Characteristics and Outcomes of Preoperatively Treated Anaplastic Wilms Tumor Patients Registered in the UK SIOP-WT-2001 and IMPORT Study Cohorts (2002–2020)

Anaplastic Wilms tumor characteristics and outcomes

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Conflict of interest

The authors declare no potential conflict of interests.

Author contributions

GMV and **WM**: Conception and design. **GMV, KP-J, RA-S**, and **TC:** provision of study material and patients. **GMV** and **WM**, **KP-J, RA-S**, and **TC:** collection and assembly of data. **GMV** and **WM**: data analysis. **GMV**, **WM** and **KP-J:** data interpretation. **GMV** and **WM**: wrote an original draft. All authors reviewed, edited, and approved the final version of the paper for publication.

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Lay summary

Anaplasia is an unfavorable feature in Wilms tumor (WT) and is classified as focal (FAWT) or diffuse (DAWT). This study reports the outcomes of patients with FAWT and DAWT who were, for the first time, treated differently. Patients with FAWT received less intensive treatment and their outcomes were comparable to identically-treated

non-anaplastic-WT. Patients with stage I DAWT also had good outcomes treated without radiotherapy, whereas patients with stage II-V DAWT had poor outcomes despite more intensive treatment.

Precis for use in the TOC

Less intensive treatment for patients with focal anaplastic WT resulted in comparable outcomes to patients with intermediate-risk non-anaplastic WT. Stage II–V diffuse anaplastic WT continue to have poor outcomes despite more intensive treatment.

Abstract

BACKGROUND: Since SIOP-WT-2001 study, focal anaplastic Wilms tumors (FAWT) have been treated as intermediate-risk (IR) Wilms tumors and diffuse anaplastic WT (DAWT) as high-risk tumors. **METHOD**: We performed a retrospective analysis of preoperatively treated patients with FAWT or DAWT recruited in two consecutive UK-CCLG-WT studies. **RESULTS:** 121/1237 (10%) patients had AWT confirmed by central pathology review (CPR), including 93/121 (77%) with DAWT and 28/121 (23%) with FAWT. Four-year event-free survival (EFS) was 51% (95%CI 41–63) for DAWT, 88% (95%CI 76–100) for FAWT, and 84% (95%CI 82–87) for IR-non-AWT. Overall survival (OS) was 58% (95%CI 48–70) for DAWT, 95% (95%CI 86–100) for FAWT, and 95% (95%CI 93–96) for intermediate-risk non-anaplastic WT (IR-non-AWT). In a multivariate analysis the presence of DAWT was a significant prognostic factor for both EFS and OS in stages II, III and IV. In a multivariate analysis of unilateral DAWT, stages III and IV remained the only significant prognostic factors for both EFS and OS. In 28% of cases there were discrepancies affecting recognition of anaplasia, classification into DAWT versus FAWT or local pathologic stage. **CONCLUSIONS**: Preoperatively treated patients with FAWT had excellent outcomes to identically treated IR-non-AWT, whereas patients with DAWT showed significantly worse outcomes. All patients with stage I had comparable good outcomes, regardless of the presence/absence of anaplasia. In contrast, the presence of DAWT was associated with significantly worse outcomes in patients with stages II–V. Finally, significant diagnostic discrepancies emphasise the value of CPR.

Key words: Wilms tumour, preoperative chemotherapy, focal anaplasia, diffuse anaplasia, outcomes

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INTRODUCTION

Anaplastic Wilms tumor (AWT) is a distinct type of Wilms tumor (WT), characterized by large, atypical multi-polar mitoses, marked nuclear enlargement, and hyperchromasia,[1,2] and associated with *TP53* mutations.[3-6] It is classified into focal anaplasia (FAWT) and diffuse anaplasia (DAWT).[1,7] Anaplasia has been strongly associated with poor prognosis in WT. In 2001, the International Society of Paediatric Oncology Renal Tumor Study Group (SIOP-RTSG) introduced a new risk stratification in the prospective randomised trial and study (SIOP-WT-2001),[8] where FAWT was classified as intermediate-risk WT (IR-WT) whilst DAWT remained high-risk.

In this retrospective analysis, we examined the outcomes of patients with FAWT and DAWT treated in the UK Children's Cancer and Leukaemia Group (UK-CCLG) according to the SIOP-WT-2001 protocol and UK Improving Population Outcomes for Renal Tumours of Childhood (IMPORT) study. We also addressed several longstanding and clinically significant questions about AWT, particularly in the context of preoperative treatment, including age and stage distribution, and whether poor outcomes were only due to AWT being chemotherapy resistant.[9] Finally, we assessed the utility of central pathology review (CPR) by comparing institutional and central pathology diagnoses, AWT sub-classification, and stage.

PATIENTS AND METHODS

Study population

The UK-CCLG SIOP-WT-2001 study was a multicenter prospective study for children with renal tumors aged up to 18 years, and recruited patients from 25 centres. The IMPORT study was a UK-CCLG multicenter observational study which continued the standard of care established in the SIOP-WT-2001 trial and study. Regulatory and ethical approval was obtained according to national and local regulations, and all participants or legal guardians gave written informed consent.

Treatment

Patients aged above six months with localised WT at presentation were treated preoperatively with four weeks of vincristine and actinomycin D. Patients presenting with metastatic WT received six weeks of preoperative vincristine, actinomycin D and doxorubicin. Postoperative treatment was determined by histologic risk stratification and tumor stage according to the SIOP-WT-2001 criteria.[8,10] The histologic diagnosis and subtypes of anaplasia, and pathologic staging were made by CPR.[1,7,11,12] Patients with stages II–III IR-WT were randomised to receive doxorubicin in SIOP-WT-2001, but not in IMPORT, since SIOP-WT-2001 showed no significant outcome difference for doxorubicin.[8]

Inclusion and exclusion criteria

Patients' records were retrieved from the SIOP-WT-2001-CCLG (March 2002–December 2011) and IMPORT (October 2012–January 2020) study databases. We included all registered patients treated with pre-operative chemotherapy

followed by surgery, with a WT diagnosis confirmed by CPR. Patients with non-WT by CPR were excluded.

Outcome analysis

Dichotomous measures were compared using the 2-tailed Fisher exact test. The Mann-Whitney *U* test was used to compare continuous variables. Event-free survival (EFS) and overall survival (OS) were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazard models were used to calculate hazard ratios (HR) and 95% confidence intervals for EFS and OS. All statistical analyses were carried out using the R system for Windows.

RESULTS

Patient characteristics

We registered 1,237 children with WT who received preoperative chemotherapy, followed by surgery and CPR. The overall prevalence of anaplasia was 121/1237 (10%), including 103/1129 (9%) in unilateral, and 18/108 (17%) in bilateral WT. DAWT was diagnosed in 93/121 (77%) and FAWT in 28/121 (23%) patients.

The overall gender, age and stage distributions are shown in Table 1 **(**patients with low-risk WT, i.e., completely necrotic WT – 69 patients, and with high-risk WT, i.e., blastemal type WT – 77 patients, were excluded). The female-male ratios were not significantly different between any of the three groups.

The median age of patients with DAWT was 55 months, 38 months for FAWT, and 37 months for IR-non-AWT (Table 1; Supplementary Figure 1). There was no patient in the first year of life diagnosed with anaplasia, and only 4% of patients were under the age of 2 years at diagnosis (all with DAWT). A significantly higher proportion of patients with DAWT (57/93, 61%) than with IR-non-AWT (342/972, 35%) were aged 4 years and above (P<.00001); this difference was not significant for FAWT versus IR-non-AWT (10/28, 36%, P=.3).

Tumor characteristics

In unilateral WT there were significantly fewer stage I DAWT (14/78, 18%) versus IR-non-AWT (344/897, 38%, P=.0002), and significantly more stage IV DAWT (27/78, 35% versus 179/897, 20%, P=.004) (Table 1). The differences were not significant for FAWT. There were no significant differences in the proportions of stage II and stage III patients with DAWT, FAWT and IR-non-WT. Nevertheless, the majority of patients with stage III DAWT (14/20, 70%) had regional lymph node involvement, as compared to patients with stage III IR-non-AWT (57/192, 30%, P=.0007). This remained true for all DAWT cases with local pathologic stage III (i.e. including local stage III cases with either distant metastases or bilateral disease in addition to localized unilateral stage III cases), where 27/40 (68%) had regional lymph node involvement versus 121/316 (38%) of IR-non-AWT (P=.0006).

There was a significantly higher prevalence of stage V in DAWT versus IR-non-AWT (15/93, 16%, versus 75/972, 8%, respectively, P=.01) (Table 1).

This difference was not significant for FAWT versus IR-non-AWT (3/28, 11%, *P*=.47). In 13 patients presenting with stage V DAWT where material was available from both kidneys, 12 patients (92%) had WT on both sides, and one patient had DAWT in one kidney and diffuse hyperplastic perilobar nephroblastomatosis (DHPLNB) in the contralateral kidney. For comparison, in 75 stage V IR-non-AWT with material from both kidneys, 46 patients (61%) had WT on both sides and 29 patients had contralateral nephrogenic rests (not DHPLNB; *P*=.03).

Patient outcomes

The median follow-up for survivors was 7.03 years (IQR 3.41–10.39 years).

Bilateral WT represent a heterogeneous group and patients are not treated uniformly. Therefore, we analysed outcomes for unilateral WT and bilateral WT separately, and showed worse outcomes for patients with bilateral DAWT than for patients with either FAWT or IR-non-AWT (Figure 1A-2D)(Table 2).

For patients with unilateral WT, the overall 4-year EFS estimate was 52% (95%CI, 41–66) for patients with DAWT, 87% (95%CI, 74–100) with FAWT, and 84% (95%CI, 82–87) with IR-non-AWT. The overall 4-year OS estimate was 56% (95%CI, 45–70) for patients with DAWT, 95% (95%CI, 85–100) with FAWT, and 94% (95%CI, 92–96) with IR-non-AWT (Table 2).

Patients with stages III or IV DAWT had significantly worse EFS and OS estimates than those with stage III or IV IR-non-AWT (Table 2). Patients with FAWT showed very good outcomes regardless of tumor stage. Of the nine

patients with stages II/III FAWT, only one patient (stage II) received doxorubicin; he subsequently relapsed but survived. One other patient (stage III) FAWT died after relapse.

Analysis of the effect of stage on outcomes in unilateral WT showed a significantly stronger impact of stage III or IV in patients with DAWT than in patients with IR-non-AWT (Figure 2A-3D). This was confirmed by univariate analyses (Table 3), which also showed no significant prognostic impact of age or gender in patients with DAWT. In patients with IR-non-AWT, both older age and female gender were associated with worse EFS and OS estimates. In multivariate analyses, stage III and IV remained the only significant prognostic factors for both EFS and OS for patients with DAWT (Table 4). For patients with IR-non-AWT, stage III and IV remained significant prognostic factors for OS but not for EFS, while age at diagnosis and female gender remained significant only for EFS but not for OS. A multivariate analysis for patients with stage I WT showed no significant effect on either EFS or OS for DAWT versus IR-non-AWT, age at diagnosis, or gender. In contrast, DAWT (versus IR-non-AWT) was a significant prognostic factor for both EFS and OS in multivariate analyses for patients grouped by stage in each of stages II, III, IV, and V (Table 5).

Patterns of recurrence

We recorded relapses or progression in 37 patients with DAWT (Table 6). The commonest sites were lungs and operative bed (each in 16/37 patients, 43%). Seven patients had relapse or progression at more than one site. In 18/37 (49%) patients, relapses occurred in the first 12 months after the diagnosis; in

another 14/37 (38%) patients during the second year after the diagnosis, in 4/37 (11%) between 24 and 36 months, and in 1/37 (3%) after 52 months.

Three patients with FAWT relapsed, including one each with lung, operative bed and combined lung and operative bed relapses. Relapses occurred from 10 to 15 months after diagnosis.

Central pathology review

The median number of slides per case was 29 (6-94). Of 130 AWT by institutional and/or CPR diagnosis, there were 37 (28%) discrepancies affecting recognition of anaplasia, classification into DAWT versus FAWT, or local pathological stage. Fifteen cases were diagnosed as non-AWT by institutional pathologists (eight cases with DAWT and seven with FAWT). Nine cases that were classified as AWT by institutional pathologists were reclassified by CPR as either non-AWTs (six cases) or non-WTs (three cases). Of the cases where the institutional diagnosis of AWT was confirmed by CPR, four were reclassified from FAWT to DAWT, and two from DAWT to FAWT. In eight patients with AWT the stage was changed by CPR (four cases up-staged, four down-staged). Patients were treated according to CPR findings which were available prior to commencing post-operative treatment (rapid CPR).

DISCUSSION

We performed an analysis of clinical and pathologic features and outcomes of AWT diagnosed and treated in two consecutive studies spanning a period of twenty years, during which patients with FAWT were, for the first time, classified

as IR-WT, and thus received less intensive treatment than those with DAWT (high-risk WT). There are few studies with a similar approach covering FAWT and DAWT at all stages.[2,12] Instead, recent reports from SIOP and COG have focused on certain AWT subgroups, such as stage I DAWT and FAWT,[13,14] stage IV DAWT[15] or stage II to IV DAWT.[16]

The overall prevalence of anaplasia in our study, where all patients received preoperative chemotherapy, was 10%, which is almost identical to the 11% overall prevalence in NWTS-5, where 81% of patients had upfront nephrectomy.[2] Both studies were based on large patient cohorts with CPR, and we believe that these figures represent the true prevalence of anaplasia in WT in the UK and the US. These figures imply that pre-operative chemotherapy has no significant impact on the prevalence of anaplasia. The prevalence of anaplasia in bilateral WT (17%) was similar to previous reports (12%–14%).[2,17,18] Stage V DAWT occurred significantly more often in patients with stage V disease who had bilateral WT than in patients with stage V disease with WT in one kidney and nephrogenic rests (not DHPLNB) in the contralateral kidney.

AWT is very rarely diagnosed in early life—there was no case in the first year of life in the present study, and only 4% of all AWT occurred in the second year, in contrast to IR-non-AWT, with 31% occurring in the first two years of life. Moreover, the majority (54%) of patients with AWT in the present series were above four years of age at diagnosis, and more than a third (35%) were above five years of age. The median age at diagnosis of patients with AWT (50 months) was 13 months older than in patients with non-AWT (37 months); for

DAWT, the median age difference was even larger (18 months), whereas for FAWT it was only two months. All these figures are broadly comparable to other large studies, such as NWTS-1–5[2,19-21] and the SIOP 6&9 studies.[12] The age distribution of DAWT shows a consistent shift towards older age, whereas the age distributions of FAWT and non-AWT are different mostly in earlier ages, with the FAWT age distribution being relatively closer to non-AWT.

There was a female predominance in AWT, which did not reach statistical significance, but it is in keeping with the significant female predominance reported in several previous studies.[2,7,12]

Outcome data were available for analysis in almost 90% of registered patients, which compares favorably to the NWTS-5 study (200/281, 71%).[2] We found comparable outcomes at all tumor stages between patients with FAWT and those with IR-non-AWT, justifying the reduction of treatment for patients with FAWT to be the same as for IR-non-AWT in the SIOP-WT-2001 protocol. Patients with DAWT had markedly worse outcomes than those with IR-non-AWT and FAWT in stages II–IV, despite more intensive treatment. In contrast, the presence of diffuse anaplasia had no significant impact on outcomes in patients with stage I, indicating that the more intensive treatment for stage I DAWT was beneficial.

Indeed, 11/12 patients with stage I DAWT survived; this was achieved with four weeks of preoperative chemotherapy with vincristine and actinomycin D (VA), and 27 weeks of postoperative chemotherapy with vincristine, actinomycin D and doxorubicin (VAD), and no radiotherapy. In the COG-AREN0321 study, 10/10 patients with stage I DAWT survived, with 24 weeks

of chemotherapy with DD4A (which includes vincristine, actinomycin D and doxorubicin) and 10.8Gy flank radiotherapy.[13] The authors also reported a composite analysis including a further 63 patients from NWTS-1–5 treated according to eight chemotherapy protocols with varying duration of chemotherapy (from 18 weeks to 15 months), and with flank radiotherapy in four protocols. It showed a borderline significant improvement in EFS (*P*=.046) with doxorubicin but not with radiotherapy, and no significant difference in OS for either doxorubicin or radiotherapy.[13]

Similarly excellent results were obtained in patients with stage I FAWT—none out of nine patients died, and only one relapsed. These outcomes were achieved with relatively mild treatment (eight weeks chemotherapy with VA, and without doxorubicin). In the recent COG-AREN0321 report, there were also no relapses or deaths in a comparable group of eight patients with stage I FAWT, but this was achieved by 24 weeks chemotherapy with DD4A and 10.8Gy flank radiotherapy.[13] Their extended analysis including a further 31 patients with stage I FAWT from NWTS-1–5 treated according to an additional eight chemotherapy protocols with varying duration of chemotherapy (from 10 weeks to 15 months), and with flank radiotherapy as an additional variable in two protocols, showed no significant improvement in EFS or OS with either doxorubicin or radiotherapy.[13]

Patients with stage II DAWT did not show significantly worse outcomes than patients with stage I DAWT, which suggests that the more intensive treatment they received was also beneficial. The treatment given to patients with stage III DAWT was the same as for stage II DAWT, but the outcomes

were markedly and significantly worse, being close to those for stage IV DAWT, suggesting that the treatment strategy for stage III DAWT should be reconsidered. Patients with stage IV DAWT represented the worst prognostic group, despite receiving the most intense treatment, with 4-year EFS and OS estimates of 36% (95%CI 21-62) and 31% (95%CI 16-62), respectively. This is similar to outcomes for all patients with stage IV DAWT treated according to the SIOP2001 protocol in a recent report from the SIOP Renal Tumor Study Group.[15]

Outcomes in bilateral WT are difficult to interpret, and to compare between studies, because of complex treatment regimens and contralateral lesions ranging from isolated nephrogenic rests to DAWT. In this study, as in NWTS-5, outcomes in patients with stage V DAWT were comparably poor,[2] and, indeed, a recent conference abstract from the COG AREN0534 study showed that 12/17 patients with stage V DAWT survived.[22]

Poorer outcomes in patients with DAWT stages III, IV and V (versus comparable outcomes in stages I and II) are particularly worrying when considering these constitute 67% (62/93) of all patients with DAWT, as compared to 46% (445/972) of patients with IR-non-AWT. These differences in tumor stages were driven by a significantly lower proportion of stage I in patients with DAWT and higher proportions of stage IV and stage V. While the proportions of stage III DAWT and stage III IR-non-AWT were similar, there was a significantly higher proportion of stage III DAWT with lymph node metastasis. Although Beckwith *et al.* postulated that anaplastic cells are more therapy-resistant but not inherently more aggressive than non-AWT cells,[9] our findings

indicate that DAWT are not only more therapy-resistant but also more aggressive by virtue of spreading more often to lymph nodes and distant sites. In contrast, the stage distribution of FAWT was not significantly different from IR-non-AWT in any category. The SIOP-6&9 study showed similar stage distributions in unilateral DAWT and FAWT.[12] In NWTS-5, bilateral and metastatic disease were also more common in DAWT, but, unlike in our series, in FAWT too. Conversely, in localised NWTS-5 cases, there were no significant differences in stage I between non-AWT, FAWT, and DAWT. However, comparing stage distributions between the present and NWTS-5 studies is inappropriate, since NWTS-5 tumors were staged according to different criteria.[2]

In view of the differences in treatment and outcomes, it is imperative that anaplasia be recognised, subtyped and staged accurately. The criteria for anaplasia were introduced more than 40 years ago,[1] and have not changed since, except for re-definitions of FAWT and DAWT subtypes in 1996,[7] and the SIOP-WT-2001 diagnostic and staging criteria were introduced 20 years ago. Nevertheless, in 28% of cases with a CPR or institutional diagnosis of anaplasia there were discrepancies in diagnosis of anaplasia, FAWT vs DAWT subtyping, or tumor staging. In other studies, the discrepancy rates were even higher,[2,12] highlighting the continuing value of rapid CPR.

A limitation of the present study is the relatively low number of patients with FAWT. However, AWT constitute only 10% of WT, and FAWT accounts for approximately only one quarter of patients with AWT. This study represents the largest single group of pre-operatively treated patients with FAWT reported to

date. In the future, it may be beneficial to analyze the validity of the findings in our study on a larger cohort such as the overall SIOP-WT-2001 study where patients from 28 countries were recruited.

In summary, in a large cohort of WT patients treated with pre-operative chemotherapy, the prevalence of anaplasia was 10%. DAWT occurred consistently in older patients. Excellent outcomes of FAWT justify their treatment as IR-WT. Metastasis to lymph nodes and distant sites accounted for the higher stage distribution of DAWT, which showed poor outcomes in stages III–V; thus, DAWT is intrinsically more aggressive as well as resistant to treatment. Significant difficulties remain in the recognition and subclassification of anaplasia, confirming the continuing need for rapid CPR.

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Figure legends

Figure 1. Estimated, A, event-free survival, B, overall survival for patients with bilateral Wilms tumor, C, event-free survival, D, overall survival for patients with unilateral Wilms tumor

Figure 2. Estimated, unilateral Wilms tumor, by stage, A, event-free survival, B, overall survival for patients with intermediate-risk nonanaplastic Wilms tumor, C, event-free survival, D, overall survival for patients with diffuse anaplasia Wilms tumor

TABLE 1. Demographics and characteristics of patients with Wilms tumor enrolled onto SIOP-WT-2001-CCLG and IMPORT studies

Characteristics		IR-non-AWT (n=972) No	%	Focal anaplasia (n=28) No	%	*P* *(vs IR-non-AWT)*	Diffuse anaplasia (n=93) No	%	*P* *(vs IR-non-AWT)*
Gender									
	Male	444	46	13	46	1	36	39	.23
	Female	528	54	15	54		57	61	
Age at diagnosis (months)									
	Median	37		38			55		
	Range	0–199		25–79			12–163		
Age at diagnosis (in whole months)									
	0-11	114	12	0	0	.3	0	0	<.00001
	12-23	186	19	0	0		5	5	
	24-35	160	16	12	43		9	10	
	36-47	170	17	6	21		22	24	
	48-59	122	13	6	21		18	19	
	60+	220	23	4	14		39	42	
Stage									
	I	344	35	9	32	1†	14	15	.005†
	II	183	19	4	14	1†	17	18	<.25†
	III	191	20	5	18	1†	20	22	.07†
	IV	179	18	7	25	.34	27	29	.02
	V	75	8	3	11	.47	15	16	.01

IR-non-AWT = intermediate-risk non-anaplastic Wilms tumor
† = comparison for localized (Stages I, II, III) WT

TABLE 2. EFS and OS by stages and types of Wilms tumors in the study

		EFS at 4 years		OS at 4 years	
Stage and WT type	n	%	95% CI	%	95% CI
Overall (I-V)					
IR-non-AWT	848	84	82 to 87	95	93 to 96
Focal anaplasia	25	88	76 to 100	95	86 to 100
Diffuse anaplasia	83	51	41 to 63	58	48 to 70
Stage I					
IR-non-AWT	304	86	82 to 90	97	95 to 99
Focal anaplasia	9	89	71 to 100	100	
Diffuse anaplasia	14	85	68 to 100	93	80 to 100
Stage II					
IR-non-AWT	161	90	85 to 95	96	93 to 100
Focal anaplasia	4	75	43 to 100	100	
Diffuse anaplasia	12	67	45 to 99	75	54 to 100
Stage III					
IR-non-AWT	165	81	75 to 88	93	89 to 97
Focal anaplasia	5	80	52 to 100	80	52 to 100
Diffuse anaplasia	18	39	22 to 69	44	27 to 74
Stage IV (metastatic)					
IR-non-AWT	154	79	73 to 86	87	82 to 93
Focal anaplasia	5	100		100	
Diffuse anaplasia	24	36	21 to 62	31	16 to 62
Stage V (bilateral)					
IR-non-AWT	64	84	76 to 94	100	
Focal anaplasia	2	100		100	
Diffuse anaplasia	15	43	24 to 79	68	46 to 100

IR-non-AWT = intermediate-risk non-anaplastic WT (i.e., excluding completely necrotic and blastemal type Wilms tumor; EFS = event-free survival; OS = overall survival

TABLE 3. Univariate analyses of outcomes by stage, age at diagnosis and gender for patients with Wilms tumor grouped by anaplastic status (diffuse anaplasia, intermediate-risk non-anaplastic)

		4-year EFS			4-year OS		
DAWT		HR	95% CI	*P* value	HR	95% CI	*P* value
Stage							
	I	1	..	..	1	..	..
	II	2·62	0·48–14·3	0·3	3·9	0·41–37·5	·2
	III	5·91	1·31–26·7	0·021	10·1	1·29–78·9	·028
	IV	5·99	1·37–26·3	0·018	12·6	1·66–95·4	·014
Age at diagnosis (years)		1·07	0·95–1·20	0·3	1·06	0·95–1·20	·3
Gender							
	Male	1	..	..	1	..	..
	Female	1·06	0·52–2·16	0·9	1·31	0·61–2·82	·5
IR-non-AWT							
Stage							
	I	1	..	..	1	..	..
	II	0·74	0·43–1·29	0·3	1·43	0·53–3·83	·5
	III	1·41	0·90–2·22	0·13	2·72	1·18–6·29	·019
	IV	1·42	0·89–2·25	0·14	4·03	1·81–8·98	<·001
Age at diagnosis (years)		1·12	1·06–1·19	<0·001	1·14	1·03–1·25	·008
Gender							
	Male	1	..	..	1	..	..
	Female	1·63	1·13–2·36	0·009	1·91	1·04–3·52	·037

DAWT: Diffuse anaplasia Wilms tumor; IR-non-AWT: Intermediate-risk non-anaplastic Wilms tumor

TABLE 4. Multivariate analyses of outcomes by stage, age at diagnosis, and gender for patients with Wilms tumor grouped by anaplastic status (diffuse anaplasia, intermediate-risk non-anaplastic)

		4-year EFS			4-year OS		
DAWT		HR	95% CI	*P* value	HR	95% CI	*P* value
Stage							
	I	1	..	..	1	..	..
	II	2·61	0·48–14·3	0·3	3·86	0·40–37·1	·2
	III	6·06	1·29–28·5	0·023	11·4	1·42–92·0	·022
	IV	6·04	1·37–26·7	0·018	13·2	1·73–101	·013
Age at diagnosis (years)		1·02	0·90–1·15	0·8	1·00	0·89–1·14	>·9
Gender							
	Male	1	..	..	1	..	..
	Female	1·30	0·62–2·71	0·5	1·66	0·76–3·62	·2
IR-non-AWT							
Stage							
	I	1	..	..	1	..	..
	II	0·73	0·42–1·27	0·3	1·39	0·52–3·73	·5
	III	1·32	0·84–2·08	0·2	2·47	1·07–5·4	·035
	IV	1·19	0·74–1·90	0·5	3·41	1·51–7·70	·003
Age at diagnosis (years)		1·10	1·04–1·17	<0·001	1·09	0·99–1·20	·081
Gender							
	Male	1	..	..	1	..	..
	Female	1·49	1·02–2·15	0·037	1·66	0·89–3·07	·11

DAWT: Diffuse anaplasia Wilms tumor; IR-non-AWT: Intermediate-risk non-anaplastic Wilms tumor

TABLE 5. Multivariate analyses of outcomes by risk group, age and gender for patients grouped by stage (I–V)

	4-year EFS			4-year OS		
Stage I	HR	95% CI	*P* value	HR	95% CI	*P* value
Risk group						
IR-non-AWT	1	..	..	1	..	..
DAWT	0·94	0·22–3·91	>0·9	2·35	0·29–19·2	·4
Age at diagnosis (years)	1·05	0·94–1·17	0·4	0·94	0·72–1·24	·7
Gender						
Male	1	..	..	1	..	..
Female	1·06	1·59–1·90	0·8	1·50	0·42–5·40	·5
Stage II						
Risk group						
IR-non-AWT	1	..	..	1	..	..
DAWT	3·84	1·24–11·8	0·019	8·93	2·08–38·5	·003
Age at diagnosis (years)	1·23	1·09–1·39	0·001	1·36	1·12–1·65	·002
Gender						
Male	1	..	..	1	..	..
Female	0·57	0·24–1·37	0·2	0·19	0·04–0·83	·027
Stage III						
Risk group						
IR-non-AWT	1	..	..	1	..	..
DAWT	3·81	1·74–8·36	<0·001	11·2	4·32–29·1	<·001
Age at diagnosis (years)	1·08	0·98–1·20	0·13	1·01	0·87–1·17	·9
Gender						
Male	1	..	..	1	..	..
Female	2·22	1·15–4·30	0·017	2·73	1·09–6·80	·032
Stage IV						
Risk group						
IR-non-AWT	1	..	..	1	..	..
DAWT	4·22	2·26–7·88	<0·001	7·32	3·64–14·8	<·001
Age at diagnosis (years)	1·07	0·97–1·17	0·2	1·06	0·95–1·19	·3
Gender						
Male	1	..	..	1	..	..
Female	2·18	1·10–4·33	0·026	2·14	0·96–4·79	·064

Stage V						
Risk group						
IR-non-AWT	1	..	..	1	..	..
DAWT	4·6	1·45–14·6	0·01	27·5	3·41–222	·002
Age at diagnosis (years)	1·06	0·73–1·53	0·8	1·01	0·58–1·74	>·9
Gender						
Male	1	..	..	1	..	..
Female	0·63	0·26–1·52	0·3	0·51	0·10–2·58	·4

DAWT: Diffuse anaplasia Wilms tumor; IR-non-AWT: Intermediate-risk non-anaplastic Wilms tumor

TABLE 6. Sites of initial recurrence in patients with AWT

Relapse site	DAWT (n = 37)	FAWT (n = 3)
Lung	16	2
Operative bed	16	2
Abdomen	6	0
Extra-abdominal site	3	0
Liver	7	0

7 patients with DAWT and 1 patient with FAWT had relapse at more than one site

DAWT = diffuse anaplasia Wilms tumor; FAWT = focal anaplasia Wilms tumor; AWT = anaplastic Wilms tumor

TABLE 1 Demographics and characteristics of patients with Wilms' tumor enrolled onto SIOP-WT-2001-CCLG and IMPORT studies

Characteristics		IR-non-AWT (n=972) No	%	Focal anaplasia (n=28) No	%	*P* *(vs IR-non-AWT)*	Diffuse anaplasia (n=93) No	%	*P* *(vs IR-non-AWT)*
Gender									
	Male	444	46	13	46	1	36	39	0.23
	Female	528	54	15	54		57	61	
Age at diagnosis (months)									
	Median	37		38			55		
	Range	0–199		25–79			12–163		
Age at diagnosis (in whole months)									
	0-11	114	12	0	0	0.3	0	0	<0.00001
	12-23	186	19	0	0		5	5	
	24-35	160	16	12	43		9	10	
	36-47	170	17	6	21		22	24	
	48-59	122	13	6	21		18	19	
	60+	220	23	4	14		39	42	
Stage									
	I	344	35	9	32	1†	14	15	0.005†
	II	183	19	4	14	1†	17	18	<0.25†
	III	191	20	5	18	1†	20	22	0.07†
	IV	179	18	7	25	0.34	27	29	0.02
	V	75	8	3	11	0.47	15	16	0.01

IR-non-AWT = intermediate-risk non-anaplastic Wilms' tumor
† = comparison for localized (Stages I, II, III) WT

TABLE 2 EFS and OS by stages and types of Wilms' tumours in the study

		EFS at 4 years		OS at 4 years	
Stage and WT type	n	%	95% CI	%	95% CI
Overall (I-V)					
IR-non-AWT	848	84	82 to 87	95	93 to 96
Focal anaplasia	25	88	76 to 100	95	86 to 100
Diffuse anaplasia	83	51	41 to 63	58	48 to 70
Stage I					
IR-non-AWT	304	86	82 to 90	97	95 to 99
Focal anaplasia	9	89	71 to 100	100	
Diffuse anaplasia	14	85	68 to 100	93	80 to 100
Stage II					
IR-non-AWT	161	90	85 to 95	96	93 to 100
Focal anaplasia	4	75	43 to 100	100	
Diffuse anaplasia	12	67	45 to 99	75	54 to 100
Stage III					
IR-non-AWT	165	81	75 to 88	93	89 to 97
Focal anaplasia	5	80	52 to 100	80	52 to 100
Diffuse anaplasia	18	39	22 to 69	44	27 to 74
Stage IV (metastatic)					
IR-non-AWT	154	79	73 to 86	87	82 to 93
Focal anaplasia	5	100		100	
Diffuse anaplasia	24	36	21 to 62	31	16 to 62
Stage V (bilateral)					
IR-non-AWT	64	84	76 to 94	100	
Focal anaplasia	2	100		100	
Diffuse anaplasia	15	43	24 to 79	68	46 to 100

IR-non-AWT = intermediate-risk non-anaplastic WT (i.e. excluding completely necrotic and blastemal type Wilms' tumor; EFS = event-free survival; OS = overall survival

TABLE 3 Univariate analyses of outcomes by stage, age at diagnosis and gender for patients with Wilms' tumor grouped by anaplastic status (diffuse anaplasia, intermediate-risk non-anaplastic)

		4-year EFS			4-year OS		
DAWT		HR	95% CI	*P* value	HR	95% CI	*P* value
Stage							
	I	1	..	..	1	..	..
	II	2·62	0·48–14·3	0·3	3·9	0·41–37·5	0·2
	III	5·91	1·31–26·7	0·021	10·1	1·29–78·9	0·028
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Age at diagnosis (years)		1·07	0·95–1·20	0·3	1·06	0·95–1·20	0·3
Gender							
	Male	1	..	..	1	..	..
	Female	1·06	0·52–2·16	0·9	1·31	0·61–2·82	0·5
IR-non-AWT							
Stage							
	I	1	..	..	1	..	..
	II	0·74	0·43–1·29	0·3	1·43	0·53–3·83	0·5
	III	1·41	0·90–2·22	0·13	2·72	1·18–6·29	0·019
	IV	1·42	0·89–2·25	0·14	4·03	1·81–8·98	<0·001
Age at diagnosis (years)		1·12	1·06–1·19	<0·001	1·14	1·03–1·25	0·008
Gender							
	Male	1	..	..	1	..	..
	Female	1·63	1·13–2·36	0·009	1·91	1·04–3·52	0·037

DAWT: Diffuse anaplasia Wilms' tumor; IR-non-AWT: Intermediate-risk non-anaplastic Wilms' tumor

TABLE 4 Multivariate analyses of outcomes by stage, age at diagnosis, and gender for patients with Wilms tumor grouped by anaplastic status (diffuse anaplasia, intermediate-risk non-anaplastic)

		4-year EFS			4-year OS		
DAWT		HR	95% CI	*P* value	HR	95% CI	*P* value
Stage							
	I	1	..	..	1	..	..
	II	2·61	0·48–14·3	0·3	3·86	0·40–37·1	0·2
	III	6·06	1·29–28·5	0·023	11·4	1·42–92·0	0·022
	IV	6·04	1·37–26·7	0·018	13·2	1·73–101	0·013
Age at diagnosis (years)		1·02	0·90–1·15	0·8	1·00	0·89–1·14	>0·9
Gender							
	Male	1	..	..	1	..	..
	Female	1·30	0·62–2·71	0·5	1·66	0·76–3·62	0·2
IR-non-AWT							
Stage							
	I	1	..	..	1	..	..
	II	0·73	0·42–1·27	0·3	1·39	0·52–3·73	0·5
	III	1·32	0·84–2·08	0·2	2·47	1·07–5·4	0·035
	IV	1·19	0·74–1·90	0·5	3·41	1·51–7·70	0·003
Age at diagnosis (years)		1·10	1·04–1·17	<0·001	1·09	0·99–1·20	0·081
Gender							
	Male	1	..	..	1	..	..
	Female	1·49	1·02–2·15	0·037	1·66	0·89–3·07	0·11

DAWT: Diffuse anaplasia Wilms tumor; IR-non-AWT: Intermediate-risk non-anaplastic Wilms tumor

TABLE 5 Multivariate analyses of outcomes by risk group, age and gender for patients grouped by stage (I–V)

	4-year EFS			4-year OS		
Stage I	HR	95% CI	*P* value	HR	95% CI	*P* value
Risk group						
IR-non-AWT	1	..	..	1	..	..
DAWT	0·94	0·22–3·91	>0·9	2·35	0·29–19·2	0·4
Age at diagnosis (years)	1·05	0·94–1·17	0·4	0·94	0·72–1·24	0·7
Gender						
Male	1	..	..	1	..	..
Female	1·06	1·59–1·90	0·8	1·50	0·42–5·40	0·5
Stage II						
Risk group						
IR-non-AWT	1	..	..	1	..	..
DAWT	3·84	1·24–11·8	0·019	8·93	2·08–38·5	0·003
Age at diagnosis (years)	1·23	1·09–1·39	0·001	1·36	1·12–1·65	0·002
Gender						
Male	1	..	..	1	..	..
Female	0·57	0·24–1·37	0·2	0·19	0·04–0·83	0·027
Stage III						
Risk group						
IR-non-AWT	1	..	..	1	..	..
DAWT	3·81	1·74–8·36	<0·001	11·2	4·32–29·1	<0·001
Age at diagnosis (years)	1·08	0·98–1·20	0·13	1·01	0·87–1·17	0·9
Gender						
Male	1	..	..	1	..	..
Female	2·22	1·15–4·30	0·017	2·73	1·09–6·80	0·032
Stage IV						
Risk group						
IR-non-AWT	1	..	..	1	..	..
DAWT	4·22	2·26–7·88	<0·001	7·32	3·64–14·8	<0·001
Age at diagnosis (years)	1·07	0·97–1·17	0·2	1·06	0·95–1·19	0·3
Gender						
Male	1	..	..	1	..	..

	Female	2·18	1·10–4·33	0·026	2·14	0·96–4·79	0·064
Stage V							
Risk group							
	IR-non-AWT	1	..	..	1	..	..
	DAWT	4·6	1·45–14·6	0·01	27·5	3·41–222	0·002
Age at diagnosis (years)		1·06	0·73–1·53	0·8	1·01	0·58–1·74	>0·9
Gender							
	Male	1	..	..	1	..	..
	Female	0·63	0·26–1·52	0·3	0·51	0·10–2·58	0·4

DAWT: Diffuse anaplasia Wilms tumor; IR-non-AWT: Intermediate-risk non-anaplastic Wilms tumor

TABLE 6 Sites of initial recurrence in patients with AWT

Relapse site	DAWT (n = 37)	FAWT (n = 3)
Lung	16	2
Operative bed	16	2
Abdomen	6	0
Extra-abdominal site	3	0
Liver	7	0

7 patients with DAWT and 1 patient with FAWT had relapse at more than one site

DAWT = diffuse anaplasia Wilms tumor; FAWT = focal anaplasia Wilms tumor; AWT = anaplastic Wilms tumor

Supplementary material

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Figure 1S. Age cumulative distribution of patients with intermediate-risk, focal anaplasia, and diffuse anaplasia Wilms' tumor.