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Primary nephrectomy and intraoperative tumor spill: Report from the Children's Oncology Group (COG) renal tumors committee

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Abstract

Purpose—Initial Children's Oncology Group (COG) management for Wilms' tumor (WT) consists of primary nephroureterectomy with lymph node sampling. While this provides accurate staging to define further treatment, it may result in intraoperative spill (IOS), which is associated with higher recurrence rates and therefore requires more intensive therapy. The purpose of this study is to determine current rates and identify factors which may predispose a patient to IOS.

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Methods—The study population was drawn from the AREN03B2 renal tumor banking and classification study of the Children's Oncology Group. All children with a first time occurrence of a renal mass were eligible for the study. At the time of enrollment and prior to risk stratification, the institution is required to submit operative notes, pathology specimens, a chest computed tomography scan (CT), and a contrast-enhanced CT or magnetic resonance imaging (MRI) of the abdomen and pelvis for central imaging review. These data are then used to determine an initial risk classification and therapeutic protocol eligibility. Patients who had a unilateral nephroureterectomy for favorable histology WT underwent further review to assure data accuracy and to clarify details regarding the spill. Analyses were performed using chi square and logistic regression. Odds ratios (OR) are shown with 95% confidence intervals.

Results—There were 1,131 primary nephrectomies for unilateral WT with an IOS rate of 9.7% with an additional 1.8% having possible tumor spill during renal vein or IVC tumor thrombectomy. IOS correlated with diameter ($>12\text{cm}$, $p<0.0001$) and laterality (right, $p=0.0414$). Simple logistic regression indicated that IOS increased 2.7% [$p=0.0240$, OR 1.027 (1.004, 1.052)] with each 1 cm increase in diameter (3 – 21cm) and 4.7% [$p=0.0147$ OR 1.047 (1.009, 1.086)] with each 100 g increase in weight (80 – 1800 g). Multiple logistic regression indicated that laterality [right $p=0.048$, OR 1.46 (1.004, 2.110)] and weight ($p=0.03$, OR 1.039 (1.003, 1.075)) were predictive of IOS when diameter was included as a continuous variable. Diameter as a binary variable was highly prognostic of IOS ($p=0.0002$), while laterality and weight were not significant.

Conclusions—Intraoperative tumor spill occurs in about one out of every ten cases of primary nephroureterectomies for WT. Right-sided and larger tumors are at higher risk of IOS.

Keywords

Wilms' tumor; Nephroureterectomy; Rupture; Spill; Surgery

In children with suspected unilateral renal malignancy, Children's Oncology Group (COG) protocols recommend proceeding directly with surgery for primary nephroureterectomy with lymph node sampling if possible. The main rationale for this approach is that it provides adequate tissue for definitive diagnosis and accurate staging. In children with Stage I and II local disease, abdominal radiation is not needed, Doxorubicin is avoided, and in a small select group, chemotherapy is not required at all on a current therapeutic study. However, a known risk of primary nephrectomy is intraoperative tumor rupture or spill, which from here forward will be referred to as intraoperative spill (IOS). IOS increase the risk of local recurrence and may lead to added short- and long-term morbidity [1–4]. Criteria exist to help guide the operating surgeon on whether to attempt a primary nephrectomy or to perform a biopsy. However, a rigorous evaluation of factors that may predispose to IOS has not yet been performed. Since COG protocol AREN03B2: Renal Tumors Classification, Biology, and Banking Study opened in 2006, enrollment on a COG therapeutic renal tumor study has required submission of computed tomography scans, operative notes, and pathology specimens that are centrally reviewed in real time by study committee members. This assessment provides information to assign patients to the appropriate risk category. Central review provides detailed operative and tumor information such as adherence to surgical protocol, tumor size, weight, laterality, and intraoperative complications. This

extensive data source provides a comprehensive picture of the patient prior to and during initial surgery. The purpose of the current study was to determine the rate of IOS and to identify those pre-surgical factors that may predispose to IOS.

1. Materials and methods

The study population was drawn from the COG AREN03B2 renal tumor classification, biology and banking study. This report addresses the classification aim of AREN03B2. Patients were enrolled from 204 institutions over the time period of February 2006 to December 2010. All participating institutions had institutional review board approval of the study protocol. All children with a first time occurrence of a renal mass were eligible for the study. At the time of enrollment, the institution was required to submit the following for central imaging review: operative notes, pathology specimens, a chest computed tomography scan (CT), and abdomen/pelvis contrast-enhanced CT or magnetic resonance imaging (MRI). Central radiological review occurs first and assesses the presence of lung metastasis, liver metastasis, tumor size, and bilateral renal lesions. Pathology specimens are reviewed for histological diagnosis and assignment of a pathological Stage of I–III. Operative notes are reviewed for rationale for surgical approach, tumor extent, and protocol compliance. The surgeon combines the review of the operative reports with the radiological and pathological review to assign a local and overall disease stage. A pediatric oncologist then collates the data from the discipline reviews to determine an overall initial risk classification and therapeutic protocol eligibility.

Eligible patients with unilateral Wilms' tumor (WT) who underwent primary nephrectomy and had favorable histology among the first 2,000 patients enrolled on AREN03B2 were included in this analysis. To minimize confounding issues with biology, only favorable WT were included in analysis. Patients were classified as having IOS only if spill occurred from the primary tumor or renal vein. All other locations and types of tumor spill were excluded from this analysis. Tumor spill status was indeterminate for 65 patients and these patients were removed from further analysis, leaving 1131 patients in the cohort.

Rates of IOS from the primary tumor and the renal vein were calculated both separately and combined. A chi-square test was used to examine the relationship between IOS (positive vs. negative) with laterality (left vs. right) and maximum tumor diameter (<12 cm vs. ≥12 cm). Logistic regression models were fit to determine if maximum tumor diameter (continuous variable), tumor weight (continuous variable, as multiple of 100 g), and laterality, maximum diameter (as continuous variable and with 12 cm cut-off), and weight together were predictive of the occurrence of IOS. Exploratory simple logistic regression models were also fit to determine the maximum diameter cut-off at which the odds of IOS were maximized. p values less than 0.05 were considered statistically significant.

2. Results

The IOS rate due to primary tumor was 110/1131 (9.7%) with an additional 20/1131 (1.8%) occurring during renal vein thrombectomy. Both types were reported in 5/1131 (0.4%) patients. In total 135/1131 (11.9%) had IOS. Of note, there were 860 cases that were local Stage III only, and 108 of these were Stage III solely due to IOS.

Univariate analysis demonstrated a statistically significant association between IOS with maximum diameter ($p<0.0001$) and right-sided tumors ($p=0.0414$) (Table 1). Simple logistic regression indicated that IOS increased 2.7% [$p=0.0240$, OR 1.0240 (1.004, 1.052)] with each 1 cm increase in diameter (3–21 cm) (Table 2a) and 4.7% [$p=0.0147$, OR 1.047 (1.009, 1.086)] with each 100 g increase in weight (80–1800 g) (Table 2b).

Multiple logistic regression indicated that laterality [right $p=0.048$, OR 1.46 (1.004, 2.110)] and weight [$p=0.03$, OR 1.039 (1.003, 1.075)] were predictive of IOS when diameter was included as a continuous variable (Table 3a). The odds of IOS were OR 1.45 (1.004, 2.110) for patients with right as compared with left tumor. In this model, the risk of an IOS increased by 3.9% with each 100 g increase in weight. Diameter as a binary variable of 12 cm was highly prognostic of IOS ($p=0.0002$), while laterality and weight were not significant (Table 3b). The odds of IOS were 2.183 times greater for patients with maximum tumor diameter ≥ 12 cm as compared with <12 cm.

To determine what size tumor maximizes the risk of IOS, a simple logistic regression model was used which showed that 15 cm was the tumor with maximal risk of IOS at 2.606 (Table 4).

3. Discussion

Children with renal tumors with tumor spill have an increased risk of local recurrence rates and mortality [1–4]. Such contamination is referred to as “soilage” and may occur at different times: preoperative rupture (spontaneous or traumatic), biopsy (needle or open), or during surgery from either the tumor (rupture of capsule or removal of the tumor in more than one piece) or by transection of involved structures (lymph nodes, vein, or ureter). Earlier National Wilms’ Tumor Study Group (NWTSG) studies reported overall rates of soilage, but are bundled together to include preoperative and intraoperative biopsy as well as preoperative rupture and intraoperative spill. Therefore it is not possible to determine earlier rates for specific causes such as intraoperative spill. The current COG renal tumor studies have not made substantive changes to the overall approach of primary nephrectomy. And there are clear published criteria defining circumstances when it is more appropriate to do an upfront biopsy and prenephrectomy chemotherapy: (1) tumor thrombus above the level of the hepatic veins; (2) pulmonary compromise from a massive tumor or extensive pulmonary metastases; (3) resection requiring removal of contiguous structures (other than adrenal gland); or (4) surgeon’s judgment that attempting nephrectomy would result in significant morbidity, tumor spill, or residual tumor. Two important tumor characteristics that guide surgeon decision-making include size and location. To date, a comprehensive review of factors that may influence the risk of IOS has not been undertaken. The current study sought to determine contemporary rates and possible risk factors associated with IOS.

Two distinct sites of IOS were identified: the primary tumor and tumor thrombus spilling from veins. IOS were accounted for by spill from the primary tumor alone (9.7%), renal vein alone (1.8%), or both (0.4%). Altogether the overall rate of IOS was 11.9%. Direct comparisons to earlier NWTSG studies are not straightforward, as the rates of each specific type of soilage were not reported. However, the most recent completed study (NWTSG-5)

describes tumor spill occurring in 253 of 1305 children reviewed. Of these spills, intraoperative tumor spill was the most common type accounting for 139 (55%) of spills. Therefore the calculated IOS rate from NWTs-5 would have been 10.7% (139/1305) [5]. These IOS rates appear comparable. Whether this or any other IOS rate should be considered acceptable is a question that is not simple to answer. One change that was made between the two studies, however, was that all biopsies would be considered Stage III disease from the outset regardless of the indication or the manner by which this was done. Whether this led to some surgeons choosing to perform biopsy upfront or trying to perform surgery when they previously would have biopsied is not clear. However, if the former, those cases would have been excluded from our current analysis. And if the latter, this might account for the slightly higher IOS rate.

Tumor size was identified as an important risk factor for IOS. Earlier, NWTs-2 demonstrated that tumor size did not influence the outcome of the patient [2], but more recently in NWTs-4, a tumor diameter ≥ 10 cm was associated with an increased risk of complications [6]. A single institution study showed that tumor volume calculated by CT scan of greater than 1000 cc to be at higher risk of IOS [7]. This study showed that a linear relationship exists between weight and volume (data not shown). Based on our data, a 1000 cc tumor roughly correlates to a 1000 g nephrectomy specimen. It was interesting to note in this study that the risk of IOS tumor became significant at 12 cm and peaked at 15 cm. It is likely that it is this size range in which great care must be exercised during primary tumor resection. The implication is that size may be related to a more challenging operation; limited operative field, distorted normal anatomy, difficult dissection from surrounding structures, more difficult to handle the tumor, difficult isolation of renal vasculature, and thinner tumor capsule due to outgrowing blood supply.

Right-sided tumors were also identified as a risk factor for IOS. There are anatomic differences between the two sides which may explain this finding. The right kidney is in close proximity to the liver, which results in less space for dissection when compared to the left upper abdomen. Further, there are anatomic differences in the renal vasculature, which may make for more difficult dissection for right-sided lesion, especially if the tumor is obscuring visualization. There are more congenital anomalous variants of the right renal arteries [8,9], and veins [10] as compared to the left sided vessels and veins. Also, due to the close proximity of the right renal vein to the IVC, it is about half the length compared to the left renal vein. When these differences in vasculature are considered together, the risk of an inadvertent tumor spill is higher on the right [10,11].

Another important finding of this study was that out of 860 Stage III patients, 108 (12.6%) had tumor spill as the sole reason for the local disease Stage of III. Tumor rupture has been shown to significantly increase local relapse [RR 2.86 (1.33–6.17)] even when correcting for histology, age, and lymph node involvement. Relapses in WT are difficult to treat and survival drops from over 90% to as low as 43%[4]. Furthermore, Stage III therapy entails additional chemotherapy (doxorubicin) and radiation therapy. Both of these therapies are associated with late effects including secondary malignancy, pregnancy related complications, and impaired cardiac and thoracic function [12–14]. However, if these patients were given pre-nephrectomy therapy to reduce the size of the tumor and subsequent

risk of IOS, they still would receive doxorubicin and flank radiation, but the risk of IOS and therefore risk of local recurrence may be lower.

While this study has identified important risk factors for IOS, there are limitations to this review. This study does not assess judgment, skill level, or surgeon experience, all of which are factors that could potentially affect the risk of spill. Spill rates of individual surgeons were not assessed or compared. One method to reduce IOS is through prenephrectomy chemotherapy. This latter approach has long been used by the Société Internationale d'Oncologie Pédiatrique (SIOP). The published SIOP studies have reported a lower intraoperative tumor spill rate of 2.8–6%. It is believed that primary chemotherapy makes subsequent surgical extirpation easier due to significant tumor shrinkage and less vascularity, providing a firmer tumor to handle, and with less extrarenal extension [15–18]. There are arguments for and against the SIOP versus the COG initial therapies, however the COG Renal Tumors Committee feels that staging (i.e. lymph node status) and pathological data is critical to accurate determination of appropriate risk-based therapy. Therefore, prenephrectomy chemotherapy is not routinely recommended in COG therapeutic studies for unilateral Wilms' tumor.

In conclusion, this data suggests that IOS on COG renal tumor trials continues to occur in one of every ten cases whether if be from the tumor or from the renal vein. Further, surgeons must exercise caution when attempting to primarily resect right-sided and/or large (≥ 12 cm) renal tumors as each factor is associated with an increased risk for IOS. If multiple risk factors for spill are present it may analogous be to another higher risk group such as WT with intravascular tumor extension where preoperative chemotherapy significantly reduces surgical morbidity without sacrificing survival [19].

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Table 1

Cross-tabulation of intraoperative tumor spill with maximum diameter and tumor laterality.

	<u>Intraoperative tumor Rupture or spill</u>		p value*
	Negative	Positive	
Maximum diameter **			
<12 cm	592	54	<0.0001
12 cm	374	80	
Laterality			
Left	543	61	0.0414
Right	453	74	

* From a chi-square test.

** 31 patients were missing maximum diameter.

Table 2a

Logistic regression model for intraoperative tumor spill testing maximum tumor diameter.

Variable (N=1100)	DF	p-value	Odds Ratio *	95% CI on Odds Ratio
Maximum Diameter (Continuous)	1	0.0240	1.027	(1.004, 1.052)

Odds ratio per 1 cm increase in maximum diameter.

Table 2b

Logistic regression model for intraoperative tumor spill testing tumor weight.

Variable (N=1099)	DF	p-value	Odds ratio *	95% CI on odds ratio
Weight (Continuous)	1	0.0147	1.047	(1.009, 1.086)

* Odds ratio per 100 g increase in weight.

Table 3a

Logistic regression model for intraoperative tumor rupture testing tumor laterality, maximum diameter (Continuous), and weight (100 g).

Variable (N =1074)	DF	p-value	Odds Ratio	95% CI on odds ratio
Maximum diameter	1	0.1522	1.018	(0.994, 1.042)
Laterality (right vs. left [*])	1	0.0477	1.456	(1.004, 2.110)
Weight	1	0.0336	1.039	(1.003, 1.075)

* Indicates the reference level. The odds ratio is the increased odds of intraoperative tumor spill comparison to this reference level.

Table 3b

Logistic regression model for intraoperative tumor spill testing tumor laterality, maximum diameter (12 cm cutoff), and weight (100 g).

Variable (N =1074)	DF	p-value	Odds Ratio	95% CI on Odds Ratio
Maximum Diameter (12 cm vs. <12 cm *)	1	0.0002	2.183	(1.445, 3.300)
Laterality (right vs. left *)	1	0.0515	1.447	(0.998, 2.101)
Weight	1	0.3871	1.015	(0.981, 1.050)

* Indicates the reference level. The odds ratio is the increased odds of intraoperative tumor spill comparison to this reference level.

Table 4

Simple logistic regression model results for intraoperative tumor rupture with maximum tumor diameter different cut-offs.

Maximum diameter cut-off *	p-value	odds ratio	95% CI on odds ratio
3	0.8887	1.112	(0.253, 4.889)
4	0.2949	1.886	(0.575, 6.184)
5	0.1876	2.000	(0.713, 5.607)
6	0.3400	1.441	(0.681, 3.049)
7	0.3053	1.370	(0.750, 2.502)
8	0.0102	2.126	(1.196, 3.781)
9	0.0020	2.152	(1.324, 3.500)
10	0.0002	2.248	(1.461, 3.459)
11	<0.0001	2.161	(1.472, 3.172)
12	<0.0001	2.345	(1.622, 3.390)
13	<0.0001	2.251	(1.561, 3.246)
14	<0.0001	2.569	(1.762, 3.745)
15	<0.0001	2.606	(1.737, 3.910)
16	<0.0001	2.582	(1.603, 4.159)
17	0.0030	2.290	(1.326, 3.957)
18	0.0839	1.830	(0.922, 3.633)
19	0.0257	2.412	(1.113, 5.230)
20	0.0756	2.337	(1.113, 5.230)
21	0.2414	1.951	(0.638, 5.967)
22	0.3582	1.821	(0.507, 6.537)
23	0.9777	1.030	(0.126, 8.439)

Boldface indicates statistical significance.

* The odds ratio is the increased odds of intraoperative tumor spill in the group of patients with maximum tumor diameter cut-off in comparison to the group with maximum tumor diameter < cut-off.