

## ORIGINAL ARTICLE

# The Relationship Between the Site of Metastases and Outcome in Children With Stage IV Wilms Tumor: Data From 3 European Pediatric Cancer Institutions

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**Summary:** The aim of this study was to analyze in detail the site of metastasis of stage 4 Wilms tumor (WT) and its correlation with outcome. The databases from 3 major European pediatric cancer institutions were screened for children with WT between 1994 and 2011. Of 208 children identified, 31 (14.9%) had metastases at diagnosis. The lung was affected in 29 children (93.5%) and the liver in 6 children (19.4%). Twenty-seven children (87.1%) had metastases isolated to 1 organ, with the lung being the most common site (80.7%). Five-year overall survival was significantly better in those children with distant disease in either lung or liver (95.8%) compared with those affected in both lung and liver (57.1%,  $P = 0.028$ ). Further, prognostic markers were the response of metastases to preoperative chemotherapy ( $P = 0.0138$ ), high-risk histology ( $P = 0.024$ ), and local stage ( $P = 0.026$ ). Five-year overall survival was 82.1% and 5-year event-free survival was 67.9%. The overall follow-up time was 74.1 and 87.2 (2 to 151) months among survivors, and the treatment-related complication rate was 16.7%. In conclusion, in our series of stage 4 WT, prognosis was excellent if histology was favorable, metastatic disease was isolated to either lungs or liver, and if metastases responded to preoperative chemotherapy.

**Key Words:** metastases, pediatric cancer, risk stratification, survival, Wilms tumor

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Wilms tumor (WT) is the most common renal malignancy in childhood and the second most frequent intra-abdominal pediatric cancer after neuroblastoma.<sup>1</sup> Many recent advances in clinical care and the biology of this tumor

have pushed the overall survival (OS) to 90%. Naturally, for children with distant metastases the OS is lower.<sup>1</sup>

Little is known on metastatic disease in stage 4 WT and its implication on therapy and outcome.<sup>2,3</sup> The lungs have long been recognized as a common site of distant tumor spread in stage 4 WT and several recent studies focus on this entity.<sup>1,2</sup> To our knowledge, no complete description of the metastatic profile of stage 4 WT at diagnosis exists at present. Therefore, in this study we reviewed children treated at 3 European pediatric cancer institutions for WT regarding their metastatic profile at diagnosis and its implication on long-term outcome.

## METHODS AND PATIENTS

### Patients

A retrospective analysis of the WT databases at the following 3 institutions was carried out: Hannover Medical School, Hannover (Germany); Dr. von Hauner Children's Hospital, Munich (Germany); and Virgen del Rocío Children's Hospital, Seville (Spain). Inclusion criteria were metastatic disease at diagnosis. Consequently, children with lower stage tumors who relapsed with metastatic disease were excluded. Additional exclusion criteria were other renal tumor entities like clear cell sarcoma, rhabdoid tumor, or renal cell carcinoma.

### Treatment

Staging criteria for WT was based on an upfront chemotherapy-based system developed by the International Society of Pediatric Oncology (SIOP). Treatment was according to SIOP protocols 93-01 and 2001 depending on the time of diagnosis.<sup>2</sup> These 2 treatment protocols were similar with the exception of the use of cyclophosphamide in SIOP 2001 instead of ifosfamide in SIOP 93-01. Radiologic treatment response of metastases was classified as either complete (disappearance), partial (regression of >50% of size/number), poor response (or stable disease, <50% regression of size/number), or progressive disease (increase in size/number). Persistent metastatic lesions after preoperative chemotherapy were considered for treatment with surgery, radiation, or both. Those children who underwent adjuvant radiation of pulmonary lesions, dose consisted of 15 Gy to both lungs. Surgery for metastatic disease was carried out shortly after removal of the primary tumor. The choice of surgical approach was due to the preference of the single institutions. After achieving local control of primary and

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metastatic disease, adjuvant chemotherapy followed according to histologic risk type.

**Statistical Analysis**

Survival and time-to-event analyses were performed using the Kaplan-Meier method. The log rank (Mantel-Cox) test was used to test differences between survival curves. When comparing 2 survival curves, additional hazard ratio with 95% confidence interval was calculated. Aggregated data are represented using the usual descriptive means. Additional statistical significance of differences between groups was determined by the 2-tailed Student *t* test for scale and the  $\chi^2$  test and Fisher exact test for dichotomous and nominal variables. In the latter case, odds ratios and 95% confidence intervals are given. All statistical analysis was carried out with the GraphPad Prism Biostatistics Software (La Jolla, CA). All reported *P*-values are 2-sided. In all tests, differences were considered significant at *P* < 0.05.

**RESULTS**

For the time period from 1994 to 2011, a total of 208 children with WT were identified (Tables 1, 2). Of these, 31 children (14.9%) initially presented with metastatic disease (Table 2). Mean age at diagnosis was 64.8 months (range, < 1 to 203). Seventeen children (54.8%) were males, and 14 (45.2%) were females (male to female ratio 1.2:1). Twelve patients (38.7%) had unilateral WT on the left, 17 (54.8%) had unilateral WT on the right, and 2 (6.5%) had bilateral disease (Table 1).

**Metastatic Profile and Treatment Response**

The lungs were the most common metastatic site in 29 children (93.5%), and 25 children (80.6%) had metastatic disease isolated to the lungs (Table 1). Of the children with pulmonary metastatic disease, the lung parenchyma was infiltrated in 28 children (96.6%). One child (3.4%) had an isolated malignant pleural effusion but otherwise clear lungs on computed tomography (CT) scan.

**TABLE 1. Patient Population and Pertinent Data**

Primary Tumor	Total (n [%])	Metastatic Profile and Treatment	Total (n [%])	Postoperative Events	Total (n [%])
General		Lungs or associated	29 (93.5)	Postoperative chemotherapy	31 (100)
Age at diagnosis (mo, range)	64.8 (< 1-203)	Isolated lungs	25 (80.6)		
Male	17 (54.8)	Lung parenchyma	28 (96.6)	Radiation (total)	20 (64.5)
Female	14 (45.2)	Pleura	2 (6.9)	Chest	9 (45.0)
Male to female ratio	1.2:1	Pleural effusion	1 (3.4)	Abdomen/tumor bed	15 (75.0)
				Both	4 (20.0)
Localization		Liver	6 (19.4)	Recurrence	7 (22.6)
Left	12 (38.7)	Isolated liver	2 (33.3)	Local	1 (14.3)
Right	17 (54.8)	Liver and lungs	3 (50.0)	Distant	6 (85.7)
Bilateral	2 (6.5)	Liver, lungs and ribs	1 (16.7)		
Treatment of primary tumor		Surgery (for primary metastasis or	10 (32.3)*	Treatment for recurrent disease	
Preoperative chemotherapy	31 (100)	Thoracoscopy	1 (10.0)	Local reexcision	1 (3.2)
Post-CTX resection of primary tumor	31 (100)	Thoracotomy/sternotomy	7 (70.0)*	CTX (high-risk/rescue protocol)	7 (22.6)
		Liver resection	2 (20.0)	Radiation	7 (22.6)
Local stage				Metastasectomy	4 (12.9)†
I	11 (35.5)	Radiation (to primary metastases)	12 (38.7)‡	Autologous stem cell transplant	1 (3.2)
II	1 (3.2)	Liver	0 (0)		
III	19 (61.3)	Lungs	8 (66.6)		
		Radiation to lung and surgery	4 (33.3)		
Lymph nodes at surgery		Histology		Long-term complications	4 (16.7)
Negative	13 (41.9)	Complete necrosis	4 (12.9)	Renal insufficiency and scoliosis	1 (4.2)
Positive	10 (32.2)	Regressive	7 (22.6)	Cardiac arrhythmia	1 (4.2)
Not sampled/no information	8 (25.8)	Blastemal	12 (38.7)	Cardiac insufficiency	1 (4.2)
		Epithelial	3 (9.7)	GI complaints	1 (4.2)
Histologic risk stratification		Mixed	5 (16.1)		
Low risk	4 (12.9)	Diffuse anaplasia	6 (19.4)	Overall salvage rate	3 (42.9)
Intermediate risk§	15 (48.4)				
High risk	12 (38.7)				

\*One child had infectious pulmonary nodules.  
 †One child had infectious pulmonary nodules.  
 ‡One child did not have surgery or radiation.  
 §Three (9.7%) had blastemal types in 93-01.  
 CTX indicates chemotherapy; GI, gastrointestinal.

**TABLE 2.** Five-year OS and 5-year EFS

Survival	Total
Total number of WT	208
Stage 4 disease	31
% Stage 4 from all	14.9
5-y OS (%)	82.1
5-y EFS	67.9
Deaths	7 (22.5%)*

Five-year OS and 5-year EFS are shown as percent value for all children. \*Of note, 2 children died of disease progression shortly after completing the 5-year follow-up (61 and 68 mo) and are listed separately. EFS indicates event-free survival; OS, overall survival; WT, Wilms tumor.

Overall, 6 children (19.4%) presented with metastatic disease in the liver. Three of these patients (50.0%) had additional metastases in the lung, and 1 (16.7%) had pulmonary lesions and bone metastases (ribs). The only organ other than the lung to show isolated metastatic disease was the liver, and this was the case in 2 children (6.5% of all patients).

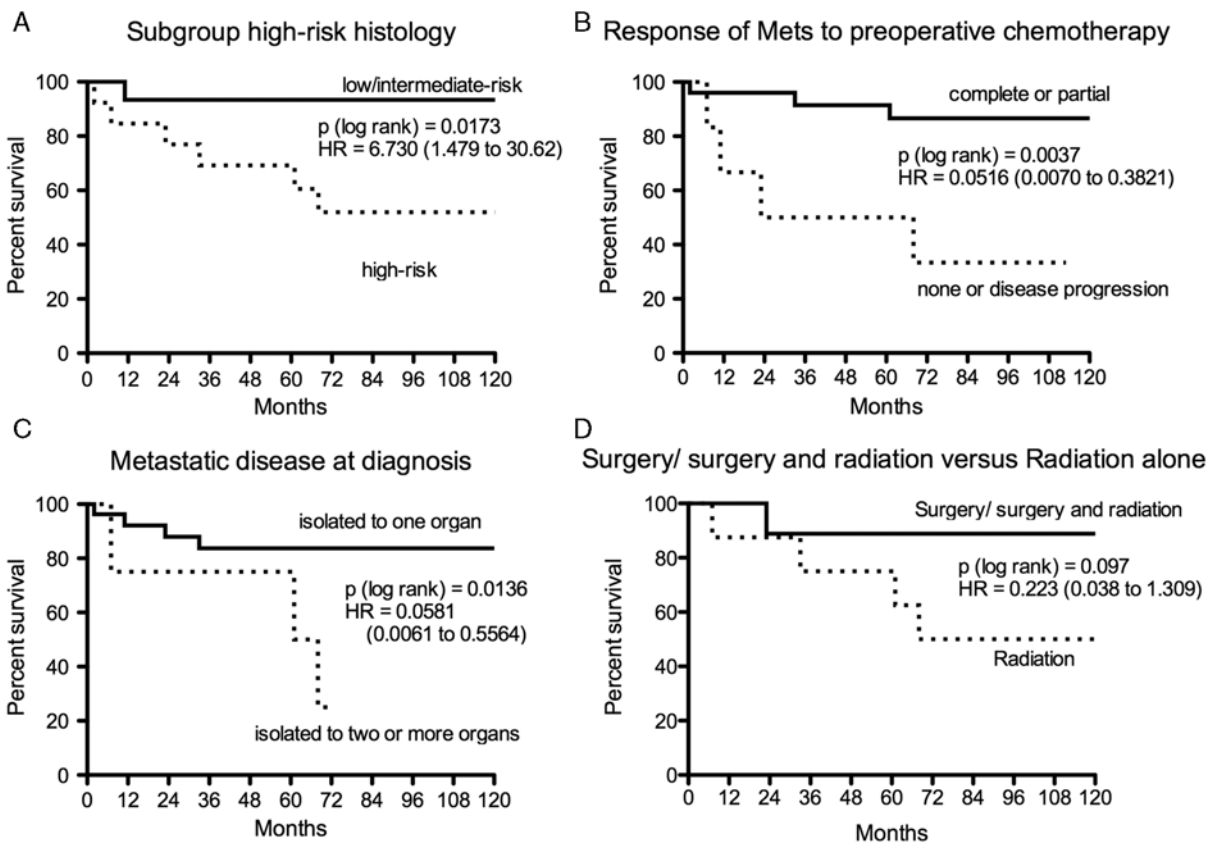
After completion of preoperative chemotherapy and before resection of the primary tumor, all children were restaged with CT scan of the chest and abdomen. Overall, 23 children (74.2%) showed partial response and 2 children

(6.5%) showed complete response of metastases. Six children (19.4%) showed no response. Of these, 3 children (9.6%) showed stable metastatic disease, and 3 (9.6%) had progressive metastatic disease.

The primary tumor of 28 children (90.3%) responded to preoperative chemotherapy, 3 (9.7%) had no response (Supplemental Table 1, <http://links.lww.com/JPHO/A37>). Twenty-four children (77.4%) showed both a response of primary tumor and metastatic disease. In 4 children (12.9%), in which response of primary tumor was found, did not have a response of metastatic disease. Two children (6.5%) showed a response of metastatic disease, but not of primary tumor. One child had no response to preoperative chemotherapy in either. Therefore, response of metastatic disease to preoperative chemotherapy was more likely if the primary tumor responded, but the difference was not significant ( $P = 0.422$ ; Supplemental Table 1, <http://links.lww.com/JPHO/A37>). There was no difference found in this respect for liver versus lung metastasis (data not shown).

**Treatment for Persistent Metastatic Disease**

Unless complete response could be achieved with preoperative chemotherapy, metastatic disease was evaluated for additional local treatment (Table 1). Overall, 8 children (25.8%) received radiotherapy only, all for metastatic pulmonary disease. Four children (50.0%) in this group died, the other 4 (50.0%) were long-term survivors. Six children



**FIGURE 1.** Survival analysis Kaplan-Meier survival analysis is shown with hazard ratio (HR) and 95% confidence interval (in parenthesis).  $P$ -value was calculated with the log rank (Mantel-Cox) test. A, the subgroups with high-risk versus low/intermediate-risk histology are shown. The blastemal subgroup from SIOP 93-01 was assigned to the high-risk group (see text for details). Partial or complete response to preoperative chemotherapy versus stable disease or disease progression (B). C, compares metastatic disease isolated to 1 organ (lung or liver) versus 2 organs (lung and liver). D, surgery either alone or together with radiation is shown versus radiation alone.

(19.4%) underwent surgical resection of metastatic disease in either lung (N = 4, 66.7%) or liver (N = 2, 33.3%) without additional radiation. All 6 children survived long term. Four (12.9%) underwent both surgical resection and radiation of primary metastatic disease, and 1 child died, the other 3 survived long term. Therefore, even though not significant, a clear trend was observed toward survival for those children who received either surgery or surgery and radiation versus radiation alone ( $P = 0.097$ , Fig. 1D).

Of the 10 children undergoing surgical resection, 7 children (70.0%) received open metastasectomies for lung metastasis (either sternotomy or thoracotomy), and R<sub>0</sub> resection was achieved in 4 children (57.1%). All 4 showed regressed, nonviable tumor. One child had R<sub>2</sub> resection (miliary metastatic disease of lung), histology showed viable tumor, and the child did not survive. Of the remaining 2 children, 1 child had R<sub>2</sub> resection, the other, even though correctly diagnosed as stage 4 and who showed partial response to some but not all pulmonary nodules, was found to have inflammatory (septic) lung granulomas in the resected specimen. In the child with R<sub>2</sub> resection, apart from atypical lung resection of obvious metastatic disease, a suspicious pleural lesion was identified but not resected. This lesion completely regressed with postoperative chemotherapy. Later, the child relapsed with pulmonary disease independent from the pleural lesion.

One child (10.0%) underwent thoracoscopic metastasectomy and histology showed viable tumor, but resection was R<sub>0</sub>. He is currently alive at 18 months.

The 2 children (22.2%) who had isolated liver metastasis (and clear lungs) underwent R<sub>0</sub> liver resection, histologically both showed regressed, nonviable tumor. None of 2 relapsed. The other 4 children with metastatic liver disease (in addition to lung disease) received radiation to the lungs but no additional treatment of the liver metastasis, and 3 of these 4 patients died.

### Local Stage

Following SIOP guidelines, children were restaged after resection of the primary tumor. Eleven children (35.5%) had local stage I disease, 1 child (3.2%) had local stage II disease. Nineteen children (61.3%) had local stage

III disease and were treated with additional adjuvant radiation to the tumor bed (Table 1).

Local stage was neither associated with whether 1 (lung or liver) or 2 organs (lung and liver) were affected (Supplemental Table 2, <http://links.lww.com/JPHO/A38>;  $P = 0.139$ ), nor with the response of primary or metastatic disease to preoperative chemotherapy ( $P = 0.544$  and  $0.630$ , respectively). Correspondingly, none was associated with histologic risk type ( $P = 0.484$ ) or recurrence ( $P = 1.000$ ). Local stage was, however, associated with survival ( $P = 0.026$ ).

### Histology and Risk Stratification

The overall histologic distribution in the primary tumors is shown in Table 1. Four children (12.9%) had complete necrosis and 7 (22.6%) regressive changes. Twelve children (38.7%) had a blastemal subtype, 3 children (9.7%) had an epithelial type, and 5 children (16.1%) were mixed. Six children had additional diffuse anaplasia (5 diffuse, 1 diffuse and focal).

Histologically, 4 children (12.9%) were considered low risk, 15 (48.4%) were of an intermediate type. Twelve children (38.7%) were high risk (Table 1). Importantly, histologic risk stratification of pretreated WT was different for SIOP 93-01 and SIOP 2001. In SIOP 93-01, blastemal predominant subtype was regarded as intermediate-risk histology. In SIOP 2001, it was considered high risk and was treated accordingly with intensified chemotherapy. Therefore, we compared the outcomes of the blastemal subtype between the 2 protocols and found a possible trend regarding survival, but no significant difference ( $P = 0.206$ ; Supplemental Table 4, <http://links.lww.com/JPHO/A40> top row). In accordance with similar studies,<sup>2</sup> for a common analysis, blastemal subgroups from both SIOP 93-01 and SIOP 2001 were assigned to the high-risk group. High-risk histology of primary tumor was a strong predictor for survival (high risk vs. low/intermediate risk; Table 3; Fig. 1A). Comparing the blastemal predominant subtype with the diffuse anaplasia subtype within the high-risk group of both SIOP 93-01 and SIOP 2001 or SIOP 2001 alone, we found a trend regarding survival, but no significant difference (Supplemental Table 4, <http://links.lww.com/JPHO/A40> middle and bottom row).

**TABLE 3. Survivors Versus Nonsurvivors**

	Survivors	NonSurvivors	P	Odds Ratio	95% CI
No. Children	24	7			
Age at diagnosis	64.75 (0-203)	64.86 (1-160)	0.9958	NA	NA
Sex (female)	12 (50%)	2 (28.6%)	0.4117	NA	NA
Metastasis isolated to 1 organ (lung or liver)	23 (95.8%)	4 (57.1%)	0.0278*	17.25	1.415-210.2
Metastasis in 2 or more organ systems	1 (4.2%)	3 (42.9%)			
Partial or complete response of primary disease	22 (91.7%)	6 (85.7%)	0.5497	1.833	0.141-23.84
No response of disease progression	2 (8.3%)	1 (14.3%)			
Partial or complete response of metastatic disease	22 (91.6%)	3 (42.9%)	0.0138*	14.67	1.827-117.7
No response of disease progression	2 (8.3%)	4 (57.1%)			
Recurrence (after established remission)‡	3 (12.5%)	4 (100.0%)	0.0017†	0.01809	0.0007-0.4151
No recurrence (after established remission)‡	21 (87.5%)	0 (0.0%)			
High-risk histology	4 (16.7%)	5 (71.4%)	0.0118*	0.080	0.0112-0.5682
Low-risk/intermediate-risk histology	20 (83.3%)	2 (28.6%)			

Statistical analysis calculated with Fisher exact test with  $P$ -value, odds ratio, and 95% CI are shown for survivors versus nonsurvivors. All survivors lived at least 5 years except in 2 cases, in which survival was at least 18 months and follow-up is currently ongoing.

\*Statistical significance with a  $P$ -value < 0.05.

† Significance with a  $P$ -value < 0.01.

‡ For analysis of recurrence, distribution was calculated without 3 children who died of disease progression without ever achieving complete remission. CI indicates confidence interval; NA, not applicable.

The histologic evaluation of the tissue obtained from the 10 children who received surgical resection of metastatic disease was compared with the histology of the primary tumor (Supplemental Table 3, <http://links.lww.com/JPHO/A39>). In 5 children (50.0%), tissue was found to be nonviable tumor. In 2 children (20.0%), histology was unavailable. In 1 case, no tumor tissue was found (erroneous diagnosis, see below). Two children showed viable tumor tissue, and histology corresponded to that of the primary tumor in both cases. One had a mixed, the other a blastemal subtype. The latter was the only one to die from this group (Supplemental Table 3, <http://links.lww.com/JPHO/A39>).

### Recurrence

Seven children (22.6%) achieved complete primary remission and then relapsed at a later time (Table 1). Relapse was early (< 12 mo after achieving complete remission) in 6 children (85.7%) and late (> 12 mo) in 1 child (14.3%). However, the latter (late relapse) relapsed at 13 months of age. One child (12.5%) had local relapse and was treated with local reexcision and local radiation. He was well without disease 10 years after recurrence. Six children (85.7%) had distant recurrence, of which 4 (66.7%) died. Therefore, the overall salvage rate for relapse disease in our cohort was 42.9% (Table 1).

From the 4 children who relapsed and died, the first had blastemal histology, relapsed at 13 months, received radiation, surgical resection, chemotherapy, and autologous stem cell transplantation. The next had blastemal histology, relapsed early, and received only chemotherapy following to the parents' wishes. The third had regressive histology, relapsed early, had radiation and chemotherapy but no surgery, and died rapidly. The fourth again had blastemal histology, relapsed early, and received radiation, multiple resections of metastatic pulmonary disease, and intensified chemotherapy, all without success. Of the 2 children who relapsed distantly and survived, both relapsed early with lung metastasis. One had a blastemal subtype histology and received chemotherapy and radiation and was in remission and well 11 years after relapse. The other had mixed histology with diffuse anaplasia and received surgery, radiation, and chemotherapy and was in remission 7 years after relapse.

### Survival Analysis and Prognostic Factors

For all children, 5-year event-free survival was 67.9% and 5-year OS was 82.1% (Table 2; Fig. 2). Seven children (22.5%) died. Of these, 4 children (57.1%) died after relapsing distantly and 3 (42.9%) died from disease progression before reaching full remission in 2 cases and intraoperatively from severe hemorrhage in 1 case. With regard to OS, several prognostic factors were appreciated. Survival was significantly better in children with metastases to either lung or liver compared with involvement of both lung and liver (Table 3; Fig. 1C). Therapeutic response of metastases to preoperative chemotherapy, regardless of its location, was associated with survival (Table 3; Fig. 1B).

### Long-term Follow-up

The overall follow-up time for all children was 74.1 (2 to 151) and for the survivors 87.2 (2 to 151) months. Survivors who received radiation of the lung as part of their therapy (7 children) were followed with chest x-ray and/or pulmonary function test in all cases, and none showed sign of fibrosis (0%). However, 1 child (4.2%) developed thoracolumbar

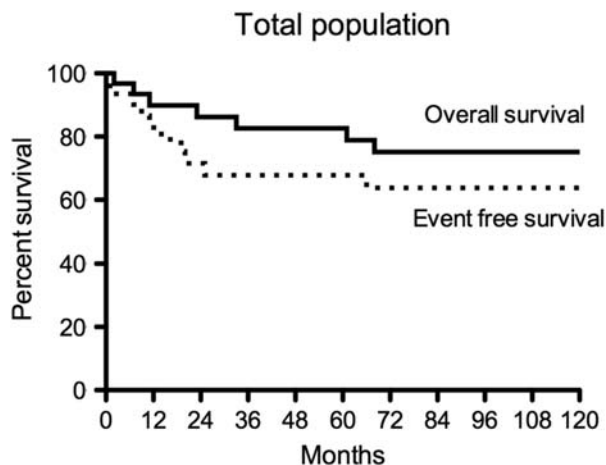


FIGURE 2. Overall survival and event-free survival for the total population.

scoliosis (this child also had thoracotomy for metastasectomy). Seventeen of the 24 survivors (70.8%) underwent either electrocardiography and/or cardiac sonogram during follow-up, which was not performed routinely in all centers after chemotherapy. One child (4.2%) was found to have cardiac arrhythmia and another congestive heart failure.

Creatinine levels were analyzed after completion of treatment and were within normal limits in all but 1 case (4.2%). This child developed chronic renal insufficiency independent from the type of surgery (partial nephrectomy for bilateral disease vs. unilateral tumornephrectomy). Tubulopathy was confirmed by biopsy. One child had chronic loose stools, which affected social life (Table 1).

Overall, among the long-term survivors 4 children (16.7%) developed at least one of the aforementioned treatment-related complications.

### DISCUSSION

Warmann et al<sup>2</sup> recently reported on 210 patients with WT and primary lung metastases. Five-year OS was 83.3% and 5-year event-free survival 72.3%, respectively, for all children. This is similar to what we report for our study. Corresponding to our results, which showed strong correlation between histologic risk type and survival, in their study survival was significantly worse in children with high-risk primary histology. In addition, they were able to show that within the high-risk group, the blastemal subtype was associated with significantly better outcome than the diffuse anaplasia subgroup. In our study, we observed a similar trend; however, perhaps because of a lower number of cases, we found no significant difference. In the study of Warmann et al,<sup>2</sup> a poor prognostic marker was no response to chemotherapy both for the primary tumor and metastatic disease. In the patient cohort presented here, we found increased survival only in those children who showed response to metastatic disease but not to the primary tumor itself. Likewise, these findings could potentially be biased by our low case number.

Breslow et al<sup>3</sup> in the past have given a detailed analysis on the metastatic pattern of children with stage IV WT. In their comprehensive study, no difference was identified in survival according to metastatic site (liver and/or lung vs. lung only). However, these data were extracted from the

National Wilms Tumor Study (NWTs) during 1969 to 1983 and are therefore difficult to compare with our data extracted from the more recent SIOP protocols.

When interpreting survival analysis with regard to histologic risk stratification, several vital aspects need to be pointed out. Importantly, blastemal subtype histology was handled differently in SIOP 93-01 and SIOP 2001. Although in SIOP 2001 it was considered high risk and received intensified chemotherapy, in SIOP 93-01 it was classified as intermediate risk and treated accordingly. Upon analysis of the blastemal subtype between the 2 protocols, we found no difference. For common analysis in this study, blastemal subtype in SIOP 93-01 was assigned to the high-risk group. This is in accordance with others.<sup>2</sup>

In our study, complete response (disappearance) of metastatic disease was seen only in 2 patients. This is in sharp contrast to what has been reported by others.<sup>2,4</sup> We explain this with the significantly higher usage of CT scan for restaging in our study. There is an ongoing debate about which diagnostic modality is appropriate for staging distant disease in WT.<sup>5</sup> In this respect, it is important to note that in children with WT not all lesions detected on CT scan are necessarily metastatic in origin.<sup>6</sup> In our study, 1 child who underwent pulmonary resection for suspected metastatic disease and another for recurrent pulmonary disease, histologic diagnosis was erroneous (nonmalignant).

Surgical treatment of pulmonary metastasis, whether alone or together with radiation, resulted in better outcome compared with radiation in our study. These findings go along with accumulating evidence identifying surgery as a safe and valuable tool for local control of metastatic disease.<sup>7</sup> One advantage of surgical resection of metastasis is the gain of additional tissue analysis, possibly altering therapeutic behavior. In our study, for the patients who underwent surgery for primary metastatic disease, tissue analysis mostly showed nonviable tumor corresponding with the histology of the primary tumor. Unfortunately, in which clinical situation surgery is indicated exactly and when it should be favored over radiation we cannot extract from our data.

In a SIOP series of children with WT and primary hepatic metastases, Szavay et al<sup>8</sup> suggested that initial surgical resection improved survival. In our study, 2 children had isolated liver metastases, both underwent anatomic resection at the time of operation of the primary tumor, and both survived long term. Three of the 4 children with both liver and lung metastases died. Therefore, in our study the presence of liver metastases seemed to be an adverse finding only in combination with additional pulmonary lesions. None of these 4 children underwent resection of their hepatic lesions. Of the 3 children who died, 2 showed progression of liver and pulmonary metastasis and 1 showed progression of pulmonary metastasis only. With respect to their primary histology, 1 had diffuse anaplasia and 2 had blastemal histology, as did the child who survived. It is tempting to speculate that the children who died in this group might have benefited from metastatic resection either at tumor excision or at a later time. Whether this is truly the case, however, must be shown in larger series focusing on this important detail.

Shamberger et al<sup>9</sup> showed in 2482 patients from NWTs-4 that advanced local tumor stages (especially local stage III) were associated with adverse outcome. However, these patients were mainly nonmetastatic patients. In our patient sample, there was a significant difference regarding survival for local stage I and II versus local stage III disease. We saw

no association between local stage and histology or the presence of metastatic disease in 1 versus 2 organs.

Relapse after achieving complete remission is a significant problem in WT with poor outcome.<sup>10</sup> It is reported to occur in approximately 10% to 20% of cases and fundamentally depends on tumor stage and biology at initial diagnosis.<sup>10-13</sup> The recurrence rate in our patient collective was 22.6%. Advances in rescue protocols mainly consisting of intensified chemotherapy regimens have led to salvage rates of 50% to 70% overall, depending on the tumor biology, disease stage, and other characteristics such as the length of remission.<sup>10,13,14</sup> The salvage rate in our study for stage 4 disease independent of tumor histology was 42.9% and therefore somewhat lower.

In our cohort, overall treatment-related long-term complications among the survivors at a mean of >7 years was 16.7%. This number is difficult to compare with others because of the selected patient cohort in our study. It is a key future objective to further reduce treatment intensities without compromising the patient's prognosis.<sup>10,15-19</sup> None of the children who received radiation to the lung developed pulmonary fibrosis. One child in this group, however, developed thoracolumbar scoliosis, potentially due to a combination of thoracotomy and radiation. Whether this complication could have been avoided with a thoracoscopic approach for metastasectomy without compromising prognosis is impossible to extract from our data. The precise role for minimal-invasive surgery for selected cases in WT remains to be clarified. Selection criteria for minimal-invasive surgery, potentially including the histology of the tumor,<sup>2</sup> should be adapted into present guidelines and protocols, and evaluation must include both the surgical and oncological outcome.

The same child who had developed scoliosis also developed renal insufficiency with confirmed tubulopathy. Important, this child was initially treated with SIOP 93/01 and therefore received ifosfamide; also, the child relapsed and was treated with additional chemotherapy. With adequate medical therapy, the child currently has a borderline normal creatinine level at 12-year follow-up.

One child developed toxic cardiopathy (after SIOP 93/01) and another cardiac arrhythmia (after SIOP 2001). None of the 2 underwent radiation therapy to the chest. One child developed chronic loose stools, possibly related to partial colectomy required during tumornephrectomy.

Taken together, in our cohort of stage 4 WT, with current treatment strategies the overall prognosis is acceptable, and long-term follow-up showed little toxicity from the invasive therapy. However, many questions remain unanswered including the optimal diagnostic workup, the treatment of distant disease, the appropriate surgical approach, and the role of biological markers as additional tools for risk stratification.

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