiologists are not blinded to the results of other imaging studies. Second, central review of Doppler sonography was not performed. However, Doppler sonography requires real time evaluation and is an operator dependent technique and central review of Doppler studies would have no added benefit. Third, 62 of the 173 cases reviewed underwent chemotherapy prior to surgical interpretation. The presence of tumor thrombus and its extent may have changed in the 6 weeks between the initial evaluation and the secondary nephrectomy. Interestingly, however, review of the pathology results (available in 28/30 cases with tumor thrombus in the secondary nephrectomy group) confirmed the presence of the tumor thrombus with post therapy changes in all 28 cases. In all of these cases the distal most extension of tumor thrombus, i.e. renal vein, IVC, or atrium, was unchanged post chemotherapy as compared to the CT findings at baseline evaluation. Also, to overcome this limitation we have evaluated the diagnostic performance of CT and Doppler separately for the primary and secondary nephrectomy groups. Fourth, as the scans submitted were from 177 different institutions, the scanning parameters, reconstructed slice thickness, and availability of multiplanar reconstructions was not uniform. Multiphase scans were submitted by some institutions, however the diagnostic performance of CT for detection of vascular invasion in this study is based on the review of the portal venous phase scans only. Routine performance of multiphase scans is not recommended to keep radiation exposure as low as reasonably achievable (ALARA). We believe that the diagnostic performance of CT hence calculated is reflective of the current CT technology as it is being practiced across several institutions in North America.

Conclusion

Contrast enhanced CT has high sensitivity and specificity for detection of cavoatrial tumor thrombus in Wilms tumor cases. Patients with Wilms tumor in whom CT fails to detect tumor thrombus are unlikely to have a tumor thrombus found at surgery that would change the surgical approach. Routine Doppler evaluation for tumor thrombus detection, after the patient has already undergone a staging CT, is not required in the preoperative evaluation of Wilms tumor.

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Table I

Demographics of the study cohort.

	Primary Nephrectomy	Secondary Nephrectomy
Age	Median 3 years (0-23 years)	Median 4 years (0-14 years)
Gender	54 male, 57 female	29 male, 33 female
Stage distribution		
Stage I	21	1
Stage II	24	2
Stage III	39	29
Stage IV	27	30

Table II

Diagnostic performance of CT and Doppler sonography in patients with primary nephrectomy.

	Computed Tomography		Doppler Sonography		
	Positive	Negative	Positive	Negative	Not performed
Tumor thrombus present (32)	21	11	11	13	8
Tumor thrombus absent (79)	12 *	67	2	45	32
Cavoatrial thrombus (13) **	11	2	7	3	3

* In the cases with false positive CT level of tumor thrombus was predicted as renal vein (n=7) and IVC (n=5).

** Cases with cavoatrial thrombus are a subset of all cases with tumor thrombus present.

Table III

Diagnostic performance of CT and Doppler sonography in patients with secondary nephrectomy.

	Computed Tomography		Doppler Sonography		
	Positive	Negative	Positive	Negative	Not performed
Tumor thrombus present (30)	26	4	12	6	12
Tumor thrombus absent (32)	3 *	29	0	19	13
Cavoatrial thrombus (25) **	24	1	11	5	9

* In the cases with false positive CT level of tumor thrombus was predicted as renal vein (n=1) and IVC (n=2).

** Cases with cavoatrial thrombus are a subset of all cases with tumor thrombus present.

Table IV

Prediction of level of tumor thrombus extension by CT in cases with primary nephrectomy (tumor thrombus was not detected preoperatively in 11 cases)

		Computed Tomography		
		Atrium	IVC	Renal vein
Surgery	Atrium	1		
	IVC		10	
	Renal vein		4	6

Table V

Prediction of level of tumor thrombus extension by CT in cases with secondary nephrectomy (tumor thrombus was not detected preoperatively in 4 cases)

		Computed Tomography		
		Atrium	IVC	Renal vein
Surgery	Atrium	5		
	IVC		17	2
	Renal vein		1	1