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Incidence and management of pleural effusions in patients with Wilms tumor: A Pediatric Surgical Oncology Research Collaborative study

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Abbreviations: FHWT, favorable histology Wilms tumor; PSORC, Pediatric Surgical Oncology Research Collaborative; WT, Wilms tumor.

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Abstract

Wilms tumor (WT) is the most common renal malignancy in children. Children with favorable histology WT achieve survival rates of over 90%. Twelve percent of patients present with metastatic disease, most commonly to the lungs. The presence of a pleural effusion at the time of diagnosis of WT may be noted on staging imaging; however, minimal data exist regarding the significance and prognostic importance of this finding. The objectives of our study are to identify the incidence of pleural effusions in patients with WT, and to determine the potential impact on oncologic outcomes. A multi-institutional retrospective review was performed from January 2009 to December 2019, including children with WT and a pleural effusion on diagnostic imaging treated at Pediatric Surgical Oncology Research Collaborative (PSORC) participating institutions. Of 1259 children with a new WT diagnosis, 94 (7.5%) had a pleural effusion. Patients with a pleural effusion were older than those without (median 4.3 vs 3.5 years; $P = .004$), and advanced stages were more common (local stage III 85.9% vs 51.9%; $P < .0001$). Only 14 patients underwent a thoracentesis for fluid evaluation; 3 had cytopathologic evidence of malignant cells. Event-free and overall survival of all children with WT and pleural effusions was 86.2% and 91.5%, respectively. The rate and significance of malignant cells present in pleural fluid is unknown due to low incidence of cytopathologic analysis in our cohort; therefore, the presence of an effusion does not appear to necessitate a change in therapy. Excellent survival can be expected with current stage-specific treatment regimens.

KEYWORDS
malignant effusion, pediatric renal tumor, pleural effusion, Wilms tumor

What's new?

Some Wilms tumor (WT) patients have fluid around the lungs, or pleural effusion, at diagnosis, but its effect on outcomes is not well known. Here, the authors evaluated data from 1259 children with WT from 21 hospitals in North America. Pleural effusion was present in 7.5% of patients, higher than the previously reported rate of 4.3%, and management was not standardized among different hospitals. The authors also report that patients with pleural effusion were more likely to present with advanced stage tumors and to have their preoperative tumor rupture, but their outcomes were not significantly worse than other patients.

1 | INTRODUCTION

Wilms tumor (WT) is the most common primary renal tumor and the second most common intra-abdominal tumor in children.[1,2] Advancements in therapy have resulted in survival rates over 90% for children with favorable histology Wilms tumor (FHWT).[3] Treatment in North America typically includes upfront surgical resection followed by adjuvant chemotherapy, with or without the addition of radiotherapy. Management is dependent upon patient and tumor characteristics, including age at diagnosis, initial tumor size, tumor weight, margin status, histologic factors, genetic and chromosomal abnormalities, lymph node involvement, the presence of tumor rupture or spill and the presence of metastatic disease. Metastatic disease is evident in 12% of patients with WT at diagnosis, with the majority of distant disease

found in the lung parenchyma (80%); less commonly in the liver (15%).[4-6]

The presence of a pleural effusion at the time of diagnosis has been previously reported in approximately 4% of patients with WT.[7] Given the rarity of this occurrence, its significance and prognostic implications remain unclear, leading to an inconsistent approach to patients with WT and pleural effusions, as some patients may be observed, while others may undergo a thoracentesis for cytopathologic analysis of the fluid.

Pleural metastases have been identified in a subset of patients with WT and pleural effusions, though the literature regarding malignant pleural effusions in the setting of WT is currently limited to case reports.[8-11] Malignant pleural effusions in WT have been successfully managed with either chemotherapy alone or chemotherapy with radiotherapy, resulting in resolution of the effusion without recurrence. These reports raise the question of whether pleural effusions in patients with WT should undergo cytologic evaluation, and how confirmed malignant effusions are optimally managed. The objectives of our study were to describe the incidence of pleural effusions in the setting of WT, and to identify the factors that indicate a malignant effusion. We hypothesize that pleural effusions are present more commonly than previously reported and that larger effusions may have oncologic significance.

2 | MATERIALS AND METHODS

2.1 | Data source

Patients from 21 hospitals participating in the Pediatric Surgical Oncology Research Collaborative (PSORC) were included in this retrospective study. PSORC is a multi-institutional consortium of North American pediatric surgeons dedicated to advancing the surgical care of children with cancer. Study data were collected and managed using REDCap electronic data capture tools hosted at Cincinnati Children's Hospital Medical Center.[12]

2.2 | Study population

Patients who were 0 to 18 years of age with a new diagnosis of WT between January 2009 and December 2019 and who had available diagnostic computed tomography (CT) of the chest and abdomen at initial staging were included in our study. Patients older than 18 years of age and those without CT imaging of the chest and abdomen at initial staging were excluded from the study. All participating institutions provided retrospectively obtained data on the total number of patients with WT, the presence of a pleural effusion on initial diagnostic imaging as interpreted by the radiologist at the time of the scan, and the management of the pleural effusion when present. Additionally, participating institutions provided supplementary data on patient demographics, age at diagnosis, tumor size, weight, laterality, local and overall staging, histologic and chromosomal abnormalities, presence and location of metastatic disease, chemotherapy regimen, radiotherapy and tumor recurrence for all patients with a pleural effusion. Supplementary data for patients without a pleural effusion were only provided by some of the participating institutions. Chemotherapy regimens were used based on the Children's Oncology Group (COG) recommendations for tumor stage and tumor genetics. However, given the participation of numerous institutions across the United States and Canada, institutional variation in management may have been a factor.

2.3 | Statistical analysis

Results are reported as proportions for categorical variables and medians with interquartile ranges for quantitative variables. Univariate comparisons between those with and without pleural effusions were completed using nonparametric methods: χ^2 or Fisher's exact tests for categorical variables and Wilcoxon rank sum tests for quantitative variables. Event-free and overall survival were summarized using the Kaplan-Meier method. All *P*-values were two-sided and those <.05 were considered statistically significant. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

Thousand two hundred and fifty-nine children with a new diagnosis of WT were evaluated, and ninety-four (7.5%) had a pleural effusion on initial diagnostic CT imaging (Figure 1). Of the children presenting with a pleural effusion, 79 also had a chest X-ray, only 29 (36.7%) of which demonstrated a pleural effusion. Effusions were identified

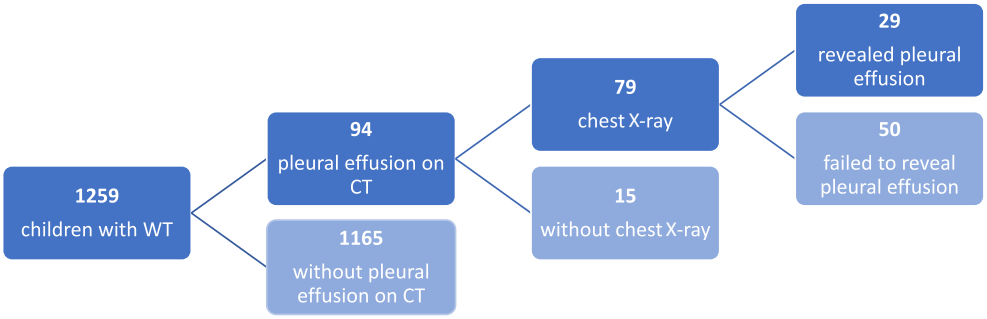

FIGURE 1 Flow diagram of children with Wilms tumor who presented with a pleural effusion on initial diagnostic CT and chest X-ray [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Demographic comparison of patients with and without a pleural effusion on presentation

	Pleural effusion	No pleural effusion	*P*-value
Number of patients	94	612[a]	
Age at diagnosis, months median (range)	52 (3-216)	42 (<1-269)	.0042
Histology			.15
Favorable	74 (78.7%)	518 (84.7%)	
Anaplastic/unfavorable	14 (14.9%)	62 (10.1%)	
Unknown	6 (6.4%)	32 (5.2%)	
Local stage			<.0001
Stage I	4 (4.3%)	116 (19.0%)	
Stage II	8 (8.4%)	164 (26.8%)	
Stage III	78 (83.0%)	316 (51.6%)	
Unknown	4 (4.3)	16 (2.6%)	
Overall stage			<.0001
Stage I	3 (3.2%)	104 (17.0%)	
Stage II	7 (7.5%)	134 (21.9%)	
Stage III	41 (43.6%)	163 (26.6%)	
Stage IV	36 (38.3%)	156 (25.5%)	
Stage V	5 (5.3%)	53 (8.7%)	
Unknown	2 (2.1%)	2 (0.3%)	
Tumor size, cm; median (range)	11.5 (1.2-25)	11.1 (1.3-28)	.76
Preoperative tumor rupture	34 (36.2%)	55 (9.0%)	<.0001

[a]Statistics for patients without a pleural effusion based on 612 (out of 1165) patients. *P*-values result from χ^2 or Fisher's exact tests for categorical variables and Wilcoxon rank sum tests for quantitative variables. Supplementary data on patients without pleural effusions only provided by some participating institutions.

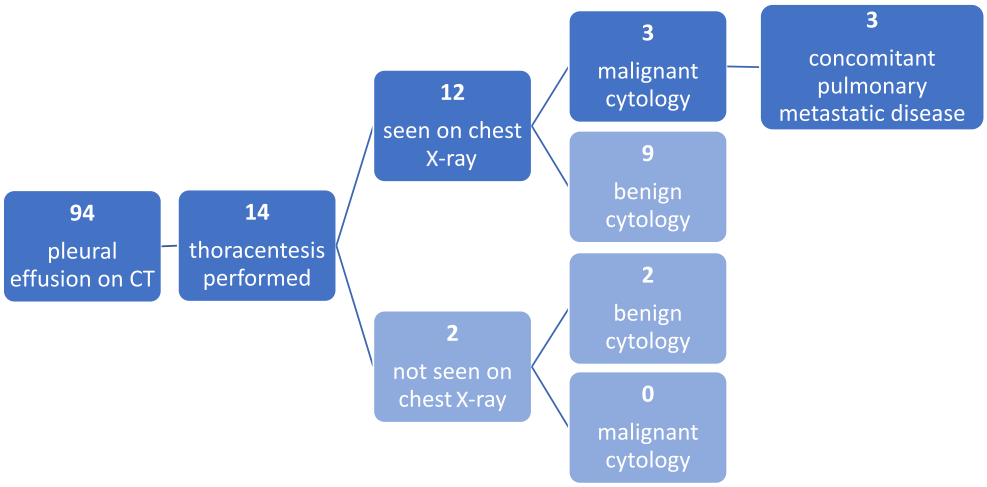

FIGURE 2 Flow diagram of children with Wilms tumor who underwent a thoracentesis with the presence of malignant cytology [Color figure can be viewed at wileyonlinelibrary.com]

ipsilateral to the tumor in 68.5% of patients and bilateral in 27.2% of patients.

Compared to children without an effusion, patients presenting with an effusion were significantly older (median age 4.3 years [0.3-18.0] vs 3.5 years [0.1-22.4]; $P = .004$), more likely to present with advanced staged tumors (local stage III 83.0% vs 51.6%; $P < .0001$; overall stage III 43.6% vs 26.6%; $P < .0001$; overall stage IV 38.3% vs 25.5%; $P < .0001$) and to have preoperative tumor rupture (36.2% vs 9.0%; $P < .0001$; Table 1). There were no significant differences seen in biological sex (female 55.3% vs 57.9%), race, histology (FHWT 83.3% vs 89.4%) or presence of loss of heterozygosity at 1p/16q (LOH) or 1q gain (all $P > .05$).

Of the 94 patients with an effusion, only 14 patients (14.9%) underwent diagnostic thoracentesis, 12 of whom had effusions large enough to be seen on chest X-ray (Figure 2). It is unknown if these patients had symptoms related to the effusion. From the sampled effusions, only three had cytopathologic evidence of malignant cells. All three of these patients presented with pleural effusions large

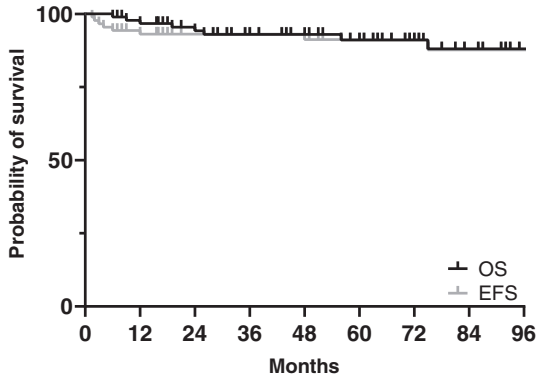

FIGURE 3 Kaplan-Meier survival curves for patients with a pleural effusion

TABLE 2 Chemotherapy regimens for patients with pleural effusion diagnosed on presentation

Regimen	N	%
DD-4A [102] VCR, dactinomycin, doxorubicin × 24 weeks; baseline nephrectomy or biopsy with subsequent nephrectomy	62	66.0
EE-4A [102] VCR, dactinomycin × 18 weeks post-nephrectomy	6	6.4
I [154] VCR, doxorubicin, cyclophosphamide, etoposide × 24 weeks post-nephrectomy	1	1.1
M [223] VCR, dactinomycin, doxorubicin, cyclophosphamide and etoposide with subsequent radiation therapy	7	7.4
UH1 [224] VCR, doxorubicin, cyclophosphamide, carboplatin and etoposide × 30 weeks with radiation therapy	8	8.5
UH2 [224] VCR, doxorubicin, cyclophosphamide, carboplatin, etoposide, vincristine and irinotecan × 36 weeks with radiation therapy	2	2.1
Other regimen	8	8.5

enough to be seen on chest X-ray and had pulmonary parenchymal metastatic disease at the time of diagnosis. Thirty patients (31.9%) with a pleural effusion received chest radiotherapy as part of their therapeutic course, 29 of whom had pulmonary or mediastinal metastases. The single patient without pulmonary parenchymal metastatic disease who received chest radiotherapy presented with a local stage III (preoperative tumor rupture), overall stage IV (liver metastases) FH tumor, 1q gain and LOH 1p and 16q and bilateral pleural effusions on initial CT that were not sampled. This patient received radiotherapy to the chest, abdomen and flank, and remained free of disease after 60 months of follow-up. Sixty-four patients (68.1%) with a pleural effusion did not receive chest radiotherapy, 59 (62.8%) of which had no associated pulmonary disease at the time of diagnosis. Only three patients (5.1%) with a pleural effusion and no history of pulmonary disease later relapsed with thoracic disease. All three had FHWT, none had their pleural effusions sampled, and only one patient obtained a chest X-ray at initial diagnosis, which did not appreciate an effusion. Event-free and overall survival in the cohort with pleural effusions was 86.2% and 91.5%, respectively, at a median follow-up of 56 months (range 1-219) (Figure 3).

The most common chemotherapy regimen given to WT patients with a pleural effusion was DD-4A (66.0%) (Table 2). For the three patients with confirmed cytopathologic evidence of a malignant effusion, three different regimens were utilized (DDA-4, I and M). Two patients were female, and two patients had anaplastic histology. All patients had local stage III disease without evidence of preoperative rupture and overall stage IV disease with metastatic disease to the lungs on presentation. Age at diagnosis was 2.2, 6.9 and 18 years. All three patients received chest and flank radiotherapy. All developed recurrent disease, one patient with new metastatic disease to the bone and brain (deceased) and two patients with recurrent pulmonary disease (alive at last follow-up at 23 and 95 months from initial diagnosis).

4 | DISCUSSION

Limited data exist regarding the significance and prognostic indications of pleural effusions in patients with WT. This cohort of 1259 patients represents a large analysis of 21 children's hospitals in North America investigating the incidence of pleural effusions in WT. In this multi-institutional cohort, we identified pleural effusions in 7.5% of patients, which is higher than the previously reported rate of 4.3% in a similar retrospective study of 233 patients.[7] As described in the prior report, CT was significantly more sensitive at identifying pleural effusions, as chest X-ray only revealed 36.7% of the pleural effusions seen on CT.[7]

We demonstrated that the presence of a pleural effusion at the time of WT diagnosis is more frequently seen with older patients, advanced stage disease, and in the setting of preoperative tumor rupture. These characteristics are also associated with an increased risk of relapse and mortality.[13-16] Despite patients with pleural effusions having these worse prognostic features, their outcomes (EFS and OS) in this cohort were not different from those patients without effusions. The etiology of pleural effusions in patients with WT is unknown but could be due to various mechanisms. A reactive transudative effusion can develop from irritation of the diaphragm from the primary tumor, diffusion of ascites from the abdominal cavity or low oncotic pressures due to hypoalbuminemia, though most patients with WT are not significantly malnourished.[8] A malignant exudative effusion can develop due to inflammation and increased capillary permeability associated with tumor in the chest, thereby increasing pleural fluid production and/or lymphatic blockage, though extensive thoracic tumor burden is also uncommon in patients with WT.[17] In patients with a reactive transudative effusion, the effusion would be expected to resolve postnephrectomy, while patients with a malignant exudative effusion require systemic therapy aimed at treating underlying pulmonary or pleural metastases. In our cohort, all three patients diagnosed with a malignant effusion had concomitant pulmonary metastases. Furthermore, all three patients had pleural effusions large enough

to be detected on chest X-ray. The question of whether larger effusions have a higher likelihood of harboring malignant cells, however, cannot be clearly determined from our dataset. Practice patterns from the participating institutions seem to favor sampling of larger effusions, perhaps due to symptoms, as 12 of the 14 sampled pleural effusions were visualized on chest X-ray.

The added benefit of chest radiotherapy in WT patients with pleural effusions in the absence of known thoracic metastatic disease remains unclear, given a rarity of pleural effusions that were cytopathologically evaluated in our cohort. Our cohort consisted of three patients with pleural effusions at initial diagnosis without any associated pulmonary disease who later relapsed with pulmonary disease. All patients had FHWT with ages ranging from 5 to 73 months. Unfortunately, none underwent thoracentesis and only one patient had a chest X-ray at the time of diagnosis, which did not detect the pleural effusion, indicating a smaller size of the effusion. Existing literature on the management of WT patients with known malignant effusions without concomitant metastatic pulmonary disease is limited to case reports. Patients with resolution of pleural effusions following treatment with either systemic chemotherapy alone or systemic chemotherapy in combination with chest radiation both had favorable outcomes, with no recurrence of disease after years of follow-up.[8-10] The added benefit of chest radiotherapy is unclear, whereas it may add significant morbidity, given that approximately 60% of pediatric cancer survivors suffer from chronic health issues as young adults.[3] Specifically, chest irradiation can result in restrictive spinal growth, scoliosis, cardiomyopathy, interstitial pneumonitis, restrictive lung disease and secondary malignancies, including a 30% risk of female breast cancer by the age of 50 years.[3,18-24] The substantial potential morbidity of these additional therapies obligates physicians to be more directive in their prescription, with cytology of pleural effusions guiding such decisions.

By pooling data from multiple institutions participating in PSORC, a larger and more diverse cohort of patients was evaluated. However, the implications of our study remain limited. Due to the retrospective nature of the study, there is a risk for inherent biases, including selection bias, as the patient outcomes are already known, as well as reporting biases, with multiple institutions contributing a large amount of data that was collected from a period that spanned many years. Furthermore, a relatively low incidence of pleural effusions underwent cytopathologic evaluation. Thus, we were unable to determine the utility of thoracentesis or make strong recommendations on the management of patients with WT who present with suspected malignant pleural effusion.

Thoracentesis may be beneficial in the setting of large, symptomatic or recurrent effusions, or when there is diagnostic utility for suspected metastatic disease. Unfortunately, we did not have knowledge of symptoms in the setting of pleural effusions or indications for why thoracentesis was performed in this retrospective study. Although pleural effusions are not currently a component of the COG staging for WT, we have found them to be a marker of more advanced stage disease. Thoracentesis at the time of surgical resection or central line placement may be considered to better understand the true incidence of malignant pleural effusions and how that may impact therapy and patient outcomes. However, the excellent outcomes we report despite the presence of an effusion need to be considered against the morbidity of an additional invasive procedure, therefore definitive recommendations to sample pleural effusions cannot be made based upon this review. Clinical judgment should dictate the need for thoracentesis in specific scenarios, such as the presence of symptoms, a large effusion visible by chest X-ray, a persistent effusion following initial therapy or if the cytology would result in treatment modification.

Given the low incidence of known malignant pleural effusions, there is currently no evidence to support a change in the management of children with WT who present with suspected benign pleural effusions. Furthermore, excellent survival can be expected with current stage-specific WT treatment regimens. We believe consideration should be given to thoracentesis for select indications at the time of initial intervention for WT, specifically if the results of the procedure would potentially modify therapy, but routine thoracentesis for all patients with WT and a pleural effusion is not currently recommended.

AUTHOR CONTRIBUTIONS

Conceptualization: Ameer Al-Hadidi and Jennifer H. Aldrink; *Methodology*: Ameer Al-Hadidi, Joseph Stanek, Bindi Naik-Mathuria, David H. Rothstein, Jennifer H. Aldrink; *Investigation*: Ameer Al-Hadidi, Hannah N. Rinehardt, Pattamon Sutthatarn, Lindsay J. Talbot, Richard Whitlock, Sienna Condon, Alan F. Utria, Stephanie Y. Chen, Shannon Wong-Michalak, Scott S. Short, Rebecka L. Meyers, Michael E. Johnston II, Tiffany Zens, Kristen Calabro, Hannah Callas, Katlyn McKay, Sarah Jane Commander, Sarah B. Lund, Jacob Davidson, Janel Dhooma, John P. Marquart, Haley Gainer, Lauren Maloney, Stephani Radu, Pei En Kwok, Nathan Rubalcava, Thomas Diehl, Valerie Polcz; *Writing - Original Draft*: Ameer Al-Hadidi, Joseph Stanek, Jennifer H. Aldrink; *Writing - Review & Editing*: Marcus M. Malek, Andrew J. Murphy, Bindi Naik-Mathuria, David H. Rothstein, Eugene S. Kim, Zachary J. Kastenberg, Roshni Dasgupta, Nelson Piché, Timothy B. Lautz, Harold N. Lovvorn, 3rd, Elisabeth T. Tracy, Stephanie F. Polites, Natashia M. Seemann, Dave R. Lal, Barrie S. Rich, Richard D. Glick, Elizabeth A. Fialkowski, Rodrigo L. P. Romao, Peter F. Ehrlich, Erika Newman, Hau D. Le, Robin T. Petroze, Jennifer H. Aldrink; *Supervision*: Jennifer H. Aldrink. The work reported in the article has been performed by the authors, unless clearly specified in the text.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this work are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Central Institutional Review Board (IRB) approval was obtained at Cincinnati Children's Hospital Medical Center (IRB#2020-0488) and each institution obtained IRB approval, either individually or through reliance on the central IRB. The need to obtain consent for collecting,

analyzing and publication of the retrospectively obtained and anonymized data for this non-interventional study was waived.

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