Outcomes of children with favorable histology wilms tumor and peritoneal implants treated on national wilms tumor studies-4 and -5

John A. Kalapurakal, MD[^], **Daniel M. Green, MD**[@], **Gerald Haase, MD**[∞], **James R. Anderson, Ph.D**[©], **Jeffrey S. Dome, MD**[&], and **Paul E. Grundy, MD**[°]

[^]Northwestern University, Chicago, IL

[@]St. Jude Children's Research Hospital, Memphis TN

[∞]Children's Hospital Denver, CO

[©]University of Nebraska, Omaha NE

[&] Children's National Medical Center, Washington, DC

[°]University of Calgary, Edmonton, Canada

Abstract

Purpose—There are no published reports on the optimal management and survival rates of children with Wilms tumor (WT) and peritoneal implants (PI).

Methods and Materials—Among FH WT patients enrolled in the NWTS-4 and 5, 57 children had PI at the time of nephrectomy. The median age was 3 years and 5 months (range, 3 months – 14 years). The majority of children (42/57, 74%) had stage III tumors; 15 had stage IV disease. All patients received multimodality therapy. Forty-eight of 56 of children (84%) who underwent primary surgery had gross total resection of all tumors. All patients received 3-drug chemotherapy with vincristine, actinomycin-D and doxorubicin. Forty-seven patients (82%) received WART and in 50 patients (88%) the RT dose was 10.5 Gy.

Results—After a median follow-up of 7.5 years, the overall abdominal and systemic tumor control rates were 97% and 93% respectively. A comparative analysis between children with and without PI revealed no significant differences in the clinical characteristics between the two groups. The 5-year EFS with and without PI were 90% (95% CI 78%, 96%) and 83% (95% CI 81%, 85%) respectively (p = 0.20).

Conclusions—Multimodality therapy with surgery, WA RT and 3-drug chemotherapy delivered according to the NWTS-4 and -5 protocols resulted in excellent abdominal and systemic tumor control rates. All children should be monitored in long-term surveillance programs for the early detection and management of therapy-related toxicities.

Keywords

Wilms tumor; peritoneal implants; child; radiation therapy; toxicity

There are no published reports on the optimal management and survival rates of children with Wilms tumor (WT) and peritoneal implants (PI). The National Wilms Tumor Study Group (NWTSG) has consistently classified such patients as stage III when peritoneal implants (PI) were detected at the time of initial surgery. The relapse-free survival rates of children with stage III favorable histology (FH) WT have improved from 55-75% in the NWTS 1-2 to 80-90% in the NWTS 3-5 (3-5). This analysis was undertaken in order to determine the clinical characteristics and treatment outcomes of children with FH WT and PI enrolled in the NWTS-4 and-5.

Methods and Materials

Patient Characteristics

Among FH Wilms tumor patients enrolled in the NWTS-4 and -5, a total of 57 children were identified as having PI at the time of nephrectomy. Thirty-six patients (63%) were female. The racial distribution was as follows: Caucasian 41 (72%), African-American 13 (23%), Hispanic 2 (3.5%) and Asian 1 (1.5%). The median age at diagnosis was 3 years and 5 months (range, 3 months – 14 years). The majority of children (42/57, 74%) had stage III tumors; 15 had stage IV disease. Among patients with stage IV tumors, 13 had lung metastases (87%) either alone (n=10) or in combination with liver (n=1), bone (n=1) or both liver and bone (n=1). Three patients had liver and 2 had bone metastases. Twenty-nine patients had right sided tumors and 28 had tumors that arose from the left kidney.

Treatment

All children received multimodality therapy according to the NWTS-4 or -5 protocols. Fifty-six children (98%) had primary surgery and one child had pre-operative chemotherapy with vincristine and dactinomycin. Two patients (4%) had thrombus in the inferior vena cava. A gross total resection of all tumors in the peritoneal cavity along with a radical nephrectomy was performed in the majority of children (48/57, 84%). In 7 children a sub-total resection of PI along with a radical nephrectomy was performed. One child had a partial nephrectomy along with sub-total resection of PI. Lymph node sampling was performed in 50 patients (88%). Twenty patients (35%) had lymph node metastases at the time of radical nephrectomy.

All patients received 3-drug chemotherapy with vincristine (V), dactinomycin (A) and doxorubicin (D) according to the regimens DD, DD4 or DD4A on the NWTS-4 or -5 protocols (4,5).

The NWTS-4 and -5 protocols recommended that all children with PI should receive whole abdomen (WA) RT to 10.5 or 10.8 Gy. A boost was allowed to areas of residual tumor after primary surgery. Among the 57 patients, 47 (82%) received WART. However, ten children did not receive RT according to the protocol guidelines. Nine patients received only flank RT after radical nephrectomy and gross total tumor resection because they had localized PI limited to the flank. One child did not receive RT and was treated with 3 drug chemotherapy alone. The median time interval (RT delay) from surgery to RT was 8 days (range, 4-30 days). Forty-six (82%) patients had RT on or before day 11 and fifty-one (91%) had RT on or before day 14 after surgery. Fifty patients (88%) received a total RT dose of 10.5 - 10.8Gy at 1.5 -1.8Gy per fraction. Six children (12%) received higher doses due to the presence of residual disease after surgery. Four children received a flank boost added to WA RT (10.5Gy) for a total tumor dose of 21 Gy in three patients and 33Gy in one patient. Two children received WART to 13Gy

and 39Gy respectively. Patients who received a WART doses of > 10-11Gy had a posterior kidney block placed in order to limit the remaining kidney dose to ≤ 14Gy as stipulated in the protocol. All children with stage IV tumors also received RT to the lungs (12Gy), liver (19.8Gy) or bone (30Gy). The nine children who were treated with flank RT received 10.8Gy without additional boost doses.

Statistics

Estimation and comparison of relapse-free survival (RFS) and overall survival (OS) rates were conducted using the Kaplan-Meier (6) and long-rank (7) procedures.

Results

The median follow-up from the date of surgery was 7.5 years (range, 1.5 – 19.7 years). Fifty-two of 57 children (91%) were alive and without any evidence of tumor recurrence. Four children had tumor recurrence and one child died of treatment-related toxicity. Among the four children with recurrence disease, two relapsed in the lungs and two relapsed in the abdomen and liver. One child who relapsed in the lungs 9 months after initial therapy with surgery, chemotherapy (DD4A) and WA RT was alive 8 years after salvage therapy with high-dose chemotherapy and autologous bone marrow transplantation. The other three children with recurrent tumor died of progressive disease despite aggressive salvage therapies. One child with stage IV disease died of radiation pneumonitis and pneumocystis carinii pneumonia.

The overall abdominal tumor control rate was 97% (55/57). Two children developed recurrent abdominal disease 6-8 months after initial therapy and both died of progressive disease. One of these children had the initial chemotherapy delayed over 2 weeks due to a surgical wound infection. Abdominal RT was delayed until day 27. The other child initially underwent partial nephrectomy followed by WA RT and a flank boost and received 3-drug chemotherapy. All 10 children treated after gross total resection with flank RT instead of WART (9 patients) or chemotherapy alone without WA RT (1 patient) were alive without tumor recurrence.

The overall systemic tumor control rate was 93% (53/57). As described above, one child was salvaged while the other 3 died of progressive disease despite aggressive salvage therapies. The overall relapse rates for stage III and IV tumors were 7% (3/42) and 6.6 % (1/15) respectively.

The number of patients with abdominal recurrence was too small to show a RT dose-response effect. Among 48 patients who underwent gross total resection of PI, 45 received 10.8Gy, one child received 39Gy (WA), another received 21.3Gy (WA 10.5Gy + flank boost 10.8Gy) and one child did not receive any RT. The rate of local recurrence among these patients was 2% (1/48). Among 9 patients who underwent a sub-total tumor resection, 2 received a higher WA RT dose (21.6Gy, 13.5Gy), 5 received WA (10.5Gy) followed by a flank boost of 10.5 – 21Gy and 2 patients received WA RT of 10.5Gy. One of these children who underwent a partial nephrectomy developed a local recurrence.

A comparative analysis was performed to compare the clinical characteristics and outcomes of patients with and without PI in the NWTS-4 and -5. Fifty-two patients with Stage III/IV FH tumors and PI were classified as either "studied" or "followed" on the NWTS-4, 5 and they were compared to 1584 patients with Stage III/IV FH tumors without PI. There were no significant differences between the two groups with respect to age, sex, tumor stage, chemotherapy or RT treatment regimens. The 5-year event free survival (EFS) for the group with PI was 90% (95% CI 78%, 96%). Their survival was not significantly different from that of children without PI who had a 5-year EFS of 83% (95% CI 81%, 85%) (p = 0.20).

A number of acute and late sequelae were recorded in the patients' charts after multimodality therapy. One patient (2%) with stage IV disease treated with regimen DD chemotherapy, and WA (10.8Gy with a flank boost of 10.8Gy) and whole lung (12Gy + 7.5Gy boost) RT developed respiratory distress syndrome and bilateral interstitial pneumonia and died approximately 2 months after completing RT. Autopsy revealed radiation pneumonitis and pneumocystis carinii pneumonia with no evidence of tumor. Five patients (9%) developed acute small bowel obstruction between 3 weeks to 2 months after initial surgery. Four of the five children required a laparotomy to relieve the obstruction. One of these children subsequently developed another episode of bowel obstruction 12 years after completion of therapy. One patient developed an intra-abdominal abscess 2 weeks after primary surgery (before WA RT) requiring partial colectomy and distal pancreatectomy. Ovarian failure and delayed puberty was observed in three children. Mammary hypoplasia was observed in one child who received both WA and whole lung RT. Scoliosis was observed in 3 patients and another 3 patients had osteoporosis. One patient has developed hypertension requiring medical therapy. One child had 3 benign colonic polyps removed six years after diagnosis of WT (WA RT, regimen DD4A). One child developed a low grade serous papillary carcinoma of the ovary approximately 9 years after her diagnosis of Wilms tumor. She was initially diagnosed at the age of 2 years and 11 months and treated with WA RT and regimen DD4A.

Discussion

The surgical management guidelines for children with Wilms tumor have remained consistent across the years encompassed by the NWTSG and COG protocols. Surgery is recommended as the initial treatment for most of these children as it facilitates accurate tumor staging and characterization that are necessary to determine the appropriate chemotherapy regimen and the need for radiation therapy. The surgical approach includes a transperitoneal radical nephrectomy, lymph node sampling and complete resection of all tumors including gross peritoneal implants. Heroic attempts to excise all or parts of adjoining organs that might be invaded were not warranted because such procedures are associated with an increased risk of surgical complications. Preoperative chemotherapy was recommended for patients in whom primary surgery was not considered safe or feasible (8-10).

There have been significant changes in the RT guidelines and systemic chemotherapy regimens that were used for children with stage III Wilms tumor enrolled on the NWTSG protocols. The RT doses recommended in the NWTS-1 and -2 ranged from 18 Gy to 40 Gy depending on the patient's age (1,2). The systemic chemotherapy used in the NWTS-1 and -2 were either single agent vincristine (V) or dactinomycin (A), combination of vincristine and dactinomycin (VA) or the combination of vincristine, dactinomycin and doxorubicin (VAD) (1,2). In NWTS-3, children with stage III disease either received 10 Gy or 20 Gy to the flank or WA rather than the age-adjusted doses utilized in prior studies. The chemotherapy regimens were either 2 drugs (VA) or 3 drugs (VAD) (3).

There have been no detailed reports on the outcomes of children with WT and PI from the NWTSG. However there are some reports that include the outcomes of these patients. In a report from the NWTS-1, 18 patients with diffuse peritoneal contamination were treated with WA RT (16/18) or flank RT (2 patients) to doses of 18-40 Gy. There were no abdominal relapses in the WA RT group, but one of two patients in the flank RT group developed an intra-abdominal relapse. Six (33%) patients developed liver and/or lung metastases. Two patients treated with high doses of WA RT developed liver metastases in spite of the liver being in the RT field (11).

Analyses of the NWTS-1 and 2 outcomes demonstrated that unfavorable histology, RT delay from surgery of ≥ 10 days and smaller field size (flank fields when WA RT was required as in

diffuse spillage and PI) were significantly associated with intra-abdominal relapse (12,13). The relapse rates among stage III FH patients after flank RT and WA RT were 4.6% and 7.5% respectively in the NWTS-3. Among the patients who relapsed, 2/9 had PI and received flank RT and 3/6 had PI and received WA RT (10-20Gy). All five of these patients with PI had abdominal relapses and subsequently died of their disease. As in the NWTS-1 and 2, RT delay ($\geq$ 10 days) was also an independent predictor for abdominal relapse in the NWTS-3 (14).

In the present report, among 57 children with WT and PI, the majority of patients were treated initially with radical nephrectomy, gross total resection of tumor and lymph node sampling. Whole abdomen RT (10.5 Gy) was delivered to >85% of patients. A flank boost or higher WA RT dose was delivered to 14% after subtotal resection. The median RT delay from surgery was 8 days and the majority of patients started RT within two weeks of surgery (15). All children were treated with 3-drug chemotherapy (VAD). Despite the large volume of abdominal disease at presentation (PI), lymph node involvement in 35% and distant metastases in > 25%, the systemic and local control rates after a median follow-up of 7.5 years were 93% and 97% respectively. These results are superior to the sparse reports on children with peritoneal implants from the NWTS 1-3 discussed above. An important difference in therapy in the NWTS-4 and -5 compared to the NWTS 1-3 was the addition of doxorubicin to vincristine and dactinomycin for all stage III children with/without PI.

These results demonstrate that with multimodality therapy including surgery, WA RT and 3-drug chemotherapy delivered according to the NWTS-4 and -5 protocol guidelines, excellent survival rates can be obtained in children with PI. These therapeutic guidelines will continue to be recommended in the current Children's Oncology Group (COG) renal tumor protocols. Whole Abdomen RT (10.5Gy in 1.5Gy daily fractions) is recommended for all patients with PI after gross total resection. After sub-total resection, a boost of up to 10.5Gy may be administered to areas of residual disease either in the flank or WA limiting the dose to the remaining kidney to $\leq$14Gy. Surgical clips placed at the time of surgery may assist with limiting the extent of boost RT fields in order to minimize the incidence of late toxicity following higher doses of WA RT. Even though a subgroup of children with localized PI were successfully treated with flank RT and chemotherapy, this approach is not recommended as it could result in higher abdominal relapse rates as discussed above in the NWTS 1-3. It is important to optimize the initial therapy of these children and to reduce abdominal relapses, as the salvage rates following second line therapies in patients initially treated with 3 drug chemotherapy and RT are < 50% (16,17).

Childhood survivors of WT and PI may develop acute and delayed complications as a result of the effects of surgery, WA RT and 3-drug chemotherapy on the different organ systems. The effects of these therapies on the gastrointestinal (9,10), pulmonary (18), skeletal (19), endocrine (20), reproductive (21,22) and cardiovascular systems (23) and on the incidence of second malignant neoplasms (24,25) have been well documented by the NWTSG and others. The more extensive abdominal surgical resection and the use of whole abdomen RT fields likely contributed to the higher rate of bowel obstruction (9%) that was observed in these patients compared to the entire NWTS-4 cohort (5%). Considering the aggressive nature of these tumors, no reduction in therapy is advised at this time. However, it is recommended that these children be enrolled in long-term surveillance programs in order to ensure the prompt detection and appropriate management of these and other therapy-related toxicities (26).

Conclusions

The clinical characteristics and treatment outcomes of children with FH Wilms tumor and PI are similar to other stage III children enrolled on the NWTS-4, and -5 protocols. Multimodality therapy with surgery, WA RT and 3-drug chemotherapy delivered according to protocol

guidelines resulted in excellent abdominal and systemic tumor control rates. A number of childhood survivors developed acute and delayed complications. All children should be monitored in long-term surveillance programs for the early detection and management of therapy-related toxicities.

Acknowledgments

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