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Surgery-Related Factors and Local Recurrence of Wilms Tumor in National Wilms Tumor Study 4

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Objective

To assess the prognostic factors for local recurrence in Wilms tumor.

Summary Background Data

Current therapy for Wilms tumor has evolved through four studies of the National Wilms Tumor Study Group. As adverse prognostic factors were identified, treatment of children with Wilms tumor has been tailored based on these factors. Two-year relapse-free survival of children in the fourth study (NWTS-4) exceeded 91%. Factors once of prognostic import for local recurrence may lose their significance as more effective therapeutic regimens are devised.

Methods

Children evaluated were drawn from the records of NWTS-4. A total of 2482 randomized or followed patients were identified. Local recurrence, defined as recurrence in the original tumor bed, retroperitoneum, or within the abdominal cavity or pelvis, occurred in 100 children. Using a nested case-control study design, 182 matched controls were selected. Factors were analyzed for their association with local failure. Relative risks and 95% confidence intervals were calculated, taking into account the matching.

Results

The largest relative risks for local recurrence were observed in patients with stage III disease, those with unfavorable histology (especially diffuse anaplasia), and those reported to have tumor spillage during surgery. Multiple regression analysis adjusting for the combined effects of histology, lymph node involvement, and age revealed that tumor spillage remained significant. The relative risk of local recurrence from spill was largest in children with stage II disease. The absence of lymph node biopsy was also associated with an increased relative risk of recurrence, which was largest in children with stage I disease. The survival of children after local recurrence is poor, with an average survival rate at 2 years after relapse of 43%. Survival was dependent on initial stage: those who received more therapy before relapse had a worse prognosis.

Conclusions

This study has demonstrated that surgical rupture of the tumor must be prevented by the surgeon, because spills produce an increased risk of local relapse. Both local and diffuse spills produce this risk. Stage II children with local spill appear to require more aggressive therapy than that used in NWTS-4. The continued critical importance of lymph node sampling in conjunction with nephrectomy for Wilms tumor is also established. Absence of lymph node biopsy may result in understaging and inadequate treatment of the child and may produce an increased risk of local recurrence.

The National Wilms Tumor Study Group has completed four studies of multimodal management of children with Wilms tumor. Prognostic factors have been identified and treatment has evolved based on these factors, with intensive therapies reserved for children with the most aggressive disease. The 2-year relapse-free survival of children in the fourth study (NWTS-4) exceeded 91%.[1] Even in this most recent study, however, there remained a group of children whose tumors recurred in the renal fossa or within the

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Table 1. SITE OF ABDOMINAL RELAPSE AMONG CASES OF LOCAL RECURRENCE

Initial Relapse	Frequency
Original Bed	46
Abdominal area	
Lymph nodes	6
Peritoneum	5
Pelvis	11
Diaphragm	3
Other unspecified	16
Multiple sites	13
Total	100

abdominal cavity. Their prognosis was worse, particularly if they had received prior flank irradiation or doxorubicin, than that of children in whom disease recurred with pulmonary metastases alone.[2,3]

Factors once of prognostic import may lose their significance as more effective therapeutic regimens are devised and relapse-free survival rates improve.[4] This study was performed to identify indicators of local recurrence in children treated according to current protocols. Contemporary regimens include such major modifications as doxorubicin, which has been added for high-risk children. Also, no flank radiation therapy is used now for stage II favorable-histology tumors, and lower radiation doses (10 Gy) are given to children with stage III disease.

PATIENTS AND METHODS

Children evaluated in this study were drawn from the records of NWTS-4. We identified all randomized and followed patients (eligible patients treated according to protocol, but not randomized for a variety of reasons including initiation of therapy before randomization, or parent or physician unwilling to accept randomization) on whom operative and pathology narratives had been submitted to the statistical center. We excluded the special followed categories of those with preoperative treatment, bilateral disease, and age at diagnosis older than 15 years.[5] A total of 2482 patients who met these criteria were identified.

Local recurrence was defined as recurrence in the original tumor bed, in the retroperitoneum, or within the abdominal cavity or pelvis, but did not include children with hematogenous hepatic metastases only. One hundred children met these criteria (Table 1). Using a nested case-control study design, two controls were selected at random from among patients who were disease-free for at least the length of time as that at which local recurrence developed in the index case.[6] The number of days elapsed between diagnosis and local recurrence was tied for nine pairs of cases. Only two controls (rather than two each) were selected to accompany the two cases in these nine instances, leading to a total of 182 matched controls. Baseline data, including surgery and pathology narratives and checklists, as well as slides for histopathologic evaluation, were available for nearly all patients selected for the case-control studies. Those missing specific data items were excluded from the respective analysis. The operative reports and surgical checklists were reviewed for consistency by one of us (RCS) with no knowledge of which were study cases and which were controls. Central pathology review was performed in all cases entered into NWTS-4 (JBB) and included assignment of histology, local stage, lymph node involvement, and extension of tumor to the margins of resection.

Factors analyzed for their association with local failure included local tumor stage, tumor histology, microscopic residual at resection margins, lymph node involvement, spillage of tumor during surgery, overall peritoneal soilage, and the surgeon's assessment of whether complete removal of the tumor had been achieved or whether there had been invasion into adjacent organs.[7] The category of overall peritoneal soilage was a summary variable combining children who had an intraoperative biopsy, spillage, preoperative rupture, tumor transection, or spill from adjacent structures. This variable included both local (confined to the renal fossa) and diffuse (wider peritoneal contamination) spillage and involved more children than those with surgical spillage alone.[8] Factors that the surgeon could influence included tumor spill during surgery, complete removal of the tumor, adequate sampling of lymph nodes, and transection of tumor during the resection.

Relative risks (RR) were calculated, taking account of the matching, to assess the association between local recurrence and the selected prognostic factors. These estimate the ratios of local recurrence rates in patients with and without the prognostic factor and have the same interpretation as parameters in the Cox proportional hazards regression model.[9] Subsequent multiple regression analyses using conditional logistic regression were performed to adjust the spillage and soilage RRs for the combined effects of histology, age, and lymph node involvement.[10]

To assess the risk of local recurrence in children based on stage and occurrence of spill, the full dataset of NWTS-4 patients registered before 1994 was used. The absolute risk of local recurrence was also assessed using a proportional hazards model and information about the sampling scheme to compare the probability of local recurrence estimated in the case-control study with that of the entire NWTS-4 cohort. The survival percentages after local recurrence for the children in the case-control study were analyzed as a group and also by the stage/spill subgroups.

RESULTS

The associations between local recurrence and the selected prognostic factors are shown in Table 2. The largest RRs were observed in patients with stage III disease (3.2); those with unfavorable histology, especially diffuse anapla-

Table 2. RELATIVE RISK OF LOCAL RECURRENCE WITH 95% CONFIDENCE INTERVALS FOR PROGNOSTIC FACTORS

	Controls	Cases	Relative Risk
Pathologic stage			
I	66	16	1.0
II	58	38	2.1 (1.0–4.3)
III	52	40	3.2 (1.4–7.2)
Histology			
Favorable	161	67	1.0
Diffuse anaplasia	9	21	4.7 (2.0–11)
CCSK*	7	6	2.8 (0.79–10)
RTK (plus other sarcoma case)†	4	5	3.1 (0.73–13)
Margins (path/hist)			
Negative	140	66	1.0
Positive	29	27	2.0 (1.1–3.6)
Lymph Nodes (path/hist)			
Negative	129	53	1.0
Hilar	20	11	1.1 (0.46–2.6)
Aortic	17	17	3.0 (1.2–7.3)
None examined	14	17	2.6 (1.1–6.0)
Age at diagnosis			
0–23 months	63	21	1.0
24–47 months	59	25	0.86 (0.39–1.9)
48+ months	60	54	2.6 (1.4–5.1)
Complete removal of tumor			
Yes	175	87	1.0
No	7	11	2.7 (1.0–7.1)
Tumor invasion of adjacent organs			
No	166	82	1.0
Yes	16	16	1.8 (0.87–3.7)
Spillage during surgery‡			
No	159	66	1.0
Yes	21	32	3.7 (1.9–7.2)
Overall peritoneal soilage§			
No	135	53	1.0
Yes	45	45	2.6 (1.5–4.5)

* Clear cell sarcoma of the kidney
† Rhaboid tumor of the kidney
‡ Local and diffuse spill combined
§ Summary variable combining peritoneal soilage from biopsy, spillage, preoperative rupture, tumor cut across or spilled from adjacent structures. Local and diffuse combined.

sia (4.7); and those reported to have tumor spillage during surgery (3.7).[1] There were too few patients with diffuse surgical spill (four cases and two controls) to distinguish between local and diffuse contamination in this analysis, so local and diffuse spills were combined in a single category.

Subsequent multiple regression analyses adjusted selected RRs for the combined effects of histology and lymph node involvement. These adjustments reduced the RR for surgical spill to 3.0 (95% confidence interval [CI] 1.4 to 6.3). They reduced the RR for peritoneal soilage to 2.2 (95% CI 1.1 to 4.1). When these factors were also adjusted for age, they remained significant at 2.9 (95% CI 1.3 to 6.2) and 2.1 (95% CI 1.1 to 4.1). Even after adjustment for the microscopic pathology findings, therefore, surgical spill (in fact, mostly local spill) remained an important factor for local recurrence. Further analyses demonstrated that much of the adverse effect of spillage occurred among those with stage II disease, who were treated with less aggressive therapy than those with stage III disease (Table 3). The children with stage II disease had more than a fourfold increased risk of local relapse if they had local spill (RR 4.5; 95% CI 1.4 to 14).

Age at diagnosis was a prognostic factor when considered alone, with increased risk of local recurrence in the older children (older than 4 years). The age effect failed to achieve statistical significance, however, when adjusted for histology and lymph node involvement (RR 2.0; 95% CI 0.95 to 4.1). Failure to remove the tumor completely was associated with a statistically significant increased RR, whereas local invasion into adjacent organs (liver, spleen, pancreas, diaphragm, and psoas muscle) was not (see Table 2).

One interesting result was that children with no lymph nodes sampled by the surgeon or examined by the pathologist fared worse than those with positive hilar nodes. Further assessment of this group (Table 4) showed that the effect of "no nodes examined" was largely confined to stage I children, who received the least aggressive treatment. Stage I children with no nodes examined had a sixfold increase in risk over stage I children with negative sampled nodes. The differences between node-negative and "node not examined" children in stages II and III were not statistically significant. Review of the operative reports and surgical checklists in the 28 patients without microscopic evaluation of lymph nodes revealed that the lymph nodes were thought to be abnormal in only 3 patients; operative reports described biopsies of the nodes in only 2.

This finding was further examined using pathology data available more recently for the entire NWTS-4 cohort. Among children with local stage I disease, 6 of 140 who had no nodes examined microscopically developed local recurrence, whereas only 12 of 770 with microscopically negative nodes did so (RR 2.8; 95% CI 1.1 to 7.5). No such effect was apparent, however, for children with local stage II or III disease.

The probability of local recurrence by stage and spill in the entire NWTS-4 cohort is shown in Figure 1. In each stage, relapse was higher among patients with spill, and it was highest in stage II disease with spill (Table 5). The estimates from the case-control sample of the probabilities of local recurrence are quite close to those observed for the larger cohort (Fig. 2). The incidence of surgical spill in the patients registered before 1994 was 11% for local spill and 3% for diffuse spill.

The survival rate of children at 2 years after local recurrence was 43% in the case-control study (Fig. 3). Survival was dependent on initial stage: those who had received more therapy before relapse (*i.e.*, stage III patients) had a worse prognosis (Fig. 4).

Table 3. EFFECT OF SPILL ON LOCAL RECURRENCE

	Stage I		Stage II		Stage III	
	Control	Case	Control	Case	Control	Case
No spill	66	16	50	25	37	21
	RR: 1.0		RR: 1.0		RR: 1.0	
			Control	Case	Control	Case
Spill			6	13	15	18
			RR: 4.5 (1.4–14)		RR: 1.9 (0.77–4.7)	

RR = relative risk (95% confidence interval)

DISCUSSION

In this analysis, higher local stage and unfavorable histology (particularly diffuse anaplasia) were strongly associated with local recurrence in the original tumor bed, retroperitoneum, or within the abdominal cavity or pelvis. Clear cell sarcoma of the kidney and rhabdoid tumor of the kidney were also associated with local recurrence, but there were only small numbers of children in these categories, and the differences detected were not statistically significant. Microscopic involvement of the resection margins of the specimen were also found to be associated with local relapse. An NWTS-1 analysis failed to demonstrate that microscopic residual disease affected the relapse-free survival rate. In contrast, NWTS-3 studies showed that the presence of microscopic tumor in the margin of the surgical resection was an independent predictor of abdominal relapse and death among stage III favorable-histology patients.[8,11] In that analysis, tumor size, tumor in the margin, and capsular penetration were the prognostic factors most significantly associated with abdominal recurrence, whereas lymph node involvement was coupled most closely with pulmonary recurrence.

Involvement of paraaortic lymph nodes is an important prognostic factor. It correlated with local recurrence in the current analyses, as it did in studies based on preoperative therapy conducted by others. Five hundred and twelve children with Wilms tumor stages I, II, and III by International Society of Pediatric Oncology (SIOP) criteria were registered in their nephroblastoma trials. These children were retrospectively analyzed to assess the prognostic value of metastatic lymph node involvement.[12] The lymph nodes of 300 patients were submitted for microscopic examination, and malignant invasion was reported in 15%. The disease-free and overall survival rates for children with metastatic lymph node invasion, all of whom received prenephrectomy chemotherapy, were significantly worse than for those without metastatic node involvement. Preoperative treatment colors these data; it provides an *in vivo* test of treatment response. Children with persistent tumor at nephrectomy represent a chemotherapy-resistant subgroup.

An evaluation of children treated in NWTS-2 showed that abdominal recurrence occurred in 16/535 children (3%) with negative nodes (or nodes not examined), 0/33 with hilar nodes positive, and 9/55 (16.4%) with paraaortic chain involvement.[13] A similar analysis of children treated in NWTS-3 with favorable histology revealed a 2.3% local recurrence rate in 1100 children with negative lymph nodes, 5.2% in 136 with positive hilar lymph nodes, and 5.9% in 68

Table 4. EFFECT OF UNEXAMINED LYMPH NODES ON LOCAL RECURRENCE

Lymph Nodes	Stage I		Stage II		Stage III	
Negative	Control	Case	Control	Case	Control	Case
	61	10	51	32	13	10
	RR: 1.0		RR: 1.0		RR: 1.0	
Positive	Control	Case	Control	Case	Control	Case
	0	0	0	0	37	28
					RR: 1.1 (0.43–2.9)	
None examined	Control	Case	Control	Case	Control	Case
	5	6	7	6	2	2
	RR: 6.0 (1.5–24)		RR: 1.4 (0.45–4.7)		RR: 1.2 (0.14–9.9)	

RR = Matched relative risk (95% confidence interval)

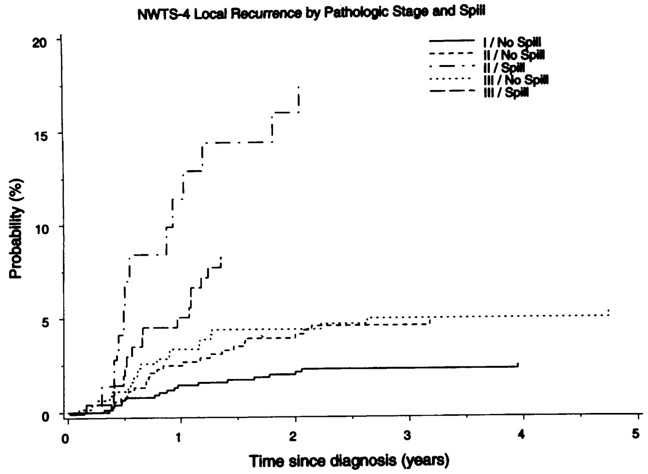

Figure 1. Local recurrence rate by pathologic stage and spill, entire cohort.

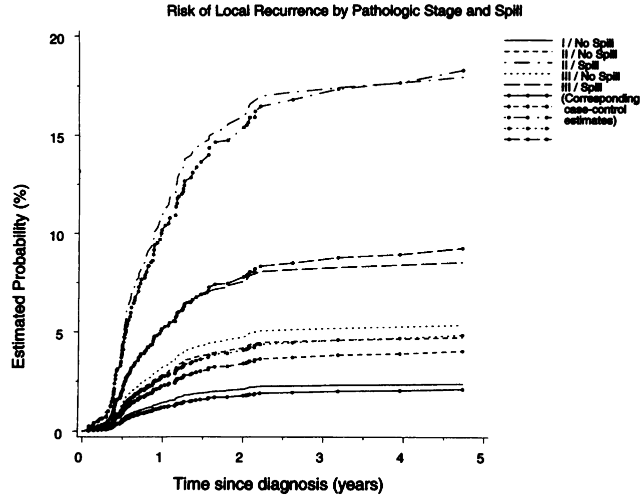

Figure 2. Local recurrence rate by pathologic stage and spill, case-control sample.

with positive paraaortic lymph nodes.[8] NWTS-3 children with involved hilar nodes, who had been treated in earlier studies as stage II, were considered and treated as stage III.

The importance of lymph node sampling is demonstrated in this study. There was a higher incidence of local recurrence in children in whom lymph nodes were not sampled than in those with histologically proven negative nodes or positive hilar nodes. Othersen et al[14] documented important clinical underestimation of lymph node involvement. Surgeons incorrectly judged as negative 10 of 32 lymph nodes found positive by pathology, for a 31.3% error rate.

Extensive lymph node resection for Wilms tumor has not been recommended, although lymph node sampling and biopsy have been strongly urged. Information on this policy has been limited. Martin and Reyes[15] reported a nonrandomized study of lymph node resection in patients with Wilms tumor who also received radiation therapy and dactinomycin. They reported survival in six of seven children with positive lymph nodes but without distant metastases. In NWTS-1, resection of hilar and paraaortic lymph nodes did not produce any significant difference in the relapse-free survival rate in patients within comparable treatment groups.[11] In a small cohort of children in the SIOP trials,

Table 5. FREQUENCY OF LOCAL RECURRENCE IN ENTIRE NWTS-4 POPULATION REGISTERED BEFORE 1994

Stage	Local Recurrence (No. of children/total)	(%)
I/No spill	18/789	2.3
II/No spill	24/555	4.3
II/Spill	12/73	16.4
III/No spill	21/429	4.9
III/Spill	16/206	7.8
Total	91/2052	4.4

radical lymph node dissection neither improved the cure rate nor decreased the rate of abdominal recurrence.[12] Sixty-two SIOP children had paraaortic and hilar lymph nodes resected and 42 of the 45 with microscopically confirmed lymph node metastases had ≥2 years of follow-up at the time of the report. In those 42, complete resection of the lymph nodes did not seem to influence survival or the rate of abdominal relapse. In the current cohort, incomplete removal of the tumor as judged by the surgeon, including patients with residual primary tumors as well as involved lymph nodes, produced a marginally significant statistical difference in the frequency of local relapse. Involvement of adjacent liver, diaphragm, pancreas, spleen, and psoas muscle did not affect local relapse rates.

Surgical spill correlated strongly with local recurrence. This correlation persisted even when multiple regression analysis adjusted for the combined effects of histology and lymph node involvement. These data provide the most con-

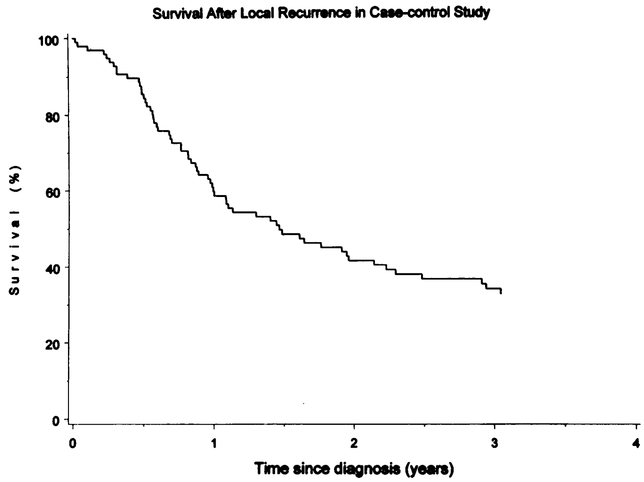

Figure 3. Survival after local recurrence.

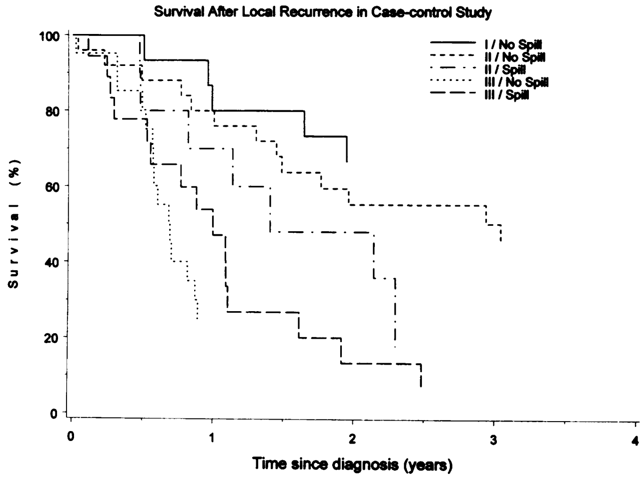

Figure 4. Survival after local recurrence by pathologic stage and spill.

vincing NWTS evidence to date that spillage of tumor by the surgeon increases the risk of recurrent disease, even after accounting for other prognostic factors. These results confirm NWTS-1, NWTS-2, and NWTS-3 data that generally correlated tumor spills with unfavorable outcomes: increased infradiaphragmatic relapse rates and death, whether as independent or associated variables, and whether local or diffuse.[8,11,13] In the current study, those with tumor spillage included primarily children with limited spills. They received neither irradiation nor doxorubicin if they were stage II by other criteria.

In a similar analysis of NWTS-3 children with favorable histology and pulmonary or local relapses, spill was found to be highly correlated with outcome, but it was not possible to establish an independent prognostic role for spill after adjusting for other factors, including lymph node involvement, age at diagnosis, and tumor size.[8] The findings in the current study suggest that no distinction should be made between patients with local *versus* diffuse spill in terms of the treatments they receive.

In NWTS-3, treatment variables seemed to affect the incidence of intraabdominal relapse in stage III patients. They were randomized in a factorial design between 10 Gy *versus* 20 Gy radiation therapy and the addition or not of doxorubicin to dactinomycin and vincristine. Those receiving doxorubicin had a lower incidence of relapse (4/134) than those who did not (11/141), although this difference was not statistically significant.[7] More than half of the intraabdominal relapses for the stage III favorable-histology patients occurred among those who were given 10 Gy of irradiation and no doxorubicin. In NWTS-4, treatment was altered to give all stage III children doxorubicin and 10 Gy radiation. The results of this study suggest that children who are stage II based on their other staging parameters (*i.e.*, absence of positive resection margins or lymph node involvement) but with local surgical spills require more aggressive therapy than that used in NWTS-4. They are at increased risk for local recurrence, which remains a poor prognostic factor for survival in children with Wilms tumor.

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