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INTRAOPERATIVE SPILLAGE OF FAVORABLE HISTOLOGY WILMS TUMOR CELLS: INFLUENCE OF IRRADIATION AND CHEMOTHERAPY REGIMENS ON ABDOMINAL RECURRENCE. A REPORT FROM THE NATIONAL WILMS TUMOR STUDY GROUP

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Purpose: We undertook this study to determine (*1*) the frequency with which spilled tumor cells of favorable histology produced intra-abdominal disease in patients treated with differing chemotherapy regimens and abdominal radiation therapy (RT) and (*2*) the patterns of relapse and outcomes in such patients.
Methods and Materials: The influence of RT dose (0, 10, and 20 Gy), RT fields (flank, whole abdomen), and chemotherapy with dactinomycin and vincristine (2 drugs) vs. added doxorubicin (three drugs) on intra-abdominal tumor recurrence rates was analyzed by logistic regression in 450 patients. Each patient was considered at risk for two types of failure: flank and subdiaphragmatic beyond-flank recurrence, with the correlation between the two outcomes accounted for in the analyses.
Results: The crude odds ratio for the risk of recurrence relative to no RT was 0.35 (0.15–0.78) for 10Gy and 0.08 (0.01–0.58) for 20Gy. The odds ratio for the risk of recurrence for doxorubicin to two drugs after adjusting for RT was not significant. For Stage II patients (NWTS-4), the 8-year event rates with and without spillage, respectively, were 79% and 87% for relapse-free survival (*p* = 0.07) and 90% and 95% for overall survival (*p* = 0.04).
Conclusions: Irradiation (10 Gy or 20 Gy) reduced abdominal tumor recurrence rates after tumor spillage. Tumor spillage in Stage II patients reduced relapse-free survival and overall survival, but only the latter was of statistical significance. These data provide a basis for assessing the risks vs. benefits when considering treatment for children with favorable histology Wilms tumor and surgical spillage.   © 2010 Elsevier Inc.

Wilms tumor, Radiation therapy, Tumor spillage, Local recurrence, Survival.

INTRODUCTION

Spillage of tumor cells during abdominal surgery for Wilms tumor has in the past been associated with an increased risk of tumor recurrence but has not affected overall survival (1, 2). In the National Wilms Tumor Study (NWTS)-1 and -2, the Wilms tumor grouping system was used, and patients with tumor spillage were classified as having Group III disease (3, 4).

The staging system in NWTS-3 and -4 has been detailed elsewhere (4). In brief, Stage II tumors were those that penetrated the capsule but were totally excised. Stage III implied

any of the following alone or in combination: positive lymph nodes, preoperative or intraoperative gross spillage of tumor cells, and residual microscopic or gross disease.

An attempt was made in NWTS-3 and -4 to discriminate between gross peritoneal contamination and more confined spillage. The definitions adopted were "local" tumor spillage when the spillage was confined to the flank and "diffuse" tumor spillage when there was contamination of the entire peritoneal cavity after tumor rupture (1, 5). In NWTS-3 and -4, patients with local tumor spillage were downstaged to Stage II, whereas those with diffuse tumor spillage were retained in

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the Stage III category (6). In NWTS-4, there was a threefold increase in abdominal tumor recurrence rates among Stage II patients of all histologies with tumor spillage compared with patients without any tumor spillage (1).

These analyses were undertaken to determine (1) the frequency with which spilled tumor cells produced clinically detectable intra-abdominal disease and the effect of treatment with chemotherapy regimens that did or did not include doxorubicin (DOX) and different abdominal radiation therapy (RT) doses and volumes on this frequency; and (2) the patterns of recurrent disease in such patients and their outcomes.

METHODS AND MATERIALS

Between May 1979 and May 1985, 992 patients with Stage II–IV favorable histology Wilms tumor (excluding focal or diffuse anaplasia, clear cell sarcoma of kidney, and rhabdoid tumors) were entered in the randomized or followed categories of NWTS-3 (5). Between August 1986 and September 1994, 1,318 patients with Stage II–IV favorable histology Wilms tumor were entered in the randomized or followed categories of NWTS-4 (7). Surgical tumor spillage was identified in 515 of the 2,310 patients. Of these 515, 42 did not receive treatment with drugs and RT appropriate for their study and tumor stage. Another 23 patients were excluded because they had gross peritoneal tumor implants. The outcomes of the remaining 450 patients form the basis of this report.

On NWTS-3, patients with Stage II disease were randomized to receive 0 or 20 Gy to the operative bed (flank). The flank irradiation (RT) portal was designed to include the volume of the affected kidney on preoperative CT scan or excretory urogram with a margin of 1 cm. The medial margin of the RT portal extended across the midline to include all of the vertebral bodies at the levels concerned (Fig 1). Patients with Stage III disease were randomized to receive 10 or 20 Gy, and all patients with Stage IV disease received 20 Gy to the tumor bed (5). On NWTS-4, patients with Stage II disease did not receive flank RT. Patients with Stage III and Stage IV disease received 10 Gy to the flank or whole abdomen (WA) (7). In this report, patients with Stage IV tumors were analyzed according to the stage and treatment of their abdominal disease (Stage II or III). In NWTS-3 and -4, patients with diffuse tumor spillage received WART. This portal extended from the diaphragmatic domes superiorly to the bottom of the obturator foramen inferiorly. Thus, the entire peritoneal cavity including the flank was included in the irradiated volume. The whole abdomen RT dose was either 10 Gy or 20 Gy in NWTS-3 (5) and 10 Gy for patients enrolled in NWTS-4 (7). In NWTS-3, among patients randomized to receive 20 Gy to the WA, the dose to the remaining kidney was limited to <15 Gy by the use of kidney shielding (5).

The RT was to be started within 11 days of surgery, and that criterion was met in most cases. The mean delay for all patients in the two studies was 10.9 days (8). Whereas the assigned RT dosages were either 10 Gy or 20 Gy, the delivered RT doses could range from 10 to 10.8 Gy or 20 to21.6 Gy, respectively, depending on the 150-, 180-, or 200-cGy dose/fraction that was used. Information regarding RT doses and fields was gathered from patient charts and was reviewed by the National Wilms Tumor Study Group (NWTSG) radiation oncologists.

The details of the chemotherapy regimens used in NWTS-3 and -4 for Stage II–IV disease have been published earlier (5, 7). For the purpose of this analysis, these regimens have been classified
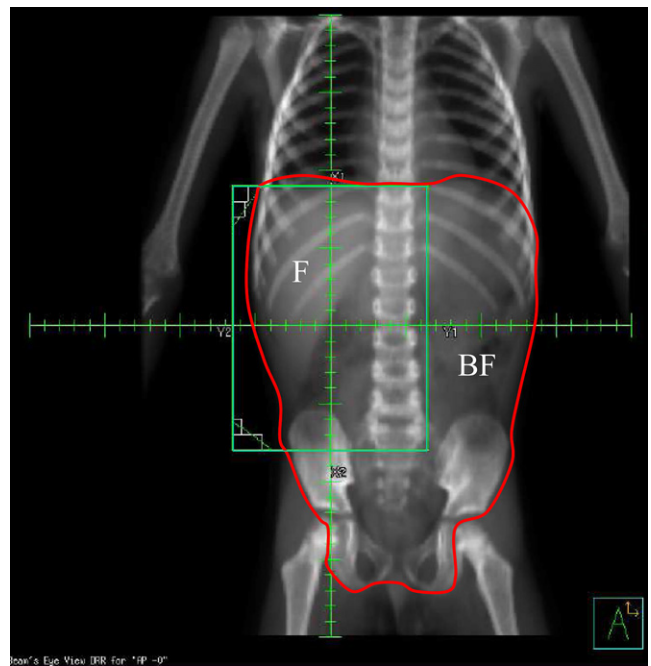

Fig. 1. Digitally reconstructed radiograph of a child receiving flank irradiation for a right-sided Wilms tumor. The regions at risk for relapse after spillage, flank (F) and beyond-flank (BF), as defined by radiation fields are shown.

as either two drugs (vincristine and dactinomycin) or three drugs (vincristine, dactinomycin, and DOX).

Surgical spillage classified as local or diffuse by the operating surgeon was reviewed by the surgical committee of the NWTSG. The reviewers often found it difficult, however, to establish whether spillage categorized as local or diffuse by the operating surgeons fulfilled the protocol criteria for this distinction. Because no anatomical barriers separate the flank (operative bed) from other areas of the peritoneal cavity, even a locally spilled tumor cell has the potential to be dispersed into the entire peritoneal cavity. To evaluate the efficacy of RT in destroying spilled tumor cells, the peritoneal cavity was divided into two sites (regions) that may have received different amounts of RT, albeit each was at risk for spilled cell implantation: ''flank'' (F) denotes the region covered by the standard flank RT portal, and ''beyond-flank'' (BF) denotes the remainder of the peritoneal cavity (Fig. 1). The site(s) of abdominal tumor recurrence were determined from surgical notes and diagnostic imaging reports and classified (by J.A.K. and G.J.D.) as F or BF if only a single site was involved, or as F+BF when both were involved. Recurrence in either site at any time was recorded whether preceded by, concurrent with, or after recurrent disease elsewhere, *e.g.,* the lung or liver.

Statistics

The RT dose to each of the two possible sites of recurrence was determined by the total RT dose and the type of RT field (flank only or whole abdomen). For example, in a patient who received 10 Gy to the flank, the RT doses to the flank and beyond-flank sites were recorded as 10 Gy and 0 Gy, respectively. If the patient received 10 Gy to the whole abdomen, by contrast, the RT doses to the flank and beyond-flank sites were both 10 Gy. The aim of the statistical analysis was to estimate the impact of the different RT doses (0, 10 Gy, 20 Gy) and DOX in preventing tumor recurrence

Table 1. Abdominal tumor recurrence by study, stage, RT dose, and chemotherapy for Stage
II–IV patients with tumor spillage.

NWT study	Stage	RT (Gy)	Drugs	Total patients	Abdominal recurrence		
					F only	BF only	F + BF
3	II	0	2	24	1	0	2
		0	3	11	1	0	0
		20 Flank	2	11	0	0	0
		20 Flank	3	17	0	1	0
	III	10 Flank	2	1	0	0	0
		10 WART	2	11	0	0	1
		10 Flank	3	17	0	0	0
		10 WART	3	17	0	0	0
		20 Flank	2	10	0	1	0
		20 Flank 10 WART	2	2	0	1	0
		20 WART	2	11	0	0	0
		20 Flank	3	11	0	1	0
		20 Flank 10 WART	3	1	0	0	0
		20 WART	3	21	0	1	0
	IV	20 Flank	3	23	0	1	0
		20 Flank 10 WART	3	1	0	0	0
		20 WART	3	6	0	0	0
4	II	0	2	70	6	1	3
	III	10 Flank	3	62	1	3	1
		10 WART	3	75	1	0	1
	IV	10 Flank	3	35	0	3	1
		10 WART	3	13	1	0	0
		Total		450	11	13	9

Abbreviations: RT = radiation therapy; NWT = National Wilms Tumor; WART = whole abdomen
radiation therapy.

in the flank and beyond-flank sites in the abdomen after tumor spillage in abdominal Stage II and Stage III patients. Each patient contributed two data records to the logistic regression analysis, one for the flank and one for beyond-flank. The odds ratios (OR) for tumor recurrence in relation to RT dose and DOX were adjusted for each other, for stage of disease and for recurrence site (F vs. BF) . The correlation between the two treatment outcomes (flank, beyond-flank) in the same patient was accounted for by using robust standard errors based on a statistical procedure known as generalized estimating equations (9, 10). Estimation and comparison of relapse-free survival and overall survival rates were conducted using the Kaplan-Meier (11) and log-rank (12) procedures.

RESULTS

Thirty-three of 450 patients (7.3%) in whom there had been operative spillage developed recurrent disease in the abdominal cavity (11 flank only, 13 beyond-flank only, and 9 both). The flank was the most common site of relapse (20/33, 61%). The frequency of abdominal recurrence after treatment with two- or three-drug chemotherapy and no RT among Stage II patients was 13.3% (14/105). Despite the entire peritoneal cavity being at risk for tumor recurrence from spilled cells, the flank was the most common site of recurrence in unirradiated Stage II patients: the flank alone was a site of recurrence in 8 of the 14 unirradiated patients (57%), beyond-flank alone in 1 patient, and both sites in 5 patients. The frequency of tumor development from spilled cells after treatment for all irradiated patients was 5.5% (19/345) (Table 1).

Effect of RT on flank and beyond-flank recurrence in Stage II and III patients

The outcomes by site of recurrence and RT dose for flank and beyond-flank recurrences in Stage II and III patients are summarized in Table 2 and Fig. 1. The flank relapse rates for 0 Gy, 10 Gy, and 20 Gy were 12.4%, 3%, and 0%, respectively. The beyond-flank relapse rates for 0 Gy, 10 Gy, and 20 Gy were 6.2%, 2.5%, and 2.6% respectively. After adjustment for site of recurrence and institutional stage of disease (Table 3), the odds ratio for the risk of tumor recurrence relative to no RT was 0.26 for 10 Gy (95% CI 0.09– 0.79, *p* value 0.02) and 0.06 for 20 Gy (95% CI 0.01–0.53, *p* value 0.01). The *p* value of the adjusted test of trend for relapse with dose of RT was 0.002.

Effect of RT on flank and beyond-flank recurrence in Stage II and only beyond-flank recurrence in Stage III patients

This analysis was performed excluding flank relapses in Stage III patients because not only spilled cells but also other factors inherent in the definition of Stage III, such as positive surgical margins and lymph node invasion, can also contribute to flank recurrence.

The outcomes by RT dose for flank recurrence in Stage II and beyond-flank recurrence in Stage II–III patients are summarized in Table 4. The flank relapse rates for 0 Gy and 20 Gy were 12.4% and 0%, respectively. None of the patients with Stage II tumors received 10 Gy in NWTS-3,4. After adjustment for the site of recurrence, the odds ratio for the risk

Table 2. Outcomes by site of recurrence and RT dose in abdominal Stage II and III patients: each patient evaluated for both sites of potential recurrence.

RT dose	Flank		Beyond-flank	
	Evaluated	Events (%)	Evaluated	Events(%)
No RT	105	13 (12.4)	292	18 (6.2)
10 Gy	231	7 (3.0)	120	3 (2.5)
20 Gy	114	0 (0.0)	38	1 (2.6)
Total	450	20 (4.4)	450	22 (4.9)

Abbreviation: RT = radiation therapy.

of tumor recurrence relative to no RT was 0.38 for 10 Gy (95% CI 0.11–1.30, p value 0.12) and 0.16 for 20 Gy (95% CI 0.02–1.26, p value 0.08) (Table 5). The p value of the adjusted test of trend for relapse with dose of RT was 0.02.

Effect of DOX on tumor recurrence after spillage

The odds ratio for the risk of local recurrence after the use of DOX in addition to vincristine and dactinomycin (three drugs) relative to two drugs only (vincristine and dactinomycin) was not significant after adjustment for site of relapse and RT dose: the adjusted odds ratio was 0.64 (95%CI 0.24–1.50, $p = 0.30$).

Site and timing of recurrent disease and outcomes in unirradiated Stage II patients who relapsed below the diaphragm

These analyses were undertaken to determine the frequency with which spilled tumor cells produced clinically detectable intra-abdominal disease and the effects of treatment with chemotherapy regimens that did or did not include DOX and different abdominal radiation therapy doses. Therefore, the sequence of recurrent abdominal disease, whether it was before, concurrent with, or after relapse elsewhere, was evaluated in the 14 children who experienced abdominal relapse.

Table 3. Multiple logistic regression analysis of recurrence on site, RT dose, and tumor stage.

	Odds ratio	95% CI*	p value*
Trial			
Flank	1.0	—	
Beyond-flank	0.56	(0.24–1.25)	0.16
RT dose (GY)			
0	1.0	—	
10	0.26	(0.09–0.79)	0.02
20	0.06	(0.01–0.53)	0.01
Stage			
II	1.0	—	
III	1.04	(0.43–2.52)	0.93
IV	1.26	(0.44–3.56)	0.66

Abbreviation: RT = radiation therapy.
* Estimated by generalized estimating equations, *p* value of test for trend with dose 0.002.

Table 4. Outcomes by RT dose for flank recurrence in abdominal Stage II and beyond-flank recurrence in abdominal Stage II–III patients.

RT dose (GY)	Flank		Beyond-flank	
	Evaluated	Events (%)	Evaluated	Events (%)
No RT	105	13 (12.4)	292	18 (6.2)
10	0	0 (0.0)	120	3 (2.5)
20	28	0 (0.0)	38	1 (2.6)
Total	133	13 (9.8)	450	22 (4.9)

Abbreviation: RT = radiation therapy.

Seven of the 14 had relapsed earlier in the thorax (6) or liver (1) before abdominal relapse, and 5 of these 7 (71.4%) were alive. Five of the remaining 7 who relapsed first in the flank (1 with simultaneous liver metastases) died of recurrent tumor in sites beyond the flank, 3 with liver and/or lung metastases as well as infradiaphragmatic tumor. Thus, none of the 7 children died solely of progressive disease in the tumor bed. Finally, 7 of the 14 patients (50%) were alive for periods ranging from 6 to 22 years after salvage therapies.

Outcomes in unirradiated Stage II NWTS-4 patients treated with two drugs with or without intraoperative tumor spillage

The 8-year relapse-free survival rates for Stage II patients in NWTS-4 available for analysis were 79% after tumor spillage (103 children, 21 relapses observed vs. 14.9 expected) and 87% in the absence of spillage (310 patients, 40 relapses vs. 46.1 expected, $p = 0.07$). The 8-year overall survival rates were 90% and 95%, respectively, in patients with spillage (11 deaths observed vs. 6.5 expected) and without spillage (16 deaths observed vs. 20.5 expected, $p = 0.04$).

DISCUSSION

The likelihood that unirradiated spilled tumor cells will produce clinically detectable intra-abdominal disease after two-drug chemotherapy is less than 15%.

The analysis of abdominal relapse rates by conventional methods does not give an accurate assessment of RT effects

Table 5. Multiple logistic regression analysis of recurrence on site and RT dose limited to patients/events shown in Table 3.

	OR	95% CI*	p value*
Trial			
Flank	1.0	—	
Beyond-flank	0.51	(0.24–1.08)	0.08
RT dose (Gy)			
0	1.0	—	
10	0.38	(0.11–1.30)	0.12
20	0.16	(0.02–1.26)	0.08

Abbreviation: RT = radiation therapy.
* Estimated by generalized estimating equations, *p* value for trend with dose 0.02.

because beyond-flank recurrences at sites that did not receive RT would be counted as relapses against flank-only RT fields. In this analysis, therefore, flank and beyond-flank relapses were analyzed separately using generalized estimating equations (9, 10). The addition of 10 Gy or 20 Gy decreased the likelihood of local treatment failure 3- and 12-fold, respectively. These results are consistent with the data reported by Breslow *et al.*, who found similar statistically significant differences in relapse rates according to the RT dose category among more than 3,500 Wilms tumor patients (13).

The addition of DOX to two drugs or RT was not shown to add to the protective effects of 10 Gy or 20 Gy. This lack of demonstrated effect by DOX may be due to the fact that RT alone was effective in sterilizing spilled tumor cells or that the degree of overlap between the use of DOX and RT increased the statistical uncertainty to the extent that it precluded the detection of a separate DOX effect.

These analyses demonstrate that two-drug chemotherapy alone without RT in Stage II patients with tumor spillage does not completely protect the patient from abdominal tumor recurrence. When the patterns of recurrence in unirradiated Stage II patients were analyzed, the tumor bed (flank) was the predominant site of infradiaphragmatic relapse. Half the unirradiated children who experienced an abdominal relapse survived. This is less than the 80% 4-year survival recorded in the retrieval study of 58 unirradiated children treated initially with two drugs as reported by Green *et al.* (14).

Tumor spillage decreased the relapse-free survival rates and overall survival in comparison with patients without spillage, but only the latter was of statistical significance. However, >85% of nonirradiated patients in whom spillage occurred did not develop abdominal relapses. Similar findings have been previously reported by the NWTSG and International Society of Paediatric Oncology investigators (1, 2, 15, 16). The Renal Tumor Committee of the Children's Oncology Group, which is the successor to the NWTSG, has adopted a policy of upstaging patients with tumor spillage to Stage III (Children's Oncology Group protocol No. AREN0533) and treating them with flank RT (10 Gy) and DOX added to vincristine and dactinomycin. The results of these studies will provide a basis for assessing the risk of overtreating with abdominal irradiation and DOX for the 85% of children with Stage II favorable histology Wilms tumor and spillage who do not relapse vs. the benefit of improving the survival rate and reducing the need for potentially toxic salvage therapy for the 15% of patients who relapse (17). A lower dose of flank RT (10 Gy) with DOX was chosen over 20 Gy for the treatment of these patients as previously published reports from the NWTSG have shown only a minimal impact on growth and development with this regimen and no cases of a second malignant neoplasm in the treatment field were reported after RT doses of <12 Gy (18–20). However, adverse consequences on pregnancy outcomes have been reported (21). The use of DOX has been associated with congestive heart failure, albeit among patients given 150 mg/m^2 of DOX no instances of CHF have been reported thus far (22).

CONCLUSIONS

Abdominal recurrence rates after tumor spillage were significantly higher among patients treated with two- or three-drug chemotherapy without RT. Irradiation with 10 Gy seemed to be successful in reducing tumor recurrence rates after tumor spillage, and 20 Gy even more so. The addition of DOX to vincristine and dactinomycin did not detectably reduce abdominal tumor recurrence rates. Tumor spillage in Stage II patients reduced relapse-free survival and overall survival, but only the latter was of statistical significance. These data provide a basis for assessing the risks vs. benefits when considering the management of Wilms tumor and surgical spillage.

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