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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

JOHN A. KALAPURAKAL,* SIERRA M. LI,† NORMAN E. BRESLOW,† J. BRUCE BECKWITH,‡ MICHAEL L. RITCHEY,§ ROBERT C. SHAMBERGER,¶ GERALD M. HAASE,|| PATRICK R. M. THOMAS,** PAUL GRUNDY,†† DANIEL M. GREEN,‡‡ AND GIULIO J. D'ANGIO§§

*Robert H. Lurie Cancer Center, Northwestern University, Chicago, IL; †University of Washington, Seattle, WA; ‡88 Brookside Way, Missoula, MT; §Pediatric Urology Associates, Phoenix, AZ; ¶Boston Children's Hospital, Boston, MA; ||Denver Children's Hospital, Denver, CO; **Hershey Medical Center, Hershey, PA; ††Cross Cancer Institute, Edmonton, Alberta; ‡‡St. Jude Children's Research Hospital, Memphis, TN; and §§University of Pennsylvania, Philadelphia, PA

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

Reprint requests to: John A. Kalapurakal, MD, Radiation Oncology, Northwestern Memorial Hospital, 251 E. Huron St, LC-178, Chicago, IL 60611, Tel: (312) 926-3761; Fax: (312) 926-6374; E-mail: j-kalapurakal@northwestern.edu

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

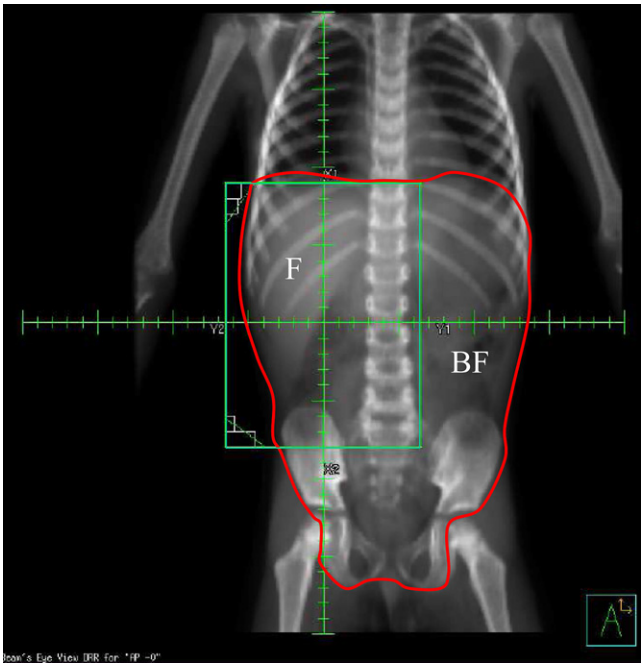

Fig. 1. Digitally reconstructed radiograph of a child receiving flank irradiation for a right-sided Wilms tumor. The regions at risk for relapse after spillage, flank (F) and beyond-flank (BF), as defined by radiation fields are shown.

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