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Advances in the Clinical Management of High-Risk Wilms Tumors

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Abstract

Outcomes are excellent for the majority of patients with Wilms tumors (WT). However, there remain WT subgroups for which the survival rate is approximately 50% or lower. Acknowledging that the composition of this high-risk group has changed over time reflecting improvements in therapy, we introduce the authors' view of the historical and current approach to the classification and treatment of high-risk WT. For this review we consider high-risk WT to include patients with newly diagnosed metastatic blastemal-type or diffuse anaplastic histology, those who relapse after having been initially treated with three or more different chemotherapeutics, or those who relapse more than once. In certain low or low-middle income settings, socio-economic factors expand the definition of what constitutes a high-risk WT. As conventional therapies are inadequate to cure the majority of high-risk WT patients, advancement of laboratory and early phase clinical investigations to identify active agents is urgently needed.

Keywords

Wilms tumor; nephroblastoma; high-risk; relapsed; SIOP; COG

Defining high-risk Wilms tumor

Risk-stratified approaches using either the Société Internationale d'Oncologie Pédiatrique (SIOP) Renal Tumor Study Group (RTSG) or Children's Oncology Group (COG) Renal Tumor Committee (RTC) strategies have led to survival rates over 90% for children with Wilms tumors (WT), in aggregate[1]. However, there remain subgroups of WT for which the risk of treatment failure and subsequent mortality are unacceptably high.

In this article, we define "high-risk" as those patients with expected overall survival (OS) of approximately 50% or lower. This "high-risk" category has evolved as we have iteratively improved clinical management through the addition of effective therapies and supportive care, as well as refined risk stratification. For example, stage I-III diffuse anaplastic WT (DAWT) and stage III/IV non-anaplastic WT with specific adverse genetic features (combined loss of heterozygosity (LOH) at chromosomes 1p and 16q) previously had poor OS, but clinical trials using augmented therapies have substantially improved outcomes (Table 1)[2]. Likewise, survival after relapse has improved over time and patients with WT relapse after receiving only vincristine and actinomycin-D up-front now surpass post-relapse OS of 80% (Table 1 and 2).

WT subgroups that continue to have poor outcomes include a) newly diagnosed metastatic WT with post-chemotherapy blastemal-type and/or diffuse anaplastic histology, b) first relapse of WT after initially three or more prior systemic agents, and c) multiply relapsed WT. Survival for these patients is 50% at best[3,4]. Historical, current, and future approaches to managing these high-risk WT patients are the focus of this manuscript. Additionally, we note that this definition of high-risk is setting dependent. In low- and middle-income countries (LMIC), additional factors influenced by socio-economic status, including malnutrition, infections, shortage of drugs and delayed access to sufficient care

may significantly contribute to treatment failure, thereby broadening the groups with OS estimates less than 50%.

High-risk Wilms tumor in the COG context

The National Wilms Tumor Study (NWTS) Group and successor COG approach to the treatment of high-risk WT including DAWT, favorable histology (FH) WT with LOH of 1p and 16q, and relapsed FHWT has evolved over the past 40 years with improvements in OS across all groups (Table 1). The NWTS-3 and 4 studies demonstrated increased OS with the addition of cyclophosphamide to vincristine, actinomycin-D and doxorubicin for stages II to IV DAWT[5]. NWTS-5 further improved OS with a regimen alternating vincristine, doxorubicin, and cyclophosphamide with cyclophosphamide and etoposide (Regimen I)[6]. AREN0321 added carboplatin for stage II-III DAWT patients employing the combinations of cyclophosphamide, carboplatin, and etoposide alternating with vincristine, doxorubicin, and cyclophosphamide (Regimen UH-1) as well as vincristine and irinotecan for stage IV DAWT (Regimen UH-2). The up-front vincristine/irinotecan combination revealed promising objective responses in 11 of 14 patients with metastatic DAWT[4]. Regimens UH-1/UH-2 led to an apparent improvement in outcomes for stages II-IV DAWT, albeit at the expense of greater toxicity compared to the historical Regimen I[4]. A revised regimen UH-1/UH-2 with lower cumulative doses of doxorubicin and cyclophosphamide to limit toxicity showed equivalent efficacy to the original AREN0321 regimens[4].

The combination of LOH of chromosomes 1p and 16q in FHWT is an adverse prognostic factor and augmentation of therapy has benefitted this population (Table 1)[7]. Compared to the NWTS-5, the addition of doxorubicin to vincristine and actinomycin-D in COG study AREN0532 increased both 4-year EFS and OS in patients with stage I and II FHWT with LOH of 1p and 16q. For patients with stage III and IV FHWT with LOH of 1p and 16q, addition of cyclophosphamide/etoposide to vincristine, actinomycin-D, and doxorubicin on AREN0533 (Regimen M) likewise significantly improved 4-year EFS and OS[8].

Outcomes for patients with relapsed FHWT who were treated on NWTS-2 or NWTS-3 were poor using non-standardized salvage therapy including actinomycin-D, vincristine, doxorubicin and cyclophosphamide with occasional cisplatin and etoposide (Table 1)[9]. NWTS-5 specified treatment recommendations for patients with WT who relapsed after initial therapy with 2- or 3-drug therapy respectively, and mainly included stages I-IV FHWT with a small subset of patients with anaplastic WT. For those who relapsed after 2-drug therapy, treatment recommendations were vincristine, doxorubicin and cyclophosphamide alternating with cyclophosphamide and etoposide (Stratum B/Regimen I) which led to a 4-year OS of 81.8%[10]. For those who relapsed after 3-drug therapy, treatment with alternating courses of cyclophosphamide/etoposide with carboplatin/etoposide (Stratum C) led to a 4-year OS of 48%[11]. Outcomes for both groups were substantially improved compared to NWTS-2 and NWTS-3[9]. However, a significant limitation to Stratum C was hematologic toxicities[11].

Based on the activity of vincristine/irinotecan on AREN0321, the current COG AREN1921 trial is assessing the benefit and harms of vincristine/irinotecan in addition to the Regimen

UH-1/2 for stage II-IV DAWT (new regimen, UH-3). AREN1921 also includes patients with relapsed FHWT: those treated initially with 2-drug therapy receive Regimen UH-3, and those treated initially with three or more drugs receive ifosfamide/carboplatin/etoposide alternating with cyclophosphamide/topotecan. The rationale for using topotecan is that in a phase II study 13 of 36 relapsed WT demonstrated an objective response on topotecan monotherapy[12] and activity of topotecan in combination with cyclophosphamide has been observed[13].

High-risk Wilms tumor in the SIOP context

Using the SIOP approach, most renal tumors in patients aged ≥ 6 months are treated with pre-operative chemotherapy (vincristine and actinomycin-D for localized and additional doxorubicin for metastatic disease)[14]. Tumor histology and stage after surgery dictate risk classification. In the SIOP 6 trial, response to preoperative chemotherapy was identified as an important stratification parameter, and the SIOP 93–01 study showed inferior outcomes for patients with blastemal-type tumors (5-year EFS 67%)[15]. Therefore, SIOP regards blastemal-type tumors as high-risk histology, similar to DAWT. The SIOP 2001 protocol was the first study to increase therapy for blastemal-type histology and that study improved EFS for patients with stage I-III (and OS for stage I) compared to the historical 93–01 study[15]. However, 5-year OS for stage IV WT with high-risk histology was disappointingly low despite increased therapy (blastemal-type 53%, DAWT 29%, Table 2)[14]. For patients with stage III and IV tumors with high-risk histology, the SIOP-RTSG 2016 UMBRELLA protocol recommends cyclophosphamide/doxorubicin alternating with etoposide/carboplatin for 34 weeks (HR-1) and higher doses of local flank radiotherapy (RT) (25.2 Gy, with or without 10.8 Gy boost to remaining tumor tissue), with additive lung RT (15 Gy) for lung metastases. Given the very poor outcomes, patients with stage IV blastemal-type or DAWT have alternative treatment options such as following the COG approach with a more intensive irinotecan-based regimen or considering consolidation with high-dose melphalan with autologous hematopoietic stem cell transplant (HSCT), but this is an individualized decision[4,16].

Similar to the COG experience, in SIOP standardized treatment of relapse has improved outcome significantly for WT that relapsed after only two drugs up-front. In the SIOP 93–01 study, 5-year OS was 64% compared to 88% in the SIOP 2001 for this group[1727]. In the SIOP-RTSG 2016 UMBRELLA protocol, a risk-stratified approach is integrated in the standard of care registration study.

Relapsed WT in the SIOP context is now classified into three risk groups (AA, BB, CC), analogous to COG (Table 3) and primarily based upon the up-front treatment, as this was a strong prognostic factor in retrospective studies[15,18]. Group AA includes patients who relapse after treatment with only vincristine and actinomycin-D (standard risk, post-relapse survival rate about 80%) and are treated with alternating cyclophosphamide/doxorubicin and etoposide/carboplatin (similar to HR-1)[10]. Group BB includes patients who relapse after at least three drugs including doxorubicin (high-risk, survival rate about 40–50%)[11] and are treated with four cycles of carboplatin, etoposide, with alternating additional either cyclophosphamide or ifosfamide followed by high dose chemotherapy (HDT) with

melphalan and autologous HSCT to consolidate previous chemotherapy response[3,14]. Group CC includes patients who relapse with initial high-risk histology (advanced-stage DAWT or blastemal-type tumors), or multiple relapses of any histology type, which all have a dismal prognosis (very high-risk, survival rate about 10%)[19–23]. For CC patients, the UMBRELLA protocol encourages administration of a camptothecin-containing regimen such as vincristine/irinotecan (VI), vincristine/irinotecan/temozolomide (VIT) or topotecan/temozolomide because they usually are naïve to these agents in the context of SIOP protocols. The rationale for this is based on a few relapsed cases that demonstrated objective responses, however outcomes data for these regimens are still limited[4,24]. Additionally, the UMBRELLA protocol endorses initiatives dedicated to performing thorough molecular analyses collaboratively with national or international precision medicine programs, using organoids or xenografts, and the potential enrollment onto relevant early phase clinical trials[25].

Local control measures for high-risk Wilms tumor

Surgery and RT have well-established roles in the treatment of newly diagnosed high-risk WT. While surgical approaches and pulmonary RT doses are generally similar between high-risk WT and non-high-risk WT, abdominal RT is often administered at augmented doses in high-risk cases. For example, in the current COG approach, patients with stage III favorable histology WT requiring flank radiation are given 1080 cGy whereas those with stage III DAWT receive 1980 cGy.

For relapsed WT, while surgery and RT with dosing similar to that used in the up-front setting are widely used, there has been limited evidence on how and when to perform local control[17,18]. There is a consensus that patients with relapsed WT who show at least a minimal response to induction chemotherapy should have surgical resection of the recurrent tumor(s), followed by RT to all sites of disease[11,26,27]. Surgical resection of relapsed disease in a chemo-responsive disease setting seems to be associated with improved survival[20,27]. Dome et al. showed that patients with complete surgical resection of relapsed disease had a higher probability of survival than patients who had partial resection or no resection[20]. Similarly, the administration of RT in patients with relapsed WT who were not previously irradiated was associated with improved survival[20,28]. The SIOP UMBRELLA and COG 1921 studies aim to collect more data on local control of relapsed WT.

Role of high-dose therapy and hematopoietic stem cell transplant

A clear role of HDT followed by HSCT has not been definitively established in either the relapsed or upfront setting in high-risk WT. The available evidence is limited by small case numbers, selection bias and lack of adequate control arms. Ha et al. reviewed and meta-analyzed[20] non-randomized studies that overall included 1,226 patients with relapsed WT, treated with or without HDT[3]. Within the caveats of such an analysis, the investigators demonstrated a potential but not statistically significant EFS benefit in patients treated with HDT with high-risk relapse (HR = 0.90, 95% CI 0.62–1.31) and significant advantage for patients with very high-risk relapse (HR = 0.50, CI 0.31–0.82), but not for lower-risk patients initially treated with only two drugs. Malogolowkin et al. reviewed 253 patients

with relapsed WT who underwent HDT in the Center for International Blood and Marrow Transplantation Research database. The 5-year EFS and OS rates were 36% and 45% respectively, comparable to salvage regimens using standard dose chemotherapy[29]. Others have attempted to evaluate the efficacy of HDT as part of upfront therapy in addition to relapse setting. Spreafico et al. reviewed 69 patients with relapsed WT who received HDT after achieving first or subsequent remission in the European Blood and Marrow Transplantation Registry and revealed a 5-year EFS and OS of 63% and 67%, respectively[30]. The authors provided initial data to further explore the benefit of HDT as frontline consolidation in high-risk patients (DAWT or blastemal-type metastatic cases). The limited data seems to support the possibility that HDT may overcome the intrinsic resistance to cytotoxic chemotherapy inherent to *TP53* mutations observed in anaplastic WT. In summary, the evidence for use of HDT in patients with high-risk WT is inconclusive. Although randomized trials would be ideal, such a trial even through international cooperation is unlikely given the small patient numbers. The currently open SIOP UMBRELLA protocol will study the use of HDT with melphalan in some patients with relapsed WT that is responsive to re-induction chemotherapy[14], or as an option for consolidation therapy in patients with initially metastatic tumors with high-risk histology.

Development of novel agents for Wilms tumor

Current treatment regimens with conventional cytotoxic therapies are reaching the limit of tolerated drug doses [1,3,4,14,18]. This is the case even for non-relapsed WT patients, where regimens UH-1 and UH-2 ultimately had to be dose reduced due to unacceptably high toxicity[4]. Accordingly, with a diminishing therapeutic window for further augmentation of conventional chemotherapy, there is a need for identification of agents with different mechanisms of action to improve survival and minimize adverse effects for patients with high-risk WT[25].

Beyond the established effective systemic agents, taxanes and vascular endothelial growth factor receptor (VEGFR)-directed kinase inhibitors represent the next most common classes of systemic agents used in the treatment high-risk WT patients. Paclitaxel given as a 24-hour continuous intravenous infusion on POG9262 revealed single agent activity in a minority of patients with relapsed WT[31]. Case reports have described single agent activity of paclitaxel as well as in combination with platinum chemotherapies[32–34]. Bevacizumab, a monoclonal antibody directed against VEGFR has shown activity when combined with irinotecan, vincristine, and temozolomide in multiply relapsed WT[24,35]. However, outside of this combination, the best responses to monotherapy or combinations including bevacizumab have been stable disease[36–38]. The multi-kinase inhibitors sorafenib and cabozantinib have shown only minimal activity in high-risk WT. Stable disease was the best response observed with sorafenib both in monotherapy and combination[39]. Cabozantinib responses were limited to prolonged stable disease in the phase I and a partial response lasting nearly two years in a case report but no responses were observed in the phase II study setting[40–42]. When used to treat high-risk WT, taxanes and VEGFR/multi-directed kinase inhibitors are generally limited to palliation of patients with multiply relapsed disease who are not eligible for therapeutic clinical trials.

Since conventional therapies are inadequate to cure many patients with high-risk WT, such patients may be more promptly directed onto early phase clinical trials. Historically, early phase clinical trials were predominantly tumor type agnostic and have not included sufficient numbers of patients with WT to definitively assess activity. Two recent reviews identified 257 WT patients across 79 early phase trials from 2000–2020 where patients with predominantly relapsed, occasionally refractory, disease were enrolled. Only nine of these trials had enrolled 10 or more WT patients (ATRA/IFN-α2A, Irinotecan, Topotecan, rTNFα/actinomycin-D, Ixabepilone, Cixutumumab, Sorafenib, Alisertib, Atezolizumab)[25,39]. Excluding studies involving irinotecan, topotecan, or actinomycin-D, there were only three patients with WT enrolled onto these studies with objective responses[25,39]. As such, our collective experience in leveraging novel agents in the treatment of relapsed or refractory WT is limited and generally underwhelming.

Current investigations of targeted and immune-based therapies for high-risk WT attempt to exploit established specific WT vulnerabilities. Given the dependency of WT on canonical Wnt-Beta-catenin signaling, NCT04851119 trial (PEPN2011) is investigating the utility of TBL1 inhibitor Tegavivint[43]. Surface proteins WT1[44] and GPC3[45] are potential therapeutic immune targets in WT and are currently being explored in immunotherapy studies NCT02789228/NCT05238792 and NCT04928677, respectively. DS-8201a, a HER2 antibody conjugated to a topoisomerase 1 payload, and Selinexor[46–48], an inhibitor of the nuclear pore XPO1, are two agents with promising laboratory data which are undergoing clinical trials in other pediatric solid tumors and thus may be amenable to clinical investigations in WT. The heterogeneous genomic landscape of WT makes it challenging to identify selective inhibitors that are effective across all high-risk WT cases however therapeutic vulnerabilities have been identified that could benefit particular subsets of patients. For example, CDK9 inhibitors in MLL1/ENL mutant tumors[49], BRD4 inhibitors in MYCN driven tumors[50], as well as WT with specific DNA damage response defects such as deleterious mutations in ATM via the ATR inhibitor Elimusertib on NCT05071209 (PEPN2112).

Clinical studies of novel agents for high-risk WT are advanced in large part based upon WT-specific preclinical data. This has been challenged by limited robust WT model systems as WT cell lines and mouse models have failed to capture the profound phenotypic and genetic heterogeneity of these tumors. Only a small number of cell lines have been described in the literature, such as the Wit49[51] and 17.94[52] cell lines representing high-risk anaplastic disease and, most recently, a small series of *WT1*-mutant WT cell cultures[53]. Wegert et al. propagated WT spheroid cell cultures, providing three-dimensional (3D) *in vitro* models that can even recapitulate the difficult-to-culture blastemal WT cells[54]. A limited number of Genetically Engineered Mouse Models (GEMMs) have been developed by exploiting mutations observed in human WT such as WT1 loss and IGF2 activation[55], or LIN28 overexpression[56]. Patient-derived xenograft (PDX) models of WT have developed rather well, with groups reporting high rates of WT engraftment compared to other tumor types[57]. Notably, kidney capsule implantation protocols have been well developed, greatly facilitating the use of anatomically appropriate orthotopic PDX WT models. Finally, a relatively new model system for studying WT is the use of organoid technology, which can be derived with high efficiency from WT and expands rapidly[25,58]. With these more efficient

model designs, future studies could potentially assess in real time the best treatment for a specific patient, but now there is a dearth of sufficiently promising therapeutic approaches.

High-risk Wilms tumor in low and low-middle income countries

Although the aforementioned laboratory investigations and early phase clinical trials are attempting to improve survival in patients with high-risk WT in high income countries (HIC), the challenges and strategies to overcome poor survival for WT patients in LMIC are inherently different. Successful treatment of patients with WT in this context requires an integrated multidisciplinary approach involving imaging, surgery, pathology, and RT services[59]. In this view, the definition of high-risk tumors in LMIC is largely influenced by non-clinical factors limiting timely access to integrated - when available - care (Table 4). Compared to HIC, patients with WT in LMIC are diagnosed later, with higher tumor volume and stage[60] and an older age[61–63]. Malnutrition and poor clinical conditions due to advanced illness are common[64] and favor a higher incidence of severe treatment-related toxicities and deaths[61,65–67]. The combination of poor clinical status at time of diagnosis, shortage of essential medicines, high cost of treatment and transportation resulting in treatment abandonment or refusal[65,68–70], low treatment compliance, and utilization of inadequately intensive treatment including omission of RT negatively impact survival[62,68].

LMICs report a higher proportion of patients with anaplasia and advanced disease, which correlate with poor prognosis[66,68,71,72]. However, the prevalence of high-risk factors may be underestimated in LMICs due to difficult access to standardized diagnostic studies like CT scans, which reduce the accuracy of staging and surgical planning[73]. There also is limited training of pathologists to recognize anaplasia[71], correctly define local stage, and to evaluate chemotherapy-induced changes in pre-treated tumors[67,68,74]. The lack of referral centers with high surgical expertise correlates with a higher incidence of tumor rupture and suboptimal surgical staging[72,75] The limited access to supportive care, RT, and certain chemotherapy medications (i.e., carboplatin, alkylating agents) limit the ability to intensify therapy in high-risk tumors[66,76,77]. The combination of underdiagnosis of metastatic disease, later detection of tumors, and lack of central pathology review could explain the lower survival for middle income countries (MIC) compared with HIC, as was seen in the international comparison of outcomes in the SIOP WT 2001 trial for the Brazilian group[67]. We also need to acknowledge that the lack of cancer registries with all information limits the capacity of LMIC to determine the actual incidence of high-risk WT.

Local research initiatives to study and validate adverse prognostic indicators specific to LMICs are expected to help better stratify patients according to realistic cure estimates and administer more reasonably deliverable adapted therapy regimens. The primary interventions that could minimize the impact of high-risk non-clinical factors that reduce the survival of WT in LMIC are (1) universal coverage to avoid late diagnosis, abandonment, and poor compliance with therapy[78], (2) ensure access to standard diagnostic procedures, supportive therapy, and essential medicines, and (3) development of twinning programs (HIC-LMIC) to train the multidisciplinary team and standardize the approach to perform accurate diagnosis, surgical planning, and risk-stratify postoperative therapy[61,64].

The parent and patient advocate perspective

Recent years have seen increased patient/family and advocate involvement in the research process, leading to faster clinical translation, improvement in the transparency of research, and enhanced trust and rapport between all stakeholders[79–81]. Despite strong curative intent, aggressive and lengthy treatment strategies for high-risk WT have so far demonstrated only partial success and can leave survivors to deal with life-long sequelae. Recently, patients, families, advocates, and medical teams have pointed out the need for more-effective and less-toxic treatments for children with high-risk WT[25,63]. Inclusive stakeholder involvement in the design and implementation of new research/protocols and clinical trials allows for improved therapeutic strategies and ultimately, safer and more-efficacious treatments for children with high-risk WT.

Conclusion

Iterative prospective clinical trials of progressively augmented therapies have systematically improved survival in the vast majority of WT patients and narrowed our definition of high-risk WT. Nonetheless, survival is less than 50% in patients with newly diagnosed metastatic blastemal-type and/or DAWT as well as relapsed WT patients excluding those treated with only two drugs in the up-front setting. Such cases of high-risk WT remain a challenge and focused efforts, both preclinically and clinically, are needed to establish better treatment approaches.

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Abbreviations Key

COG	Children's Oncology Group
DAWT	diffuse anaplastic Wilms tumor
EFS	event free survival
FH	favorable histology
GEMM	genetically engineered mouse models
HDT	high-dose chemotherapy
HIC	high income countries
HSCT	hematopoietic stem cell transplant
LMIC	low and middle income countries

LOH	loss of heterozygosity
MIC	middle income countries
NWTS	National Wilms Tumor Study
OS	overall survival
PDX	patient-derived xenograft
RT	radiotherapy
RTC	Renal Tumor Committee
RTSG	Renal Tumor Study Group
SIOP	Société Internationale D'oncologie Pédiatrique
VEGFR	vascular endothelial growth factor receptor
WT	Wilms tumor

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TABLE 1:

Event free survival (EFS) or relapse free survival (RFS) and overall survival (OS) for selected high-risk or relapsed Wilms tumors in COG trials.

Diffuse anaplastic Wilms tumor				
	NWTS-3 and 4; Regimen DD-RT	**NWTS-3 and 4; Regimen J**	**NWTS-5; Regimen I**	**AREN0321; Regimen UH-1 or UH-2 (original or revised)**
Stage II	4-year RFS 40.0% 4-year OS 46.9%	4-year RFS 71.6% 4-year OS 70.1%	4-year EFS 79.2% (95% CI, 60.9–97.5%) 4-year OS 78.4% (95% CI, 60.0–96.9%)	4-year EFS 86.7% (95% CI, 68.8–100%) 4-year OS 86.2% (
Stage III	4-year RFS 33.3% 4-year OS 20.8%	4-year RFS 58.7% 4-year OS 56.3%	4-year EFS 61.3% (95% CI, 47.8–74.7%) 4-year OS 64.7% (95% CI, 51.6–77.8%)	4-year EFS 80.9% (95% CI, 65.8–96.0%) 4-year OS 88.6% (95% CI, 76.4–100%)
Stage IV	4-year RFS 0% 4-year OS 0%	4-year RFS 16.7% 4-year OS 16.7%	4-year EFS 32.1% (95% CI, 14.8–49.4%) 4-year OS 32.1% (95% CI, 14.8–49.4%)	4-year EFS 41.7% (95% CI, 19.6–63.7%) 4-year OS 49.2% (95% CI, 27.5–71.0%)
Favorable histology Wilms tumor with LOH of 1p and 16q				
	NWTS-5; EE4A	**NWTS-5; DD4A**	**AREN0532; DD4A**	**AREN0533; Regimen M**
Stage I-II	4-year EFS 68.8% (95% CI, 55.2–82.3%) 4-year OS 91.6% (95% CI, 83.6–99.6%)	NA	4-year EFS 87.3% (95% CI, 75.1–99.5%) 4-year OS 100%	NA
Stage III-IV	NA	4-year EFS 61.3% (95% CI, 44.9–77.6%) 4-year OS 86.0% (95% CI 90.5–100%)	NA	4-year EFS 90.2% (95% CI, 81.8–98.6%) 4-year OS 96.1% (95% CI, 90.5–100%)

Relapsed favorable histology Wilms tumor			
	NWTS-2 and −3 (varied, see below)	**NWTS-5; Stratum B/Regimen I**	**NWTS-5; Stratum C**
2-drug pretreated	Stage I: 3-year OS 56.6% Stage II/III: 3-year OS 42%	4-year EFS 71.1% 4-year OS 81.8%	NA
3-drug pretreated	Stage II/III: 3-year OS 26% Stage IV: 3-year OS 17.3%	NA	4-year EFS 42.3% * 4-year OS 48% *

Note: adapted from Green, 1994[5], Daw, 2020[4], Gundy, 2005[7], Dix, 2019[8], Green, 2007[10], Malogolowkin, 2008[11]

*mainly included FHWT, but also included small portion of patients with focal anaplastic WT

RFS: relapse-free survival; OS: overall survival; EFS: event-free survival;

DD-RT: Vincristine, Actinomycin-D, Doxorubicin

Regimen J: Vincristine, Actinomycin-D, Doxorubicin, Cyclophosphamide

Regimen I: Vincristine, Doxorubicin, Cyclophosphamide alternating with Cyclophosphamide, Etoposide

Regimen UH-1: Cyclophosphamide, Carboplatin, Etoposide alternating with Vincristine, Doxorubicin, Cyclophosphamide

Regimen UH-2: Cyclophosphamide, Carboplatin, Etoposide alternating with Vincristine, Doxorubicin, Cyclophosphamide plus Vincristine, Irinotecan

EE4A: Vincristine, Actinomycin-D

DD4A: Vincristine, Actinomycin-D, Doxorubicin

Regimen M: Vincristine, Actinomycin-D, Doxorubicin alternating with Cyclophosphamide, Etoposide

NWTS-2/−3 relapse regimens: patients were retreated with different regimens, most commonly containing Vincristine, Actinomycin-D, Doxorubicin and Cyclophosphamide; Cisplatin and Etoposide were used occasionally

Stratum B/Regimen I: Vincristine, Doxorubicin, Cyclophosphamide alternating with Etoposide, Cyclophosphamide

Stratum C: Cyclophosphamide, Etoposide alternating with Carboplatin, Etoposide

TABLE 2.

Event free survival (EFS) and overall survival (OS) for selected high-risk or relapsed Wilms tumors in the SIOP 93–01 and SIOP 2001 trial.

			SIOP 2001		
Stage	**Histology**		**N**		
II/III	Blastemal-type		153	5-year EFS 77% (95% CI 69–86%)*	5-year OS 82% (95% CI 74–91%)
III	All high-risk histology		141	2-year EFS 68%	5-year OS 70%
IV	All high-risk histology		75	2-year EFS 31%	5-year OS 35%
IV	Blastemal-type		34	5-year EFS 44% (95% CI 27–61)	5-year OS 53% (95% CI 36–70%)
IV	Diffuse anaplastic		40	5-year EFS 28% (95% CI 13–43%)	5-year OS 29% (95% CI 13–45%)
Relapse					
Initial stage	**Histology**		**SIOP 93–01**		
I	Excluding blastemal-type and diffuse anaplastic		33	5-year EFS 55% (95% CI 38–70)	5-year OS 64% (95% CI 47–78)
	Relapse		**SIOP 2001**		
I/II + III (no RT)	Excluding blastemal-type and diffuse anaplastic		76	5-year EFS 83% (95% CI 73–90)	5-year OS 88% (95% CI 79–94)
All stages	Relapse (all histology types)		538	NA	5-Year OS 56% (95% CI 51–61%)

Note: Adapted from van den Heuvel-Eibrink, 2015[15], Brok, 2016[82], Pasqualini, 2020[16], Groenendijk 2022[17] and Brok 2018[83]

EFS: event free survival; OS: overall survival; RT: radiotherapy

TABLE 3.

Relapse classifications currently used by COG and SIOP

	COG definition (COG-RTC AREN1921)		SIOP definition (SIOP-RTSG 2016 UMBRELLA)	
Standard risk relapse	Initial therapy with two chemotherapy agents; generally vincristine and actinomycin-D		AA	Relapse after treatment with vincristine and actinomycin-D
High risk relapse	Initial therapy with three chemotherapy agents; primarily vincristine, actinomycin-D and doxorubicin OR vincristine, actinomycin-D and irinotecan		BB	Relapse after treatment with at least three drugs including doxorubicin
Very high risk relapse	Initial therapy with four or more chemotherapy agents.*		CC	Relapse with initial high-risk histology (advanced-stage diffuse anaplasia or blastemal-type tumors)

*COG AREN1921 includes patients with very high-risk FHWT relapses; patients with relapsed anaplastic histology WT are also considered in a very high-risk category but are not eligible for the treatment regimens proposed because there is too much overlap with up-front therapy.

TABLE 4:

High-risk features identified in patients diagnosed with Wilms tumor in LMIC.

Characteristic	Sub-Saharan Africa* 65	AHOPCA** 70
Year (s)	2014–2018	2012–2015
No. Patients.	201	182
Age (median)	3.6 y	3.5 y
Diagnostic approach	Clinical, abdominal US, chest x-ray	Abdominal/chest CT if available; otherwise, clinical, abdominal US, chest x-ray
Tumor volume	Median Size: 14 cm	Median Volume: 579 cc
% Advanced disease	Stage IV: 62 (31%)	Stage III: 116 (63%) Stage IV: 37 (20%)
Radiotherapy	Available in Ghana but not in Malawi or Cameroon.	Available, with late delivery
Chemotherapy (drugs used)	SIOP-Adapted. (VAD)	COG-Adapted. (VAD and CE)
Abandonment	24/201 (12%)	19/182 (10%)
Deaths (First event)	30/201 (15%)	5/182 (3%)
Survival	49%	68%

*** Sub-Saharan Africa:** Includes centers from Malawi (1), Cameroon (3), and Ghana (2).

**** AHOPCA:** Includes centers from Guatemala (1), El Salvador (1), Honduras (2), Nicaragua (1), and Dominican Republic (1).

VAD: Vincristine + actinomycin D +/− Doxorubicin.

CE: Cyclophosphamide and Etoposide (Note: intensified for high-risk cases).