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Results of Treatment for Patients with Multi-centric, or Bilaterally-Predisposed Unilateral Wilms Tumor (AREN0534): A report from the Children's Oncology Group.

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Precis: In children with bilaterally-predisposed unilateral Wilms tumors, a standardized approach of preoperative chemotherapy, surgical resection within 12 weeks and histology-based post-operative chemotherapy results in an excellent EFS/OS and preservation of renal parenchyma.

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Abstract

Background

A primary aim of Children's Oncology Group (COG) study AREN0534 was to facilitate partial nephrectomy in 25% of children with bilaterally-predisposed unilateral tumors (WAGR, multifocal and overgrowth syndromes). The purpose of this prospective study was to achieve an excellent EFS and OS, while preserving renal tissue through pre-operative chemotherapy, completing definitive surgery by 12 weeks from diagnosis, and modifying post-operative chemotherapy based on histologic response.

Methods

The treating institution identified if a predisposition syndrome existed. Patients had central review of imaging studies through the biology and classification study AREN03B2 and then were eligible to enroll on AREN0534. Patients were treated with induction chemotherapy determined by localized or metastatic disease on imaging (and histology if a biopsy had been undertaken). Surgery was based on radiographic response at 6 or 12 weeks. Further chemotherapy was determined by histology. Favorable Histology Stage III or IV disease patients received radiotherapy as well as Stage I-IV with anaplasia.

Results

34 patients were evaluable. 13 were males and 21 were females with a mean age at diagnosis of 2.79 years (range: 0.49 – 8.78). Median follow-up was 4.49 years (range: 1.67-8.01). Underlying diagnosis included 9 with BWS, 9 with hemihypertrophy, 10 had multicentric tumors, 2 had WAGR syndrome, 2 had a solitary kidney 1 had DDS, and 1 had Simpson-Golabi-Behmel syndrome. Four-year EFS and OS were 94.0% (95% CI: 85.2% - 100%) and 100%. Two patients relapsed (one tumor bed, one abdomen) and none had disease progression during induction. Using RECIST 1.1 criteria, radiographic response was CR (2), PR (21), SD (11) and PD (0). Post therapy histologic classification were 13 low-risk (including the 2 complete responders), 15 intermediate-risk, and 6 high-risk (one focal anaplasia and five blastemal subtype). Prenephrectomy chemotherapy facilitated renal preservation in 22/34 patients (65%).

Conclusions

A standardized approach of preoperative chemotherapy, surgical resection within 12 weeks and histology-based post-operative chemotherapy results in an excellent EFS/OS and preservation of renal parenchyma.

Introduction

The outcome for patients with unilateral favorable histology Wilms tumor (WT) is excellent with 4-year event free survival (EFS) greater than 85%. (1-4) A majority of these children never develop a metachronous tumor and the overall incidence of renal failure following treatment for most children with unilateral WT is low. However, there is a subpopulation of patients who are not only at risk for a unilateral WT but are predisposed to develop metachronous bilateral Wilms tumor.(5, 6) They are also at higher risk of developing renal failure.(7) Examples of patients at risk for a second primary renal tumor include those with *WT1* deletions and mutations, as seen in the Wilms tumor/Aniridia/Genitourinary anomalies/Range of developmental delays (WAGR), Denys-Drash and Frasier syndromes; overgrowth syndromes such as Beckwith-Wiedemann Syndrome (BWS), and syndromes associated with other chromosomal anomalies.(8) Many of these children will present with multi-centric disease due to an increased incidence of nephrogenic rests in comparison to patients with unilateral WT not associated with a genetic

predisposition.(9) Porteus reviewed the National Wilms Tumor Study Group experience with 53 BWS patients; 44 had nephrogenic rests and 52/53 had favorable histology (FH) WT. Those with unilateral disease at presentation were reported to be at a significant risk (P = .02) for the development of metachronous contralateral lesions within 4 years (4.5%) compared to non-BWS controls (0.5%).(10) Breslow's 1993 paper defined the subpopulations that are risk for either synchronous or metchronous bilateral tumors including BWS. In A more recent paper on BWS refines this risk based on the underlying genetic abnormality.(11)

The incidence of end stage renal disease (ESRD) is also much higher in these patients. Breslow reported a 38% risk of renal failure, occurring a median of 20 years after diagnosis of WT in these patients. The highest rate is in those with WT1 deletions. In contrast, the 20-year cumulative incidence of ESRD for the non-syndromic group for survivors of sporadic unilateral WT was less than 0.6%. Possible etiologies for the ESRD include repeated chemo-, surgical- and radiotherapy resulting in loss of renal units, as well as the known impact of *WT1* mutation on glomerular development and function.

The increased risk of metachronous disease, coupled with the increased risk of ESRD, provided the impetus to maximize sparing of renal units in patients with unilateral WT and an underlying WT predisposition. The Children's Oncology Group (COG) study AREN0534 was the first clinical trial to prospectively enroll and uniformly treat these patients. The aim was to *facilitate partial nephrectomy in lieu of nephrectomy in 25% of children with unilateral tumors and bilateral predisposition syndromes, by using prenephrectomy induction chemotherapy.* We report the results of this study.

Methods

Study

The COG study AREN0534, *"Treatment for Patients with Bilateral, Multi-centric, or Bilaterally-Predisposed Unilateral Wilms Tumor"* had three arms: one for treatment of patients with bilateral Wilms tumor , one for patients with unilateral tumors at risk for metachronous disease or multi-centric tumors, and one for patients with diffuse hyperplastic perilobar nephroblastomatosis (DHPLN).(12) This report presents the results of children with unilateral tumors who are at risk for metachronous disease.

Enrollment and Eligibility

The National Cancer Institute Central Institutional Review Board (CIRB) reviewed and approved the study protocol. Where regulatory agreements were in place, the CIRB approval was accepted by the local institutional review board. In collaborating sites without such an agreement, the local institutional research ethics board provided approval. All patients or their guardians provided written informed consent prior to enrollment. Enrollment was required within 14 days of diagnosis or 7 days after starting therapy. To enroll on the unilateral arm of the study of AREN0534 patients were first enrolled on the COG biology and classification study AREN03B2 which provided central review of operative notes, diagnostic imaging and when available pathology review (10-12). Patients had to be < 30 years old at the time of initial diagnosis and have one of the following conditions unilateral WT *and* aniridia (WAGR), Beckwith-Wiedemann Syndrome, idiopathic hemihypertrophy, Simpson-Golabi-Behmel-Syndrome, Denys-Drash Syndrome (DDS) or other genitourinary anomalies associated with bilateral Wilms tumor; multicentric WT (any age); or unilateral WT with contralateral nephrogenic rest(s) (any size) by imaging in a child under one year of age.(13) Patients with a solitary kidney could also enroll. Patients could enroll with or without a diagnostic biopsy but were excluded from this arm of the study if they had undergone a nephrectomy at diagnosis. If they had undergone a nephrectomy at diagnosis, they were treated on the standard unilateral protocol. Patients with a horseshoe kidney or inadequate cardiac or liver function were not eligible.

Staging

Patients received both a local stage and an overall disease stage designation. The final local stage was based on the abdominal tumor burden, whereas the disease stage accounted for the presence of distant metastatic disease. All patients who had an initial biopsy (open, trucut or fine needle) were considered stage III. Open biopsies were strongly encouraged and fine needle biopsies because of the inherent difficulty in diagnosing rests from tumor were strongly discouraged The COG and Société Internationale d'Oncologie Pédiatrique (SIOP) staging system have been well described and were used to classify patients treated with preoperative chemotherapy (14) Table 1.

Treatment

The overall strategy of the study was to administer prenephrectomy chemotherapy with the aim of shrinking the tumor to allow maximum preservation of renal parenchyma. Initial induction therapy included vincristine and dactinomycin (regimen EE4A) if no biopsy was performed and

imaging revealed local disease only. Vincristine, dactinomycin and doxorubicin (regimen VAD) was used if no biopsy was performed and imaging revealed metastatic disease or if the tumor was biopsied and found to have favorable histology WT. If anaplastic histology was found on biopsy regimen UH-1 was mandated by protocol (Table 2). Regimen UH-1 was revised mid-study due to greater than expected toxicities observed on the companion AREN0321 study for high-risk renal tumors. Initial therapy included two 3-week cycles of chemotherapy (dosing and regimen in supplemental files 1). After two cycles (approximately six weeks) cross-sectional imaging was performed and a tumor response was assigned by central radiological review. If partial nephrectomy was deemed feasible by the local institution, surgery was to be undertaken. If the tumors achieved a partial response (PR) but were not amenable to partial nephrectomy, chemotherapy was continued for another two cycles. If there was progressive disease after 2 cycles or in some tumors stable disease a total nephrectomy was performed If the tumors did not achieve a partial response (PR) after induction, a total nephrectomy was required by protocol. After four cycles of chemotherapy (12 weeks), repeat cross sectional imaging was performed and either a partial or total nephrectomy was required. Table 3 (ABC) show the treatments based on response and histology from enrollment through to definitive surgery. Adverse events were reported using the Common Terminology Criteria for Adverse events version 5.

Radiology Response Criteria. Criteria used to assess tumor response included reduction in size and the ability to perform a nephron-sparing procedure. Response was based on the Response Evaluation Criteria in Solid Tumor (RECIST 1.1). (15) Target lesions were defined as lesions greater than 10 mm within the kidney. If multiple target lesions were present, the three largest of them were described. Overall response was not modified by extra renal target lesions nor non-target disease. PR was defined as at least a 30% decrease in the sum of the diameters of target lesions (which equals to a 50% decrease in volume), taking as reference the baseline sum diameters. Progressive disease (PD) was defined as at least a 20% increase in the sum of the diameters of target lesions and stable disease (SD) as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Chemotherapy. Adjuvant therapy was based on a final risk stratification taking into account SIOP tumor stage and histologic response after definitive renal surgery at either 2 or 4 cycles of chemotherapy. (Tables 1, 2, 3) The details of the chemotherapy regimens have been previously published.(16)

Radiation Therapy. Patients with favorable histology (FH) tumors who were stage III due to biopsy alone did not receive radiation therapy. For the other FH patients that were classified as abdominal stage III or focal anaplasia stage I-III or diffuse anaplasia stage I-II received flank radiotherapy with 10.8 Gy (19.8 Gy for ≥16 years old), . Patients with stage III diffuse anaplastic histology received 19.8 Gy. Patients required whole abdomen radiation due to preoperative tumor rupture, peritoneal metastases or a large intraoperative tumor spill affecting areas outside the tumor bed as determined by the surgeon. For those with FH received 10.5 Gy and those with diffuse anaplastic histology received 21 Gy. All patients with stage IV disease with pulmonary metastasis received whole lung irradiation to a dose of 12 Gy (10.5 Gy for patients < 12 months old), independent of radiological response.

Statistical Considerations

The study was opened in July 2009, monitored by an independent data safety monitoring board, and was closed in June 2015 after reaching the accrual goal. AREN0534 had three study arms with the statistical driver being the BILATERAL WILMS TUMOR arm. A target accrual of 234 patients was required to enroll a minimum of 115 eligible patients with favorable histology bilateral Wilms tumor without high risk (blastemal subtype) features to meet the study's statistical considerations. Interim efficacy monitoring was done at 25%, 50% and 75% of the expected information using an O'Brien-Fleming boundary (truncated at 3 standard deviations).(17) The unilateral predisposition arm accrued patients as long as the main bilateral Wilms tumorwas open. Statistical methods used included Fisher exact test and Kaplan Meier estimates and log-rank tests of the OS and EFS curves. Patient follow-up was current through 12/31/19.

Results

Patient characteristics

Thirty-nine patients enrolled on the unilateral arm. Five patients were excluded for the following reasons: one started treatment before signing the consent, one did not receive protocol therapy, and three had bilateral renal tumors at diagnosis. Table 4 describes the demographic and clinical characteristics of the 34 remaining patients: 13 were males and 21 were females with a mean age at diagnosis of 2.79 years (range: 0.49 – 8.78). Median follow-up was 4.49 years (range: 1.67-8.01). Underlying diagnosis included 9 with BWS, 9 with hemihypertrophy,

10 had multicentric tumors, 2 had WAGR syndrome, 2 had a solitary kidney (one of these had a previous history of WT without a known predisposition syndrome and one was born with a single kidney also without a predisposition syndrome), 1 had DDS, and 1 had Simpson-Golabi-Behmel syndrome.

Tumor Response and Surgical Resection

The tumor response to pre-nephrectomy chemotherapy among 34 patients with unilateral high risk tumors using the RECIST criteria for the least responsive tumors was CR (2), PR (21), SD (11) and PD (0). Three patients were biopsied prior to starting therapy and the remaining 31 were treated based on clinical and radiographic evidence. Thirty-two patients subsequently underwent surgery; 12 had a complete nephrectomy and 20 had a partial nephrectomy. There were 11 partial nephrectomies performed after two cycles of chemotherapy and 9 after four cycles of chemotherapy. Two tumors completely resolved on chemotherapy requiring no subsequent surgery. Prenephrectomy chemotherapy facilitated renal preservation in 22/34 patients (65%). Table 5 shows the surgical and clinical outcomes based on enrollment eligibility criteria.

Of the 32 with surgery, 15 had surgery after two cycles (week 6) of chemotherapy and 17 had surgery after 4 cycles (week 12). The two patients who had complete resolution of their tumor were considered stage I disease and treated as such. Of the 32 who underwent a surgical procedure, post-surgical SIOP staging demonstrated 21 stage I, four stage II, six stage III (three due to positive margins) and one patient with local stage I was stage IV due to pulmonary metastasis. All but the child who was born with a solitary kidney had favorable histology. This child had focal anaplasia stage I. Using the SIOP post therapy histologic classification there were 13 low-risk (including the 2 complete responders), 15 intermediate-risk, and 6 high-risk (one focal anaplasia and five blastemal subtype). For the 10 multicentric tumors, multiple nodules were examined in 9 with 1/9 having discordant pathology. In this patient, one nodule was low risk and the other nodule was intermediate risk.

There were 22 patients with a known predisposition syndrome where routine ultrasound screening would have been expected. Sixteen were stage I, three were stage II and three were stage III. In these cases, based on operative reports, 13 tumors were detected through routine US. In the other nine patients, we could not confirm whether routine US was performed.

Outcomes

Four-year EFS and OS were 94.0% (95% CI: 85.2% - 100%) and 100%. (Figure 1) There were two events, one was a relapse in a child with BWS. This relapse occurred at 18 months off therapy and was in the original tumor bed. The initial treatment was with EE4A. The relapse histology was favorable histology WT. The second event was a relapse in a child with multicentric disease. This child was given prenephrectomy chemotherapy, then underwent a partial nephrectomy with a positive margin and post-surgery had high-risk histology. The patient developed a new ipsilateral para-aortic lesion in the original radiation field at six months after completion of therapy. There was one grade IV toxicity (sinusoidal obstruction syndrome) on regimen DD4A that was self-limited.

Discussion

The study aim for the multicentric or bilaterally- predisposed unilateral Wilms tumor treatment strata was to achieve partial nephrectomy in lieu of nephrectomy in a minimum of 25% of children by using prenephrectomy chemotherapy induction and a prescribed surgical timing approach. We successfully exceeded that aim with renal preservation occurring in 65% of patients. In addition, we had outstanding outcomes with four-year EFS and OS estimates of 94.9% (95%CI: 85.1% - 100%) and 100%.

Several interventions implemented on AREN0534 likely contributed to this improvement in outcome and renal unit preservation. First, chemotherapy was tailored according to post-chemotherapy SIOP-based histologic response. Patients with diffuse anaplasia and blastemal subtype (high risk) received more intensive chemotherapy compared to previous studies.(18, 19) A second intervention implemented on AREN0534 was to mandate definitive surgical resection after 2 or 4 cycles of chemotherapy, which was achieved in all patients. This is in contrast to historical practice where definitive surgery was often delayed months.(20) A third factor that likely contributed to a better outcome is that we targeted a population of infants and children with an elevated risk for developing Wilms tumor due to their underlying genetic syndrome. Hence, many were followed by screening ultrasound which may have resulted in patients being detected early with low stage tumors where both the outcomes and ability to perform renal preservation surgery would be predicted to be greater. Sixty-eight percent of the patients had stage I disease after induction therapy and surgery (if applicable). This is

consistent with previously published SIOP 2001 data in which 1397/2569 (55%) of patients were stage I after induction chemotherapy.(21)

In this protocol we used induction prenephrectomy chemotherapy with the goal of nephron sparring surgery. Our justification was two-fold. First, these patients have a much higher risk of developing bilateral WILMS tumor.(6, 7, 22) Children with these high-risk syndromes also have a higher incidence of nephrogenic rests which are recognized as precursor lesions to WT.(9, 13) Our second justification is that syndromic Wilms tumor patients have a much higher risk of renal failure than non-syndromic unilateral WT patients. Breslow reported renal failure rate from the NWTS studies in these syndromic at close to 38% at 14 years after diagnosis of Wilms Tumor with the highest risk group being those with WT-1 related syndromes.(23-25) Also any syndrome associated with metachrounous WT carries an increased risk of ESRD due to the need for repeated surgical procedures.

Although published after our study closed, the SIOP renal tumor group retrospective study done over 43 years with 34 BWS and hemi-hypertrophy patients supports our rationale for the study.(26) Nine of 34 had renal preservation surgery and 25 had a complete nephrectomy. The risk of local relapse was similar in both groups. There were two deaths in that study. In a second retrospective single center study published in 2012, Romao et al reported on 13 children with predisposition syndromes; 8 were detected by screening and 6 underwent renal preservation.(27) They also reported excellent outcomes.

A study from the National Wilms Tumor Study Group indicated that WT treatment was as effective in the setting of WAGR syndrome as in the general population of WT patients. (28) However, long-term survival was decreased in WAGR syndrome due to the high incidence of renal failure. More intensive therapy was recommended. This was concerning because WAGR patients have an intrinsic risk of renal failure developing in their teenage years whether or not they develop WT. The results of this study demonstrated excellent disease control without intensifying chemotherapy for the WAGR patients.(29) Both in this unilateral cohort and in the bilateral WILMS tumor cohort reported from AREN0534, the WAGR patients had outstanding outcomes without intensive therapy.(16) In this current report, the WAGR patients receive EE4A, a less toxic regimen as induction and after surgery. Furthermore, the 5 WAGR patients on AREN0534 who presented with bilateral WILMS tumor had VAD on induction were all found to be low risk at resection with stage I or II disease. They were subsequently treated with EE4A following resection. All of these children are alive without recurrences or renal dysfunction. This prospective study suggests that WAGR patients do not require more intensive therapy. We

hope that the renal preservation that the nephron-sparing approach allowed will decrease the long-term risk of ESRD. We plan to perform a long term follow up in this patient population

All patients on this study had favorable histology except one who was born with a single kidney and no recognized underlying predisposition syndrome. Following neo-adjuvant treatment, five patients with favorable histology WT were blastemal subtype according to the SIOP criteria. Four were stage I treated with DD4A and one was stage III treated with Regimen I and all are alive. Possibly with larger cohort of cases, anaplasia would have been encountered but we speculate that a different underlying biology may characterize these subpopulations.

COG renal tumor studies generally require pathology prior to treatment and study enrollment. This study was an exception because patients could enroll based on imaging alone. The primary reasons to perform a biopsy at initial presentation are to avoid misdiagnosis of Wilms tumor and to detect anaplasia, as well as to identify biomarkers such as LOH 1p, 16q and 1q gain. The rate of misdiagnosis of Wilms tumor is low, between 1.6% to 5.5 % for unilateral renal tumors on SIOP studies.(30) The rate is estimated to be even lower for the bilaterally predisposed unilateral tumor and in our study 32/34 started therapy without a biopsy and none were misdiagnosed.

The limitations of the study are inherent in its design. Although the EFS and OS reported here are outstanding and similar to non-syndromic unilateral WT, this was not a randomized controlled trial. Second, the study was not designed to determine the impact of this treatment strategy on late effects such as renal failure. Patients will be followed for 10 years to track the rate of renal failure during this extended time period. Third, while radiographic criteria were well defined for this study, we cannot be certain that some of the smaller lesions which resolved with neoadjuvant therapy may have been nephrogenic rests. This might be true in the 2 patients in whom the lesions completely resolved. We did not use any of the biomarkers such as LOH at 1p and 16q or 1q gain that have been since validated in sporadic unilateral WT to direct therapy. We also noted that some patients underwent a total nephrectomy at week six based on the institutional choice rather than continuing with chemotherapy to see if a partial nephrectomy could have been performed Future work will examine the incidence and impact of these biomarkers in the bilateral and unilateral predisposed population. Finally, although we could determine from the operative notes that 13/22 patients with a known predisposition syndrome underwent routine ultrasound screening, in the other nine it was undocumented, thus limiting our conclusions on whether screening detected early stage tumors.(31, 32)

In summary, this is the largest prospective study of bilaterally-predisposed unilateral WT patients reported to date. This treatment approach including standardized two-drug preoperative chemotherapy, surgical resection within 12 weeks of diagnosis and histology-based post-operative therapy showed excellent EFS and OS and preservation of renal parenchyma.

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Figure Legends

Figure 1

Four year Event Free Survival (EFS)and Overall Survival (OS) for patients on the unilateral arm of ARENO534. The X axis represents years from study entry and the Y axis represent survival probability

Table 1

Post chemotherapy pathology staging system

Risk	**Histology**
Low	Completely Necrotic Favorable Histology
Intermediate	Nephroblastoma epithelial type Nephroblastoma stromal type Nephroblastoma mixed type Nephroblastoma regressive type Nephroblastoma focal anaplasia type
High	Nephroblastoma blastemal type Nephroblastoma diffuse anaplasia type

Table 2 Chemotherapy Regimens for the AREN0534

*for specific dosing details please see supplemental files

Regimen	Agents
VAD	Vincristine, dactinomycin, doxorubicin (maximum 12 weeks)
EE-4A	vincristine and dactinomycin (19 weeks)
DD-4A	Vincristine, dactinomycin, doxorubicin and radiation therapy (XRT) (25 weeks)
Regimen I	Vincristine, dactinomycin, doxorubicin, cyclophosphamide, and etoposide, as well as radiation therapy (XRT) (28 weeks)
UH-1/Revised UH-1	Vincristine, dactinomycin, doxorubicin, cyclophosphamide carboplatin, etoposide and radiation (31 weeks)

Table 3 A, B and C Treatment Regimens

A. Treatment Regimens at induction

	Initial imaging	Initial Regimen
Imaging only (no histology)	Localized disease by imaging no biopsy performed	EE4A
Imaging only (no histology)	Evidence of distant disease by imaging	VAD
Imaging and biopsy reveal favorable histology	All patients	VAD
Imaging and biopsy reveal unfavorable histology	All patients	UH-1/Revised UH-1

B. Treatment regimen after 2 cycles of chemotherapy

CR by imaging	Localized disease by imaging no biopsy	EE4A
CR by imaging	Evidence of distant disease by imaging no biopsy	EE4A
Initial biopsy FH Wilms and CR by imaging after 6 weeks of chemotherapy		DD4A
Initial biopsy revealed anaplastic Wilms tumor and CR by imaging after 6 weeks of chemotherapy	Localized abdominal disease by imaging with or without distant metastases	UH-1/Revised UH-1
PARTIAL NEPHRECTOMY PERFORMED AT 6 WEEKS. FURTHER CHEMOTHERAPY IS BASED ON HISTOLOGY OF REMOVED TUMOR AND HIGHEST TUMOR STAGE.		
Histology	Stage	Regimen
Blastemal subtype	I	DD-4A
Blastemal subtype	II	Reg. I
Blastemal subtype[1]	III-IV	Reg. I (Section 4.5) +XRT
Diffuse anaplastic Wilms tumor	I	DD-4A + XRT
Focal anaplastic Wilms tumor	I-III	DD-4A + XRT
Focal anaplastic Wilms tumor	IV	UH-1/RevisedUH-1 + XRT
Diffuse anaplastic Wilms tumor	II-IV	UH-1/Revised UH-1 + XRT
Completely necrotic tumor	I-II	EE-4A (Section 4.2)

Intermediate risk histology	I-II	EE-4A (Section 4.2)
Completely necrotic tumor[1]	III-IV	DD-4A + XRT
Intermediate risk histology[1]	III-IV	DD-4A + XRT
INITIAL TREATMENT WAS BASED ON IMAGING ALONE WITH LESS THAN A PARTIAL RESPONSE. THESE PATIENTS REQUIRE TOTAL NEPHRECTOMY.		
Blastemal subtype	I	DD-4A
Blastemal subtype	II	Reg. I
Blastemal subtype[1]	III-IV	Reg. I (Section 4.5) +XRT
Diffuse anaplastic Wilms tumor	I	DD-4A + XRT
Focal anaplastic Wilms tumor	I-III	DD-4A + XRT
Focal anaplastic Wilms tumor	IV	RevisedUH-1 + XRT
Diffuse anaplastic Wilms tumor	II-IV	Revised UH-1 + XRT
Completely necrotic tumor	I-II	EE-4A (Section 4.2)
Intermediate risk histology	I-II	EE-4A (Section 4.2)
Completely necrotic tumor[1]	III-IV	DD-4A + XRT
Intermediate risk histology[1]	III-IV	DD-4A + XRT
PARTIAL RESPONSE BUT PARTIAL NEPHRECTOMY NOT FEASIBLE. NO SURGERY SHOULD BE PERFORMED.		
All	I-IV	Continue with chemo and reevaluate at week 12

[1]Biopsy makes the patient Stage III for chemotherapy but patient will NOT require radiation therapy unless they meet other criteria for Stage III designation, such as positive lymph nodes. However , patients with anaplastic histology receive radiation therapy

C. Treatment regimen after 4 cycles of chemotherapy

IF DEFINITIVE SURGERY OCCURRED AT END OF WEEK 6 OR IF THERE WAS COMPLETE RADIOLOGICAL RESOLUTION AT END OF WEEK 6.		Continue with regimen assigned at end of week 6
AT END OF WEEK 6, THERAPY WAS TO CONTINUE WITH CHEMOTHERAPY		
Histology	Stage	Regimen

CR by imaging after 12 weeks of chemotherapy	Localized disease by imaging no biopsy	EE4A
CR by imaging after 12 weeks of chemotherapy	Evidence of distant disease by imaging or even if biopsy performed	EE4A
Biopsy reveals FH Wilms and CR by imaging after12 weeks of chemotherapy		DD4A
Biopsy reveals anaplastic Wilms and CR by imaging after12 weeks of chemotherapy	Localized disease by imaging	UH-1/Revised UH 1
Initial biopsy revelaed anaplstic WT and CR by imaging after 12 weeks of chemotherapy	Evidence of distant disease by imaging	UH-1/Revised UH 1
Nephrogenic Rest without WT	NA	EE4A
AT END OF WEEK 6, THERAPY WAS TO CONTINUE WITH CHEMOTHERAPY BUT CR NOT ATTAINED. DEFINITIVE SURGERY REQUIRED EITHER PARTIAL NEPHRECTOMY IF FEASIBLE OR TOTAL NEPHRECTOMY IF NOT.		
Histology	Stage	Regimen
Blastemal subtype	I	DD-4A
Blastemal subtype	II	Reg. I
Blastemal subtype[1]	III-IV	Reg. I (Section 4.5) +XRT
Diffuse anaplastic Wilms tumor	I	DD-4A + XRT
Focal anaplastic Wilms tumor	I-III	DD-4A + XRT
Focal anaplastic Wilms tumor	IV	RevisedUH-1 + XRT
Diffuse anaplastic Wilms tumor	II-IV after surgery no measureable disease	Revised UH-1 + XRT
Nephrogenic Rest without WT	NA	EE4A
Completely necrotic tumor	I-II	EE-4A (Section 4.2)
Intermediate risk histology	I-II	EE-4A (Section 4.2)
Completely necrotic tumor[1]	III-IV	DD-4A + XRT
Intermediate risk histology[1]	III-IV	DD-4A + XRT

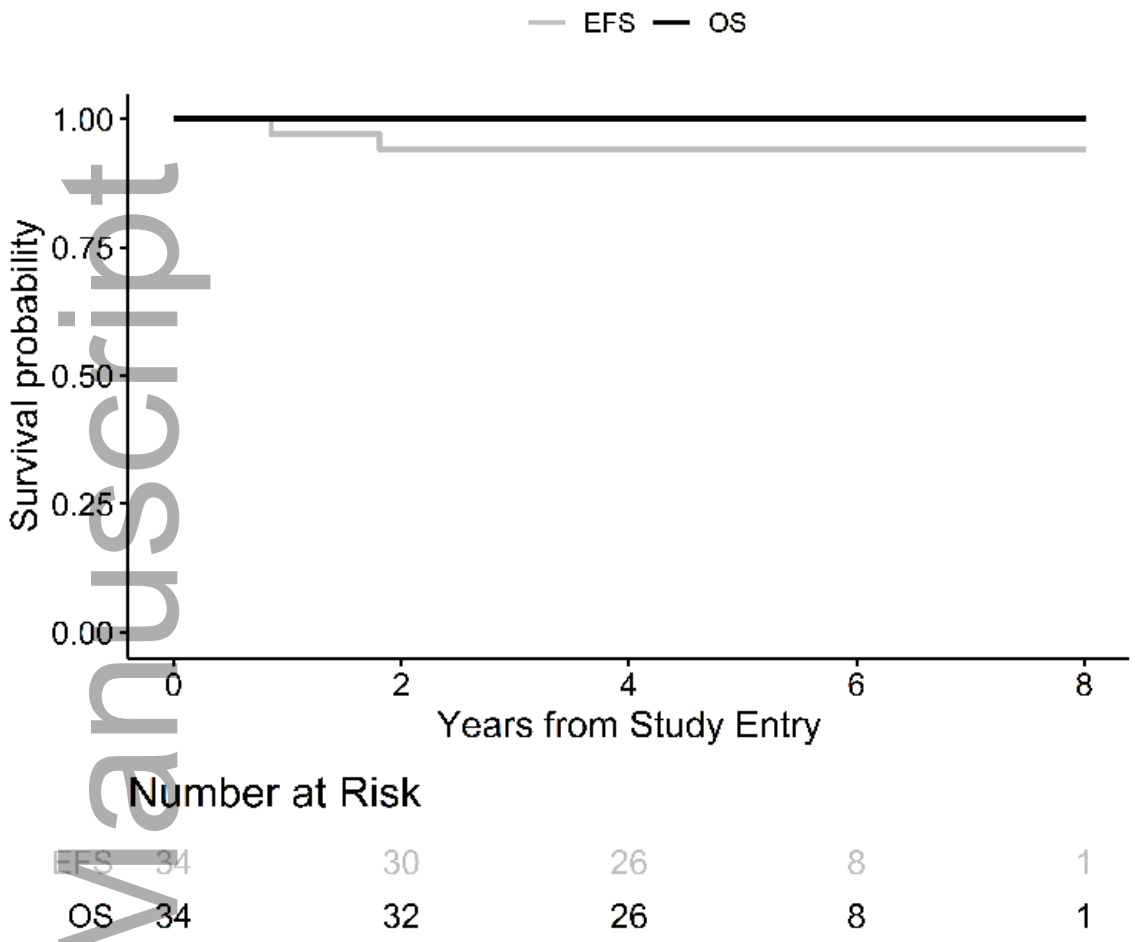
[1]**Biopsy makes the patient Stage III for chemotherapy but patient will NOT require radiation therapy unless they meet other criteria for Stage III designation, such as positive lymph nodes. However, patients with anaplastic histology receive radiation therapy**

Table 4 Patient Demographics

Characteristics	**Category**	**Total N (%)**
Gender	Female	21 (62%)
	Male	13 (38%)
Race	American Indian or Alaskan	1 (3%)
	Black or African American	4 (12%)
	Unknown	3 (9%)
	White	26 (76%)
Ethnicity	Hispanic or Latino	3 (9%)
	Not Hispanic or Latino	30 (88%)
	Unknown	1 (3%)
Syndromes	Beckwith-Wiedemann Syndrome (BWS)	9 (26%)
	Denys-Drash Syndrome (DDS)	1 (3%)
	Hemihypertrophy	9 (26%)
	Simpson-Golabi-Behmel	1 (3%)
	Wilms Tumor Aniridia Syndrome (WAGR)	2 (6%)
	Miscellaneous	12
	Solitary Kidney	2 (6%)
Age (years) at diagnosis	Median (range)	2.8 (0.5-8.8)

Table 5 Surgical and Clinical Outcomes by enrolment eligibility on AREN0534

Beckwith Wiedemann **N=9**	8 partial nephrectomies 1 total nephrectomy	One relapse/disease progression at 18 months
Hemihypertrophy **N=9**	2 complete resolution 4 partial nephrectomies 3 total nephrectomies	None
Multicentric **N=10**	4 partial nephrectomies 6 total nephrectomies	One relapse in para-aortic region with high risk positive margin
WAGR **N=2**	1 partial nephrectomy 1 total nephrectomy	None
Solitary kidney **N=2**	2 partial nephrectomies	None
Denys Drash Syndrome **N=1**	1 total nephrectomy	None
Simpson-Golabi-Behmel **N=1**	1 partial nephrectomy	None



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