Original Article

Outcomes based on histopathologic response to preoperative chemotherapy in children with bilateral Wilms tumor: A prospective study (COG AREN0534)

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BACKGROUND: An objective of the Children's Oncology Group AREN0534 Study was to improve the survival of patients with bilateral Wilms tumors (BWT) by using preoperative chemotherapy of limited duration and tailoring postoperative therapy based on histopathologic response. The authors report outcomes based on postoperative histopathologic responses. **METHODS:** Patients with BWT received treatment with vincristine, dactinomycin, and doxorubicin for 6 or 12 weeks followed by surgery. Postoperative therapy was prescribed based on the highest risk tumor according to the International Society of Pediatric Oncology classification and the Children's Oncology Group staging system. **RESULTS:** Analyses were performed on data from 180 evaluable children. The 4-year event-free survival (EFS) and overall survival (OS) rates were 81% (95% CI, 74%-87%) and 95% (95% CI, 91%-99%), respectively. Seven patients who had completely necrotic tumors had a 4-year EFS rate of 100%. Of 118 patients who had tumors with intermediate-risk histopathology, the 4-year EFS and OS rates were 82% (95% CI, 74%-90%) and 97% (95% CI, 94%-100%), respectively. Fourteen patients who had blastemal-type tumors had 4-year EFS and OS rates of 79% (95% CI, 56%-100%) and 93% (95% CI, 79%-100%), respectively. Eighteen patients who had diffuse anaplasia had 4-year EFS and OS rates of 61% (95% CI, 35%-88%) and 72% (95% CI, 47%-97%), respectively; and the 4-year EFS and OS rates of 7 patients who had focal anaplasia were 71% (95% CI, 38%-100%) and 100%, respectively. There was no difference in the outcomes of patients who had different histopathologic subtypes within the intermediate-risk group ($P = .54$). **CONCLUSIONS:** A risk-adapted treatment approach for BWT results in excellent outcomes. This approach was not successful in improving the outcome of patients who had diffuse anaplasia. ***Cancer* 2022;128:2493-2503**. © *2022 American Cancer Society*.

KEYWORDS: bilateral Wilms tumors, blastemal-type Wilms, histopathologic response, preoperative chemotherapy in Wilms tumors, risk stratification.

INTRODUCTION

Children with bilateral Wilms tumor (BWT) account for 5% of all patients with Wilms tumor. Historically, chemotherapy before definitive surgery was the standard of care to preserve an adequate number of normal functioning renal units.[1-3] Although this continues to be an important goal, the outcome of children with BWT from the National Wilms

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Tumor Study (NWTS-5) was suboptimal, with 4-year event-free survival (EFS) and overall survival (OS) rates of 56% and 80.8%, respectively (ClinicalTrials.gov identifier NCT00002610).[4]

Among patients in NWTS who had BWT with favorable histology, the relapse-free survival rate was 65%.[5] For those who had focal anaplastic and diffuse anaplastic BWT, the 4-year EFS estimates were 76% and 25%, respectively.[6] The reasons for this suboptimal outcome were likely because of 1) inadequate staging, 2) a delay in definitive surgery and thus a delay in the assessment of final histopathology, and 3) prolonged chemotherapy before definitive surgery, exposing patients to both acute and long-term toxicities but with no effect on renal preservation or overall treatment outcome.[7-10] The Children's Oncology Group (COG) launched the first prospective, multi-institutional study of children with BWTs to address the factors mentioned above and to improve the outcome of these patients.[11] Children who had bilateral renal masses with typical clinical and radiologic features of BWT could start therapy without a diagnostic biopsy. In patients who did not meet these criteria or were older than 10 years, a diagnostic biopsy was strongly encouraged. All received preoperative chemotherapy with 3 drugs for 6 or 12 weeks, depending on tumor response and the feasibility of nephron-sparing, definitive surgery (see Materials and Methods, below). The subsequent treatment was based on risk assignment, which took into account the histopathologic response and stage. In particular, when assigning treatment postoperatively, we decided to use the lessons learned from the International Society of Pediatric Oncology (SIOP) experience, especially with regard to *necrotic-type* and *blastemal-type* tumors. The initial report describing the excellent outcomes and the advantages of this approach was recently published.[11] Here, we report the outcomes of patients stratified into risk groups based on their histopathologic response to preoperative chemotherapy.

MATERIALS AND METHODS

COG study AREN0534 (2009-2015) (Treatment for Patients with Bilateral, Multicentric, or Bilaterally Predisposed Unilateral Wilms Tumor; Clinical Trials.gov identifier: NCT00945009) had 3 arms: 1 for the treatment of patients with BWT, 1 for patients with unilateral tumors who were at high-risk for metachronous disease or multicentric tumors, and 1 for patients with diffuse hyperplastic perilobar nephroblastomatosis (see Supporting Materials).

Enrollment and Eligibility

Patients were enrolled after obtaining approval from the Institutional Review Board or Research Ethics Board and patient or guardian consent. Patients younger than 30 years who had synchronous, bilateral renal masses ≥1 cm on radiographic imaging were eligible. All patients received an initial risk assignment through the biology and classification study AREN03B2 (ClinicalTrials.gov identifier NCT00898365), with a real-time central radiology review (and a pathology review, if a biopsy was performed). A diagnostic biopsy was not required, but patients who had a diagnostic biopsy or who underwent definitive surgery at diagnosis were still eligible. Enrollment was required within 14 days of diagnosis or 7 days after starting therapy. Patients who had an isolated lesion <1 cm in the contralateral kidney could be treated by nephrectomy with postoperative therapy based on the pathologic findings. These patients were eligible to enroll on another therapeutic study.

Staging

Patients with BWT were assigned both a local stage and an overall disease stage. The final local stage was based on the abdominal tumor spread, whereas the disease stage accounted for the presence of distant metastatic disease.[12] In the setting of bilateral renal tumors, the highest local stage is III, stage IV represents liver involvement or extra-abdominal metastatic disease, and stage V is assigned to patients with bilateral disease regardless of disease extent.[12]

Treatment

Preoperative treatment was to begin within 14 days of a surgical procedure (for those who underwent a procedure) or a radiologic diagnosis of BWT. The overall strategy of the study was to administer preoperative chemotherapy with the goal of performing bilateral partial nephrectomies. Initial induction therapy included vincristine, dactinomycin, and doxorubicin (the VAD regimen) for 2 cycles with 3 weeks per cycle (for dosing and regimen, see Supporting Materials). After 6 weeks, cross-sectional imaging was performed, and a tumor response was assigned for each kidney (for response criteria, see below). If it was deemed feasible by the local institution to perform bilateral partial nephrectomies, surgery was to be undertaken. If the tumors achieved a partial response (PR) but were not yet amenable to bilateral partial nephrectomy, chemotherapy was continued for another 2 cycles. At week 6, if tumors in either kidney did not achieve a PR, bilateral open renal biopsies were recommended to assess the histologic

reason for nonresponsiveness. After 4 cycles of VAD (12 weeks), repeat cross-sectional imaging was performed, and definitive surgery was required by protocol.

Chemotherapy

Adjuvant therapy was based on local and overall tumor stage and by histologic response after either 6 or 12 weeks of chemotherapy (see Supporting Materials). The final risk stratification was based on both postsurgery staging as well as the postchemotherapy pathology classification based on previous SIOP experience, which demonstrated that histologic type with complete necrosis indicated an excellent prognosis, whereas blastemal-type tumors indicated a high risk for progression.[12] This is the first experience within the COG of a prospective study that required preoperative chemotherapy, and we wanted to use treatment regimens and staging that were familiar to COG investigators while acknowledging the prognostic significance of postoperative histopathologic types from the SIOP experience. Favorable-histology Wilms tumors (FHWTs) were subclassified based on the percentage of tumor necrosis and the percentage of viable components of the blastemal, epithelial, or stromal types in the tumor after preoperative chemotherapy. The histologic risk category was determined by the degree of necrosis and by the component comprising >65% of the viable tumor (blastemal, epithelial, stromal, or, in the absence of a predominance, mixed). Completely necrotic tumor (allowing for residual, viable nephrogenic rest elements) was classified as low risk. FHWTs with >67% necrosis (considered regressive by SIOP) were classified as intermediate risk (regardless of histologic subtype). Also within the intermediate-risk category were FHWTs with >35% viable elements that had >67% stromal or epithelial histology or no predominant pattern (mixed). FHWTs with >35% viable tumor of which >67% was blastema were considered to be high risk, for which treatment was intensified using regimen I. Tumors with focal and diffuse anaplasia were treated according to current treatment regimens for their respective histology and stage in unilateral tumors (for details, see Supporting Materials). Treatment was assigned based on the highest risk Wilms tumor (WT) in each patient. For example, if 1 kidney had a completely necrotic tumor and the other had a mixed-type tumor, then the patient was assigned to the intermediate-risk category and not the low-risk category. If there was diffuse anaplasia in 1 tumor and the other had mixed or epithelial components, then the patient was assigned to the diffuse anaplasia regimen. The chemotherapy regimens have been used in previous COG studies; however, in recent studies, the regimens have changed with respect to mg/kg versus mg/m^2 dosing (regimens VAD, EE-4A, DD-4A, I, and UH-1/revised UH-1) (for regimen details, see Supporting Materials).

Patients with diffuse anaplasia were on the UH-1 regimen at the beginning of this study and then switched to the revised UH-1 regimen when AREN0321 was amended (November 23, 2009; ClinicalTrials.gov identifier NCT00335556). Assignment of stage was based on the kidney with the highest stage. For example, if 1 kidney was stage I and the other was stage III, the latter was considered in risk assignment.

Radiation therapy

For FHWTs that were classified as abdominal stage III, flank radiotherapy with 10.8 Gy was used (19.8 Gy for those aged 16 years and older). A difference from other COG studies for unilateral WT was that, although needle or open biopsies before chemotherapy were considered as a criterion for stage III, these patients were not mandated to receive flank radiation therapy if there were no other reasons for a stage III designation. Tumor necrosis present at the margin or within lymph nodes was considered local stage III, and tumor necrosis without viable tumor outside of the kidney but completely excised was considered stage I. Completely necrotic tumors were assigned to receive irradiation in case they were stage III, which is different from practice in the SIOP. The details of radiation therapy are as described by Ehrlich et al and are included on page 6 of the Supporting Materials.[11]

Response

Response was based on Response Evaluation Criteria in Solid Tumors, version 1.1, modified to include 3 lesions per kidney. Target lesions were defined as lesions >10 mm within the kidney. If multiple target lesions were present, then ≥3 of them were described. Each kidney was assessed separately. A PR was defined as a decrease ≥30% in the sum of the greatest dimensions of target lesions, progressive disease (PD) was defined as an increase ≥20% in the sum of the greatest dimensions of target lesions, and stable disease was defined as neither sufficient shrinkage to qualify for a PR nor a sufficient increase to qualify for PD.

Statistics

Survival time was calculated from the date of study entry to the time of event or last follow-up. Tumor progression, relapse, occurrence of second malignancy, or death from

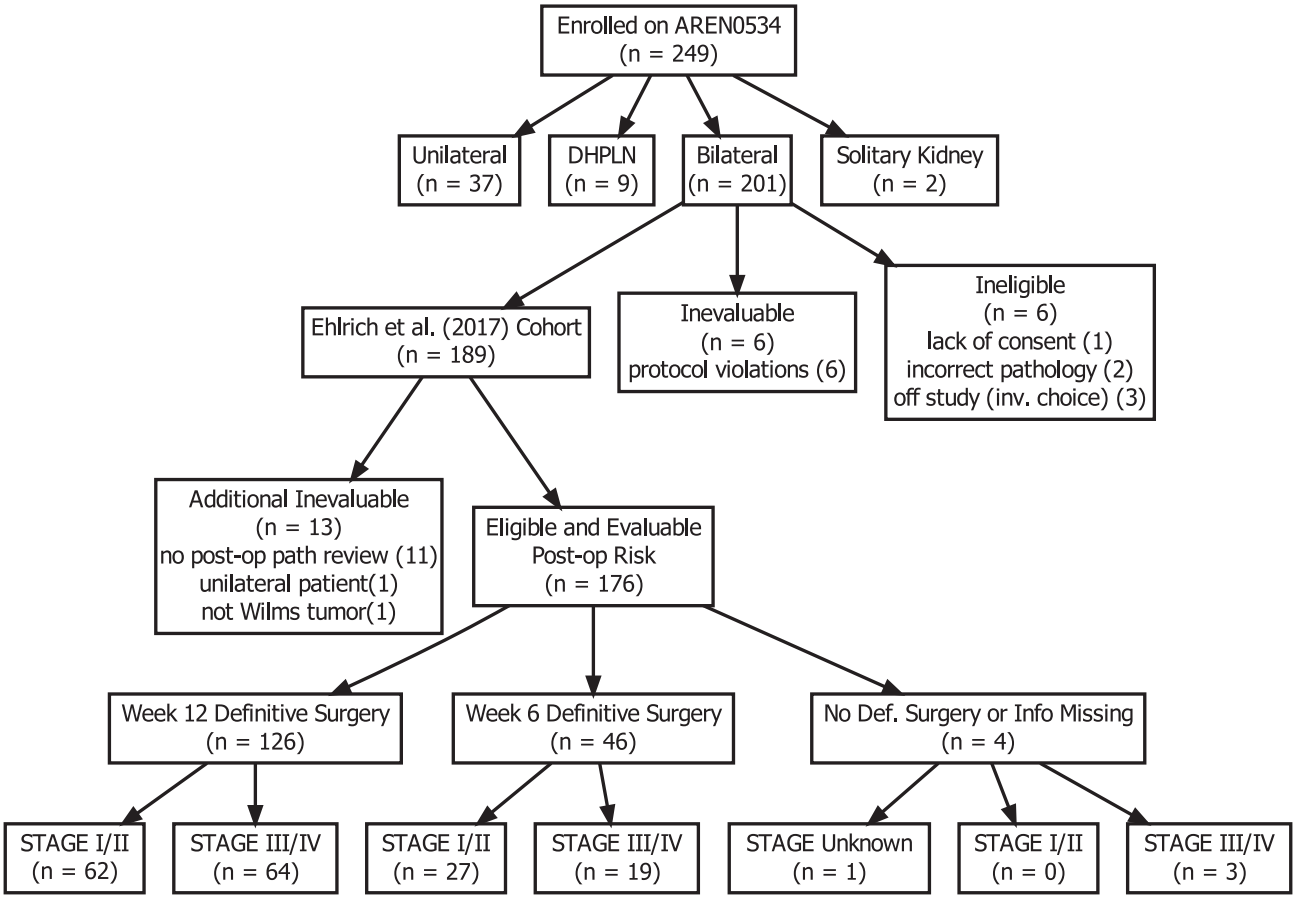

FIGURE 1. This is a Consolidated Standards of Reporting Trials (CONSORT) diagram of the current study. AREN0534, Children's Oncology Group trial; Def., definitive; DHPLN, diffuse hyperplastic perilobar nephroblastomatosis; inv. choice, investigator's choice; post-op, postoperative.

any cause were considered for EFS. OS was measured from the date of study entry to the date of death from any cause. Patients who remained alive at the time of data cutoff (September 30, 2018) were censored at the date of the last observation. Survival probability was calculated using the Kaplan-Meier method, with 95% confidence intervals (CIs) computed using the Peto-Peto method.[13] Survival curves were compared using the log-rank test. Categorical variables were reported as counts and percentages and were compared using the Fisher exact test. All data analyses were performed using R version 4.0.1.

RESULTS

Patients

The study enrolled 201 patients (Fig. 1). All children were younger than 10 years. The numbers differed slightly from those reported by Ehrlich et al for the reasons listed in the Consolidated Standards of Reporting Trials [CONSORT] diagram (Fig. 1). Six patients were ineligible, and 15 were unevaluable, as explained in the CONSORT diagram. Biopsies were performed in 12 patients at diagnosis. Of the 3 patients who underwent biopsies of both kidneys, 1 had a fine-needle biopsy, and 2 had open biopsies. Of the 9 patients who underwent biopsies of 1 kidney, 7 had open biopsies, and 2 had Tru-Cut needle biopsies. Of the 3 patients who underwent biopsies of both kidneys, 2 had FHWTs in both kidneys, and 1 had findings of *nephroblastic lesion, indeterminate between rest and Wilms tumor* in 1 kidney (because of insufficient material) and FHWT in the other. Of the 9 patients who underwent biopsies of 1 kidney, 6 had FHWTs, and 3 had findings of *nephroblastic lesion, indeterminate between rest and Wilms tumor*.

At week 6, biopsies were performed in 23 patients, including 16 who had biopsies of both kidneys, and 7 who had biopsies of 1 kidney. Of the 16 who underwent bilateral biopsies, open biopsies were performed in 13 patients, Tru-Cut and fine-needle biopsies were performed in 1 patient each, and 1 patient underwent a fine-needle

TABLE 1. Responses to Preoperative Therapy According to Histology[a]

	No. of Patients					
Response	Anaplasia	Blastemal	Complete Necrotic	Epithelial	Mixed	Stromal
CR	1	0	0	1	1	0
NE	1	0	0	1	2	0
PD	2	0	0	0	5	5
PR	9	12	6	13	43	3
SD	12	2	1	3	27	13
Total	25	14	7	18	78	21

Abbreviations: CR, complete response; NE, not evaluated; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Twelve patients who had rests only and 1 patient with a predominantly necrotic tumor (regressive type) were not included in this table.

TABLE 2. Event-Free Survival and Overall Survival Based on Histopathology and Staging After Preoperative Chemotherapy

Histology[a]	Stage	No. of Patients	4-Year EFS (95% CI), %	4-Year OS (95% CI), %
Blastemal	I	2	50.0 (0.0-100.0)	50.0 (0.0-100.0)
Blastemal	II	4	100.0	100.0
Blastemal	III	6	83.33 (50.0-100.0)	100.0
Blastemal	IV	2	50.0 (0.0-100.0)	100.0
Completely necrotic	I	6	100.0	100.0
Completely necrotic	II	0	NA	NA
Completely necrotic	III	0	NA	NA
Completely necrotic	IV	1	100.0	100.0
Epithelial	I	7	71.43 (38.0-100.0)	100.0
Epithelial	II	3	100.0	100.0
Epithelial	III	6	83.33 (36.2-100.0)	100.0
Epithelial	IV	2	50.0(0.0-100.0)	100.0
Mixed[b]	I	27	76.84 (60.2-93.5)	96.3 (88.9-100.0)
Mixed	II	12	91.67 (70.5-100.0)	100.0
Mixed	III	29	89.66 (76.7-100.0)	96.55 (88.9-100.0)
Mixed	IV	9	77.78 (41.8-100.0)	88.89 (59.9-100.0)
Stromal	I	8	100.0	100.0
Stromal	II	2	50.0 (0.0-100.0)	100.0
Stromal	III	10	78.75 (49.7-100.0)	100.0
Stromal	IV	1	100.0	100.0

Abbreviations: CI, confidence interval; EFS, event-free survival; NA, not available; OS, overall survival.
[a]This table does not include 25 patients with anaplasia.
[b]One patient with a mixed tumor had an unknown stage and was not included.

biopsy in 1 kidney and an open biopsy in the other. All 7 patients who had only 1 kidney biopsied underwent an open biopsy.

Of the 180 patients who had evaluable postsurgery pathology determined by central review, 19 were considered low risk, including 7 who had complete necrosis and 12 who had rests only. There were 122 patients who had intermediate-risk histopathology, including 78 mixed, 21 stromal, 18 epithelial, and 1 predominantly necrotic (regressive). There were 4 patients who did not undergo definitive surgery at either week 6 or week 12 but did have centrally reviewed pathology when they finally had surgery performed. These 4 patients were not included in the survival analyses, although the pathology was reviewed. All 4 of these patients had intermediate-risk histopathology. There were 14 patients with blastemal-type histopathology. Of the 25 patients who had anaplasia, 18 were diffuse and 7 were focal.

Response

Definitive surgery was performed at 6 weeks in 47 patients and at 12 weeks in 129 patients. As shown in Table 1, of the 21 patients who had stromal differentiated tumors, 13 were stable and 5 had PD after preoperative chemotherapy. However, the 4-year OS rate was 100%. The majority of patients who had other histologies achieved a PR to preoperative chemotherapy (Table 1). There were no differences in survival based on responses or stages within each histologic category (Table 2 and Fig. 2); however, the numbers in each of these categories were low, thus definite conclusions cannot be drawn.

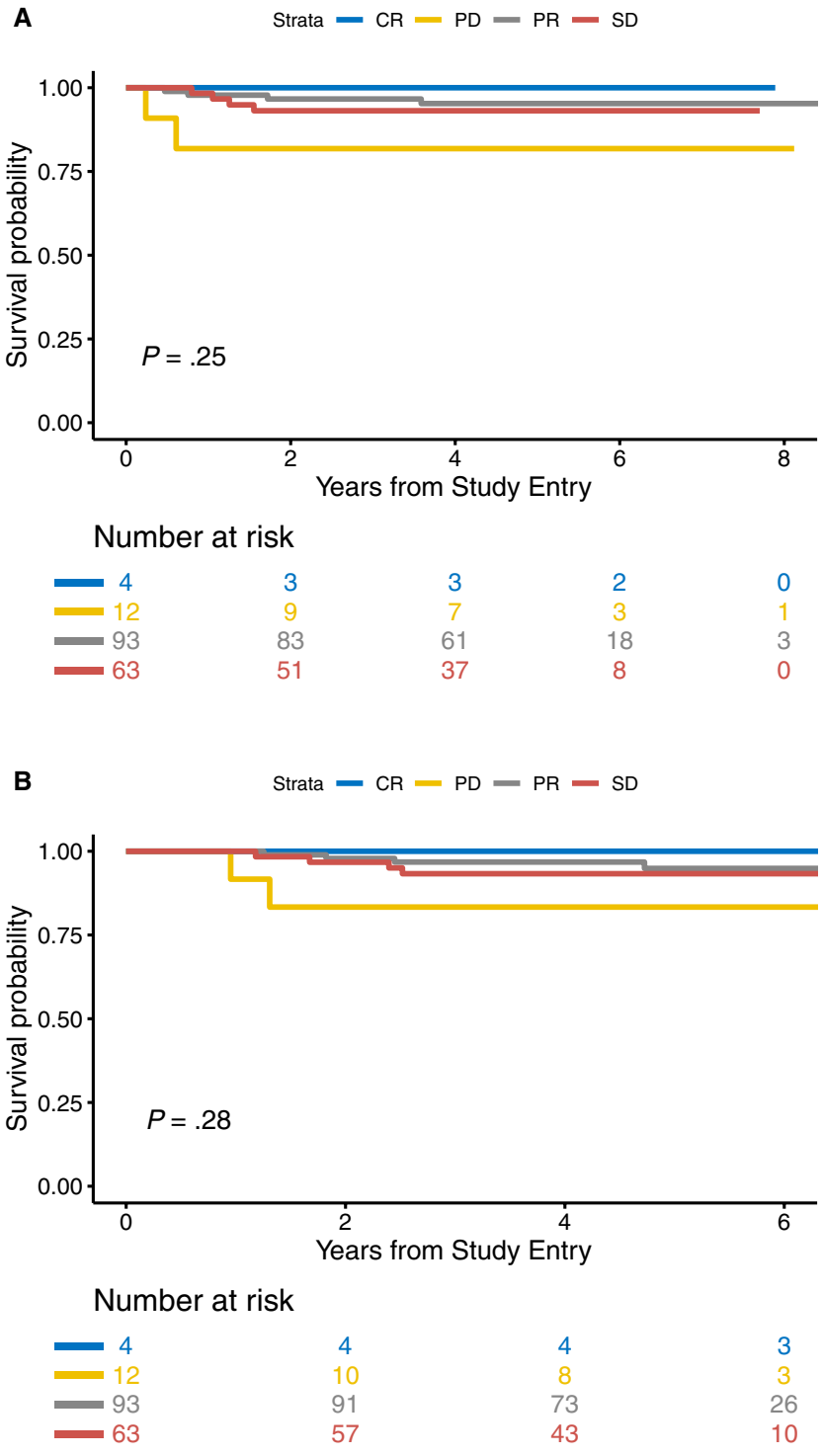

FIGURE 2. (A) Event-free survival and (B) overall survival are illustrated based on response to preoperative chemotherapy. CR indicates complete response; PD, progressive disease; PR, partial response; SD, stable disease.

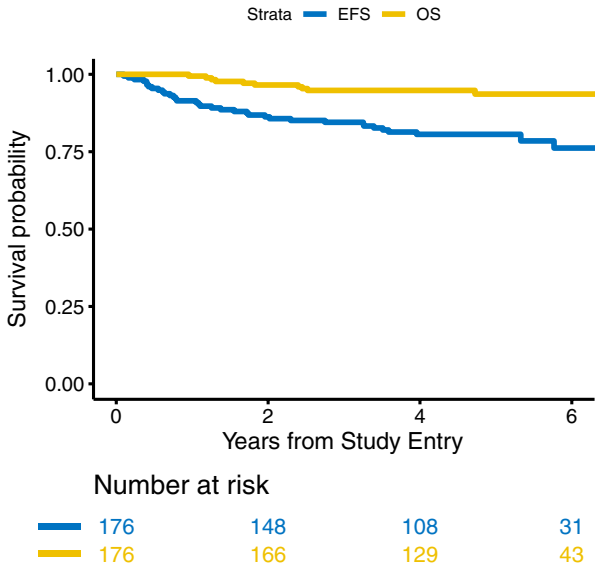

FIGURE 3. Event-free survival (EFS) and overall survival (OS) are illustrated for all 176 evaluable patients.

Outcome

The 4-year EFS rate for all 176 patients was 80.6% (95% CI, 73.9%-87.3%), whereas the OS rate was 94.8% (95% CI, 91.1%-98.5%) (Fig. 3). The 4-year EFS and OS rates for low-risk, intermediate-risk, and high-risk patients were 94.7% (95% CI, 82.9%-100%) and 100%, 82% (95% CI, 74.3%-90.3%) and 97.4% (95% CI, 94.1%-100%), and 78.6% (95% CI, 56%-100%) and 92.9% (95% CI, 78.8%-100%), respectively (Fig. 4). Of the18 patients who had diffuse anaplasia, the 4-year EFS and OS rates were 61.1% (95% CI, 34.7%-87.5%) and 71.8% (95% CI, 46.9%-96.7%), respectively; and, for those who had focal anaplasia, the 4-year EFS and OS rates were 71.4% (95% CI, 38%-100%) and 100%, respectively. Three patients had stage IV disease with diffuse anaplasia, and 1 of them died of disease. Among the patients who had low-risk tumors, those with completely necrotic tumors had 100% 4-year EFS and OS rates (Fig. 5). Within the intermediate-risk category, the EFS rate for the epithelial subtype was 77.8% (95% CI, 53.8%-100%), compared with the mixed subtype (EFS, 83.43%; 95% CI, 73.8%-93%) and the stromal subtype (EFS, 85.21%; 95% CI, 68%-100%; $P = .54$). Those who had stage III disease with blastemal-type histology had a 4-year EFS rate of 83.3% (95% CI, 50%-100%). There were only 2 patients who had stage IV disease with blastemal-type histology.

DISCUSSION

Synchronous BWTs are observed in only approximately 5% of all children with WTs. There has not been a uniform approach to the management of these tumors, given their rarity and the variations in their presentations (nephrogenic rests vs tumors). To our knowledge, this is the first prospective study for children with BWTs to prescribe more intensive initial therapy and definitive surgery after 6 or 12 weeks of chemotherapy.[11]

Preoperative chemotherapy without a biopsy has not been standard practice in the clinical trials conducted by the National Wilms Tumor Study Group and, later, the COG. Therefore, risk grouping based on postoperative histopathology was not previously incorporated into treatment assignment in prior studies. The current study in BWT marks the first attempt within the COG to assign treatment based on postoperative histopathology. We pursued this approach because there were no established guidelines regarding: 1) how long preoperative chemotherapy should be given, 2) how tumor size response should guide the timing of surgery (given that a lack of response could represent a spectrum from differentiated tumors to anaplastic histology tumors), and 3) the lack of prospective evidence that earlier definitive surgery and therapy stratified on postoperative histopathology improves outcomes in patients with BWTs.[11] Although postoperative histopathology risk stratification is a hallmark of SIOP trials, the current study differs in the following ways: 1) this was a prospective study of BWTs, 2) the preoperative therapy was uniformly intense with VAD of either 2 or 4 courses before surgery at either 6 or 12 weeks, 3) the pathology was reviewed centrally before assigning treatment, and 4) postoperative clinical staging was based on COG staging guidelines while incorporating histopathology findings after preoperative chemotherapy (modified from the SIOP experience). Risk assignment for treatment was based on both staging and postoperative histopathology. For the final postoperative assignment of treatment, we took the SIOP experience into account. We did assign patients who had complete necrosis to the low-risk category and those with blastemal-type histopathology to the high-risk category to assign subsequent treatment.

One of the challenges of initiating chemotherapy without a prior tissue evaluation is the interpretation of histopathology and risk assignment after postchemotherapy definitive surgery. Trials from the SIOP have provided information about the histopathologic data and outcomes based on these postoperative histopathologic

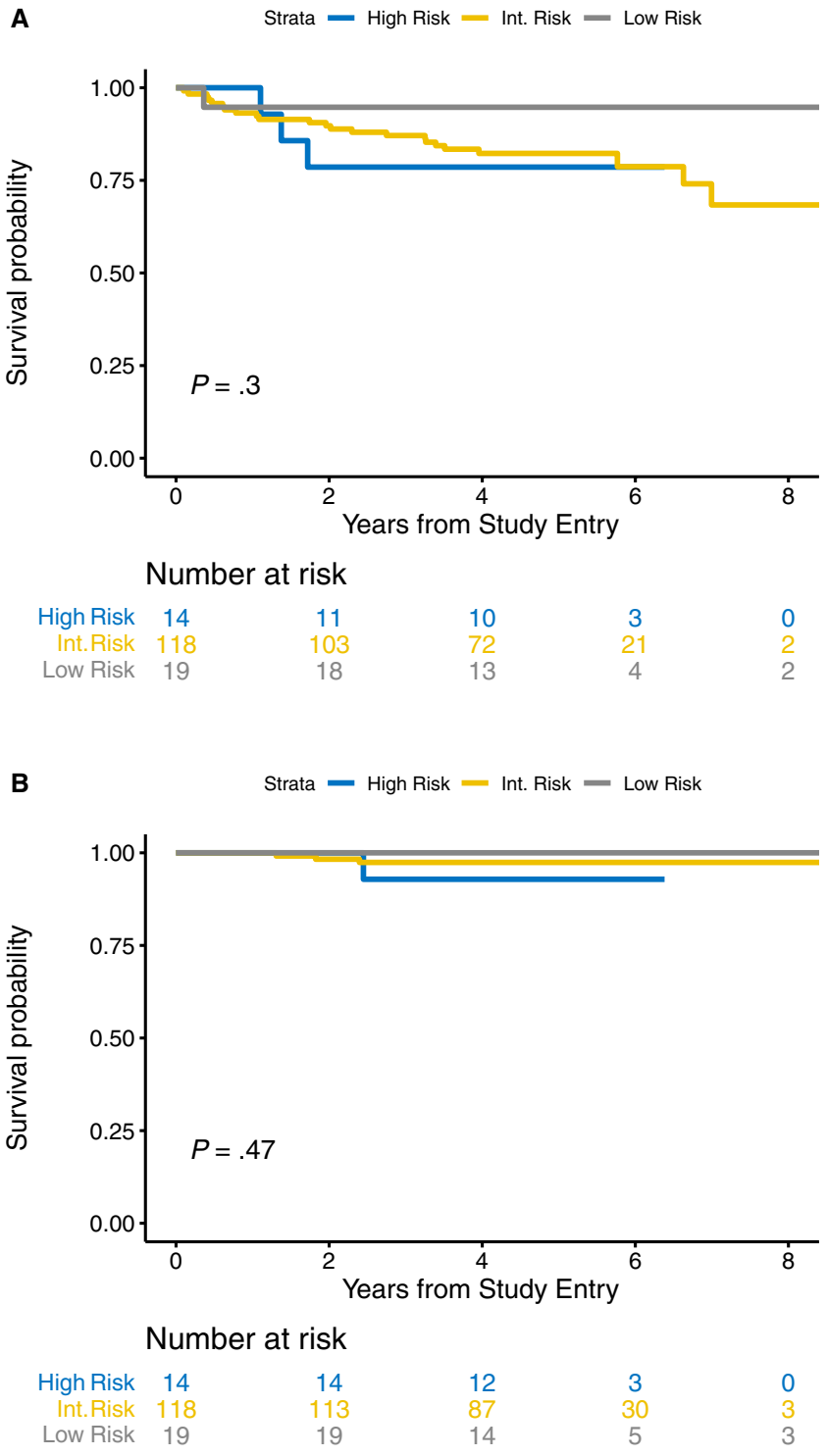

FIGURE 4. (A) Event-free survival and (B) overall survival are illustrated in patients who had low-risk, intermediate-risk, and high-risk tumors based on histopathology after preoperative chemotherapy (high-risk represents blastemal type only and does not include tumors with anaplasia).

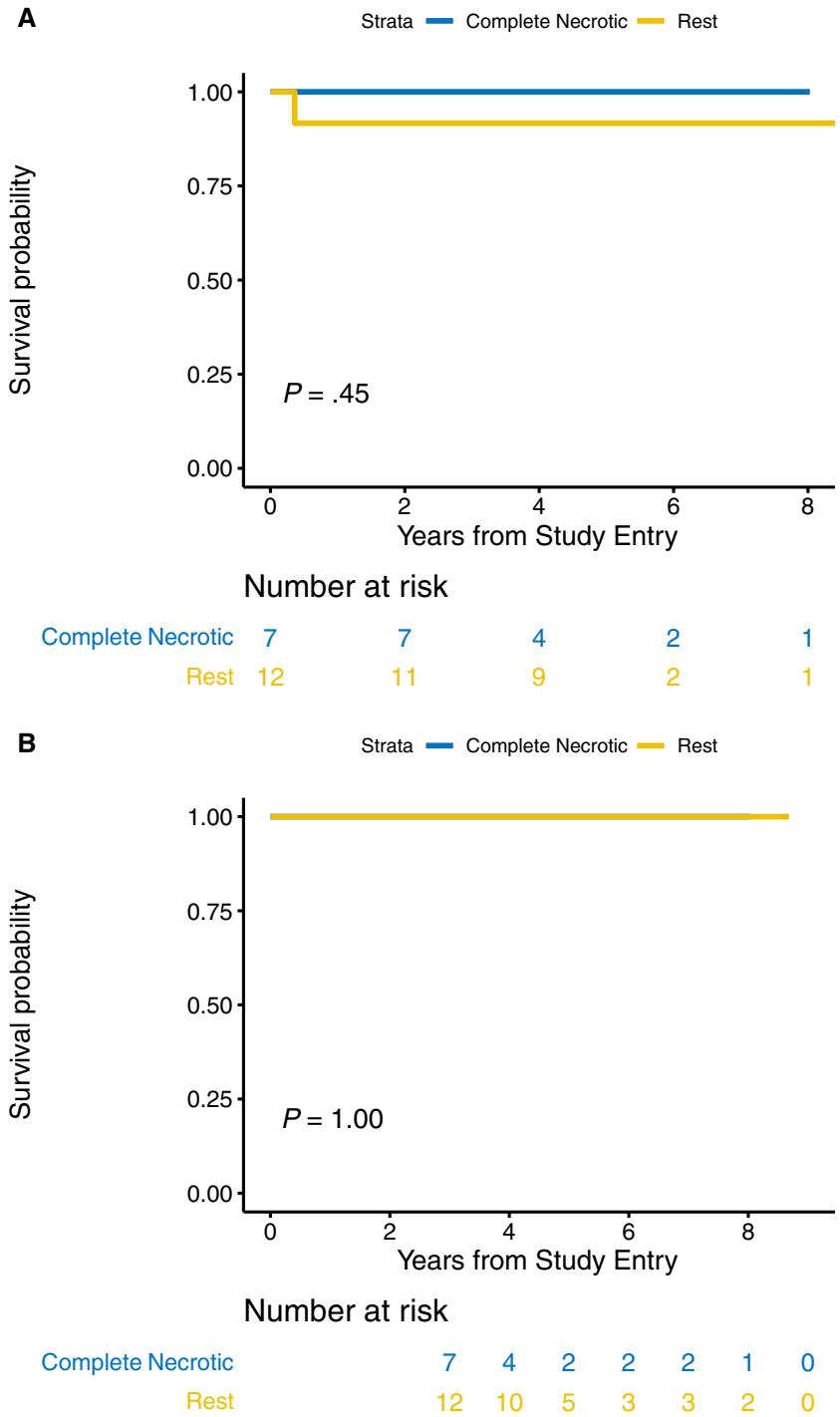

FIGURE 5. (A) Event-free survival is illustrated in patients who had tumors with complete necrosis and those who had rests only. (B) Overall survival is illustrated in patients who had rests only.

assessments in children with unilateral WT. Children with completely necrotic tumors, stromal-predominant pathology, or epithelial-predominant pathology have been described as having an excellent prognosis, whereas those with blastemal-type tumors have the worst prognosis.[14-18] Weirich et al reported that recurrences were not observed in epithelial-predominant, stromal-predominant, or completely necrotic tumors; whereas 38% of blastemal-type

tumors and 11% of mixed-subtype tumors recurred. The 4-year RFS rate was 61% and 89% for blastemal-type and mixed-subtype tumors, respectively.[15] The results from SIOP 93-01 (ClinicalTrials.gov identifier NCT00003804) again demonstrated that patients who had blastemal-type tumors had an inferior 5-year EFS rate of 82% compared with those who had other histologic subtypes.[16] A report from the SIOP Renal Tumor Study Group described results from the SIOP WT-2001 protocol trial (ClinicalTrials.gov identifier NCT00047138), in which patients who had blastemal-type WT after preoperative chemotherapy were considered to be at high risk for recurrence: patients who had stage I blastemal-type tumors were treated with the addition of doxorubicin to actinomycin D and vincristine; and those who had stage II and III blastemal-type tumors were treated with a more intensive regimen of doxorubicin, etoposide, cyclophosphamide, and carboplatin.[14] This approach improved the 5-year EFS rate for patients who had stage I blastemal-type tumors (96% compared with 71% in SIOP 93-01; $P = .03$) and stage II and III blastemal-type tumors (77% vs 61%; $P = .05$), although only those who had stage I disease demonstrated a statistically significant difference in OS with the augmented treatment approach. Volume at surgery, age, stage, and treatment protocol appeared to be prognostic variables for EFS by multivariable Cox regression analysis.[14] As noted in SIOP data, response to preoperative therapy does not always predict outcome (Fig. 4).[15] Eighteen of 21 patients with stromal differentiation in our study who had either stable disease or PD still had an excellent outcome. A recent report also indicated that patients who had subtotally necrotic WT with >95% chemotherapy-induced changes shared the same excellent prognosis as those who had completely necrotic WT. In our study, we did not further classify tumors into subtotally necrotic WTs.[17]

A report from SIOP-9 demonstrated that there was a significant difference in tumor response based on histopathologic subtypes. Stromal and epithelial types showed little change after preoperative chemotherapy; whereas >50% of the mixed, blastemal, and completely necrotic types were good responders and showed a reduction ≥40% in volume.[15] In our study, the majority of patients with epithelial-type tumors also had a PR. This could be due to the moderately intensive preoperative chemotherapy with vincristine, dactinomycin, and doxorubicin, eliminating the nonepithelial components or eliciting responses in predominantly epithelial tumors.

In a recent report from the COG on patients with stage III, favorable-histology, *unilateral* WTs, 116 of 535 patients underwent delayed nephrectomy.[19] Of these, 80 patients had specimens submitted for central pathology review. The 7 patients who had low-risk tumors had a 4-year EFS rate of 100%, 63 who had intermediate-risk tumors had a 4-year EFS rate of 90.5%, and 7 who had blastemal-type/high-risk tumors had a 4-year EFS rate of 28.6%. All of these patients were treated as stage III with favorable histology and received the standard regimen of DD-4A, consisting of vincristine, dactinomycin, doxorubicin, and radiation therapy, as indicated. In the current study, 6 patients with stage III blastemal-type histology had a 4-year EFS rate of 83%. The combination of preoperative therapy, as prescribed in this study, along with risk-stratified regimen I with or without radiation therapy for stages II, III, and IV blastemal-type tumors may have contributed to the improved outcome.

The AREN0534 data also suggest improved EFS in patients with BWTs and diffuse anaplasia treated with regimens UH-1/revised UH-1 (4-year EFS rate, 61.1%; 95% CI, 34.7%-87.5%) compared with regimen I on NWTS-5 (4-year EFS rate, 25.1%; 95% CI, 5.88%-51%).[6] This parallels the improved disease control observed in patients with unilateral, diffuse, anaplastic WT using more intensive treatment regimens.[20]

Information regarding 1q gain and loss of heterozygosity for 1p and 16q was not available for the current study. Another limitation of this study was the lack of genomic studies, which could have shed light on the development of these tumors and may have provided a better understanding of the histologic types. Given the rarity of these tumors, any prospective study would be limited by the small sample size of the various histologic types.

In conclusion, moderately intensive preoperative chemotherapy with early surgical intervention and appropriate treatment modification based on postoperative histopathology and clinical staging improved the outcome of patients with BWTs compared with historic outcomes for children with BWTs within the COG.[11] Innovative approaches are required to improve the outcome for children who have diffuse anaplasia.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Murali M. Chintagumpala: Conceptualization, formal analysis, methodology, supervision, writing–original draft, and writing–review and editing. **Elizabeth J. Perlman:** Conceptualization, formal analysis, project administration, and data curation. **Brett Tornwall**, **Yueh-Yun Chi:** Formal analysis and data curation. **Yeonil Kim:** Formal analysis and data curation. **Frederic A. Hoffer:** Formal analysis, project administration, methodology, and supervision. **John A. Kalapurakal:** Conceptualization, formal analysis, project administration, and data curation. **Anne B. Warwick:** Conceptualization. **Robert C. Shamberger:** Conceptualization, formal analysis, methodology, supervision, and writing–review and editing. **Geetika Khanna:** Formal analysis, project administration, methodology, and supervision. **Thomas E. Hamilton:** Conceptualization; methodology, and supervision. **Kenneth W. Gow:** Data curation and supervision. **Arnold C. Paulino:** Conceptualization, formal analysis, project administration, and data curation. **Eric J. Gratias:** Conceptualization. **Elizabeth A. Mullen:** Data curation, supervision, validation, and investigation. **James I. Geller:** Data curation, supervision, validation, and investigation. **Conrad V. Fernandez:** Supervision, funding acquisition, and writing–review and editing. **Michael L. Ritchey:** Conceptualization and writing–review and editing. **Paul E. Grundy:** Conceptualization, formal analysis, methodology, and supervision. **Jeffrey S. Dome:** Conceptualization, formal analysis, methodology, supervision, funding acquisition, and writing–review and editing. **Peter F. Ehrlich:** Conceptualization, formal analysis, project administration, methodology, supervision, writing–review and editing, data curation, funding acquisition, and investigation.

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