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Prognostic significance of histopathological response to preoperative chemotherapy in unilateral Wilms' tumor: An analysis of 899 patients treated on the SIOP WT 2001 protocol in the UK-CCLG and GPOH studies

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Abstract

In the SIOP Wilms' tumor (WT) studies, preoperative chemotherapy is used as primary treatment, and tumors are classified thereafter by pathologists. Completely necrotic WTs (CN-WTs) are classified as low-risk tumors. The aim of the study was to evaluate whether a subset of regressive type WTs (RT-WTs) (67%-99% chemotherapy-induced changes [CIC]) showing an exceptionally good response to preoperative chemotherapy had comparably excellent survivals as CN-WTs, and to establish a cut-off point of CIC that could define this subset. The study included 2117 patients with unilateral, nonanaplastic WTs from the UK-CCLG and GPOH-WT studies (2001-2020) treated according to the SIOP-WT-2001 protocol. There were 126 patients with CN-WTs and 773 with RT-WTs, stages I-IV. RT-WTs were subdivided into subtotally necrotic WTs (>95% CIC) (STN-WT96-99) (124 patients) and the remaining of RT-WT (RR-WT67-95) (649 patients). The 5-year event-free survival (EFS) and overall survival (OS) for CN-WTs were 95.3% (±2.1% SE) and 97.3% (±1.5% SE), and for RT-WTs 85.7% (±1.14% SE, $P < .01$) and 95.2% (±0.01% SE, $P = .59$), respectively. CN-WT and STN-WT96-99 groups showed significantly better EFS than RR-WT67-95 ($P = .003$ and $P = .02$, respectively), which remained significantly superior when adjusted for age, local stage and metastasis at diagnosis, in multivariate analysis, whereas OS were superimposable (97.3 ± 1.5% SE for CN-WT; 97.8 ± 1.5% SE for STN-WT96-99; 94.7 ± 1.0% SE for RR-WT67-95). Patients with STN-WT96-99 share the same excellent EFS and OS as patients with CN-WTs, and although this was achieved by more treatment for patients with STN-WT96-99 than

Abbreviations: CCLG, Children's Cancer and Leukaemia Group; CIC, chemotherapy-induced changes; CN-WT, completely necrotic Wilms' tumor; COG, Children's Oncology Group; EFS, event-free survival; GPOH, Gesellschaft für Pädiatrische Onkologie und Hämatologie; IMPORT, Improving Population Outcomes for Renal Tumors of Childhood; OS, overall survival; RR-WT, rest of regressive type Wilms' tumor; RT-WT, regressive type Wilms' tumor; SE, standard error; SIOP, International Society of Paediatric Oncology; STN-WT, subtotally necrotic Wilms' tumor; STS, soft tissue sarcoma; WT, Wilms' tumor.

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for patients with CN-WT, reduction in postoperative treatment of these patients may be justified.

KEYWORDS
preoperative chemotherapy, prognosis, response, Wilms' tumor

What's new?
Patients with Wilms tumor showing complete necrosis (CN-WT) after preoperative chemotherapy experience excellent outcomes with significantly less treatment relative to other subsets of Wilms tumor patients. The authors of this study sought to determine whether patients with chemotherapy-responsive regressive type Wilms tumor (RT-WT) might also be candidates for reduced treatment. Analyses show that patients with RT-WT, particularly subtotally necrotic disease, with good response to preoperative chemotherapy have outcomes comparable to those observed in CN-WT patients and thus are candidates for reduced treatment. Treatment reduction for subtotally necrotic Wilms tumor patients could significantly improve quality of life and reduce long-term sequelae.

1 | INTRODUCTION

The outcomes for patients with Wilms' tumors (WTs) have significantly improved over the last decades, with >90% overall survival for those with localized, and 80% for those with metastatic nonanaplastic WT.[1-3] It is now increasingly important to refine the risk groups and find prognostic factors which identify WT subgroups requiring more aggressive treatment, as well as those who need less treatment to reduce the long-term sequelae and improve patients' quality of life. In the Children's Oncology Group (COG) trials and studies, a selected group of patients with stage I WTs which are regarded as very low-risk WTs are treated with surgery only.[4-5]

In the International Society of Paediatric Oncology (SIOP) Nephroblastoma Trials and Studies, preoperative chemotherapy has been used in the treatment of WTs and responsiveness to preoperative chemotherapy has been considered for tumor risk and treatment stratification. The SIOP 9 study has demonstrated that completely necrotic WTs (CN-WTs) had a significantly better prognosis than other subtypes[6] and they have been moved to the low-risk group in the subsequent SIOP classifications.[7,8] The regressive type WT (RT-WT), defined as WTs showing 67%-99% of chemotherapy-induced changes (CIC), has been placed in the intermediate-risk group.[8]

Thus, an important stratification and treatment boundary depends on the absence or presence of *any* viable tumor at all. However, no study has ever scrutinized whether the presence of a small amount of viable tumor is associated with good outcomes comparable to those of CN-WT. In contrast, in bone tumors the histologic response to neoadjuvant chemotherapy in terms of the extent of necrosis has been established as a prognostic indicator for many years.[9-12] Recently, a similar approach has been suggested in soft tissue sarcomas (STS),[13] although the results of different studies were difficult to compare since there is no standardized scheme for histopathologic assessment of tumor response for STS, and no optimum cut-off to differentiate responders from nonresponders. Further, it is unclear whether the cut-off of prognostic significance is similar in different histological subtypes of STS, anatomic primary sites and treatment modalities (radiotherapy, chemotherapy, chemotherapy schedules). Some studies demonstrated favorable outcome using a cut-off ≤5% of viable tumor cells,[14-16] but others found no correlation between the extent of necrosis and clinical outcome.[17,18]

The multiple assessment limitations of STS do not represent such a challenge in WT, making it an ideal candidate for the assessment of the correlation between histopathologic response to preoperative treatment and prognosis. Preoperative chemotherapy given in the SIOP studies is standardized, as is the sampling of tumor, and the assessment performed to a benchmarked standard by a small group of experts, through a system of central pathology review.[19,20]

The aim of our study was to evaluate whether patients with RT-WTs showing a particularly good response to preoperative chemotherapy had comparably excellent survivals as seen in CN-WTs and could be candidates for reduced treatment.

2 | PATIENTS AND METHODS

2.1 | Study population

The cases were identified from the UK Children's Cancer and Leukaemia Group (UK-CCLG) and Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH) Nephroblastoma Study Group studies (2001-2020). The UK-CCLG-SIOP 2001 Study (2001-2011) was a part of the SIOP-WT-2001 Study which registered patients with renal tumors from all CCLG centers. The UK Improving Population Outcomes for Renal Tumors of Childhood (IMPORT) study (2012-2020) is a UK-CCLG multicenter observational study testing the prognostic value of imaging and, in the United Kingdom and Republic of Ireland, molecular biomarkers against a background of continued standard of care based on the results of the SIOP 2001 trial (https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/study-improving-treatment-children-kidney-cancer). The SIOP-2001/GPOH Study (2001-2020) is a multicenter study that includes pediatric oncology centers from Germany, Austria and parts of Switzerland.

The inclusion criteria were: (a) unilateral, localized or metastatic, nonanaplastic WTs diagnosed in children between 6 months and 18 years of age; (b) preoperatively and postoperatively treatment according to the SIOP-WT-2001 study protocol; and (c) submission of cases for central pathology review.

For different results and analyses, only cases with relevant information available were included.

2.2 | Histologic assessment

A retrospective analysis of WTs was done to identify cases that were either CN-WT (ie, tumors that showed 100% CIC) or RT-WTs (tumors with 67%-99% CIC). In order to be able to assess whether there were differences in survival within the RT-WT group, we further subdivided them into subtotally necrotic WTs (STN-WT96-99) (defined as WTs showing >95% of CIC) and the remaining of the RT-WTs (RR-WT67-95) (tumors showing 67%-95% of CIC). Finally, the RR-WT67-95 group was subdivided into RR-WT67-89 and RR-WT90-95% groups which were then analyzed separately.

All cases were sampled according to the SIOP-WT-2001 Study Pathology protocol and submitted for central pathology review for diagnosis, risk classification and abdominal tumor staging,[8] performed by the SIOP-UK (GMV) and SIOP-GPOH (CV) Pathology Panels. The sampling of lymph nodes was recorded as "yes" or "no/unknown." The number of slides submitted for central pathology review was readily available in 1203 cases. It varied from 9 to 94 (median 29).

2.3 | Treatment

All patients were treated according to the SIOP-WT-2001 Study protocol (Table S1).

Follow-up information was obtained from the Study databases containing information documented in case report forms specific to each phase of diagnosis, treatment and follow-up and received regularly from the participating centers.

2.4 | Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 13). The overall survival (OS) and event-free survival

TABLE 1 Clinical and pathologic characteristics of patients included in the study

Characteristics	CN-WT (N = 126) n (%)	P	RT-WT (N = 773) n (%)	STN-WT96-99 (N = 124) n (%)	P	RR-WT67-95 (N = 649) n (%)
Age (months)						
Range	14-205		6-202	6-198		6-202
Median	55		49	53		48
Overall stage						
I	47 (37%)		287 (37%)	40 (32%)		247 (38%)
II	0 (0%)		126 (16%)	11 (9%)		115 (18%)
III	13 (10%)		126 (16%)	13 (11%)		113 (17%)
IV	66 (52%)	<.00001	234 (30%)	60 (48%)	<.00001	174 (27%)
NRs (N*)	(N = 64)		(N = 409)	(N = 90)		(N = 319)
	6 (9%)	.0002	138 (34%)	29 (32%)		109 (34%)
Lymph nodes sampled						
Yes	108 (86%)		677 (88%)	110 (89%)		567 (87%)
No	18 (14%)	.08	96 (12%)	14 (11%)	.7	82 (13%)
Tumor size (N*)	(N = 52)		(N = 315)	(N = 72)		(N = 243)
Range (cm)	1.5-22		1-21	1-18		2-21
Median (cm)	7		8	7		8
N (%) ≥ 10 cm	14 (27%)	.3	106 (34%)	14 (19%)	.004	92 (38%)
Follow-up (N*)	(N = 114)		(N = 722)	(N = 111)		(N = 611)
Range (mo)	5-187		1-198	2-189		1–198
Median (mo)	80		64	88		62

Abbreviations: CN, completely necrotic; N*, number of cases with available data; NRs, nephrogenic rests; RR, rest of regressive type; RT, regressive type; STN, subtotally necrotic; WT, Wilms' tumor.

(EFS) rates were estimated according to the Kaplan-Meier method, the influence of presumed prognostic factors was determined with the log-rank test and Fisher-exact-test. EFS was calculated as the time from the diagnosis to the first recurrence or event, and OS was calculated as time from the diagnosis to death for any reason. Multivariate analysis of survival times was carried out applying the Cox regression model. Simple coding was applied for categorical covariates. A P value of ≤.05 was considered statistically significant. Patients were censored at the time of the last follow-up.

3 | RESULTS

3.1 | Clinical characteristics

The inclusion criteria fulfilled 2117 patients including 126 (6%) with CN-WTs and 773 (37%) with RT-WTs. RT-WTs comprised 124 STN-WT96-99 (16% of RT-WTs and 6% of all non-high-risk WTs) and 649 RR-WT67-95 (84% of RT-WTs and 31% of all non-high-risk WTs).

The main clinical and pathologic features of the groups are presented in Table 1. There were no significant differences in age, lymph nodes sampling and duration of follow-up between the groups. There was no significant difference in the prevalence of WT ≥10 cm in the largest diameter at nephrectomy between CN-WTs vs STN-WT96-99 (P = .3), but it was significant between STN-WT96-99 vs RR-WT67-95 (P = .004). The prevalence of nephrogenic rests in CN-WTs was significantly lower than in other groups.

In five cases there was no precise record about viable tumor components in STN-WT96-99 cases. There were 72/119 (61%)

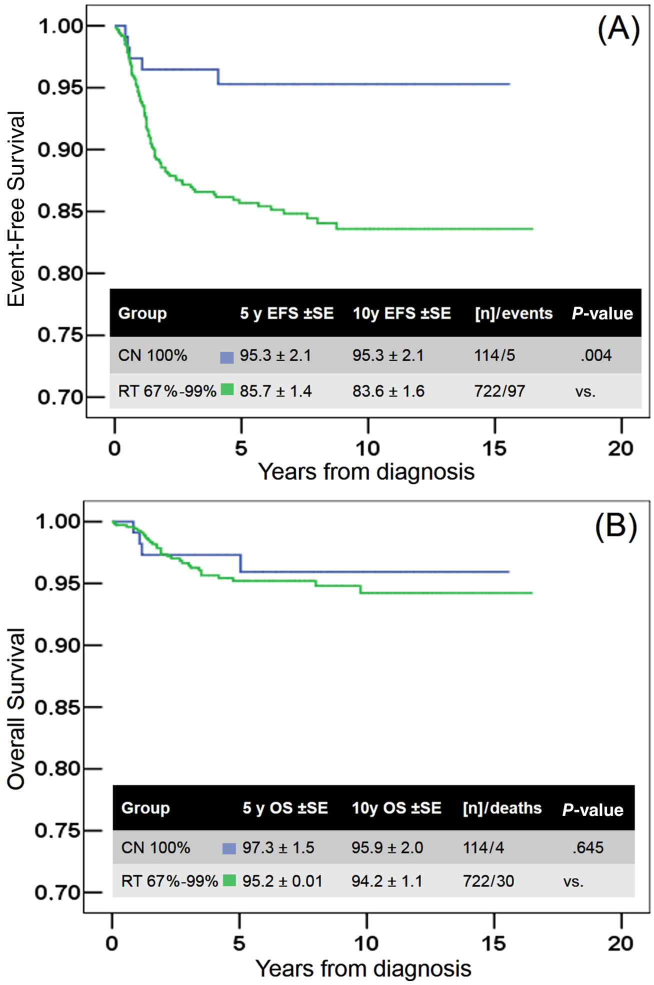

FIGURE 1 Estimated, (A) event-free survival for patients with CN-WT and RT-WT67-99, (B) overall survival for patients with CN-WT and RT-WT67-99 [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Event-free and overall survivals by stages and types of Wilms' tumor in the study

Stage and Subtype	Total	No. of patients: Events	Deaths	EFS at 5 years: %	SE	P values vs RR-WT67-95	OS at 5 years: %	SE	P values vs RR-WT67-95
All stages (I-IV)									
CN-WT	114	5	4	95.3	±2.1	.002	97.3	±1.5	n/s
RT-WT	722	97	31	85.7	±1.14			±0.01	
STN-WT96-99	111	8	2	92.9	±2.6	.02	97.8	±1.5	n/s
RR-WT67-95	611	89	29	85.2	±1.6		94.7	±1.0	
Localized stage (I-III)									
CN-WT	56	—	—	100		.01	100		n/s
STN-WT96-99	59	3	—	94.4	±3.2	.16 (n/s)	100		n/s
RR-WT67-95	449	46	15	90.4	±1.5		96.4	±1.0	
Metastatic (stage IV)									
CN-WT	58	5	4	90.7	±4.0	.006	94.6	±3.0	n/s
STN-WT96-99	54	5	2	91.2	±4.2	.016	95.1	±3.4	n/s
RR-WT67-95	162	43	14	72.7	±3.8		90.2	±2.5	

Abbreviations: CN-WT, completely necrotic Wilms' tumor; EFS, event-free survival; n/s, not significant; OS, overall survival; RR-WT, rest of regressive type Wilms' tumor; RT-WT, regressive type Wilms tumor; STN-WT, subtotally necrotic Wilms' tumor.

STN-WT96-99 that contained no blastema, 23/119 (19%) cases in which blastema was the only viable component and 24/119 (20%) cases in which blastema occupied 10%-50% of viable tumor. Amongst STN-WT96-99, the largest blastemal volume was 13.2 mL (stage I STN-WT96-99, measuring 18 × 10 × 7cm), followed by 5.8, 5.4, 3.6, 3.4, 2.6 mL, and all other tumors that contained blastema had blastemal volume <2 mL.

The stage distribution showed significant differences between localized and more intensively pretreated metastatic WTs. The CN-WT group had significantly more metastatic cases than the RT-WT group (*P* < .00001), but not when compared to the STN-WT96-99 group (*P* = .53). A highly significant difference remained when the STN-WT96-99 group was compared to the RR-WT67-95 group (*P* < .00001).

In further survival analyses, 836/899 (93%) patients with available follow-up were included (114 CN-WTs and 722 RT-WTs—the latter included 111 patients with STN-WT96-99 and 611 patients with RR-WT67-95).

3.2 | Patient outcomes

The median follow-up time was 5.8 years (mean 6.3 years, range from 9 to 178 months). The 5-year EFS and OS estimates for all analyzed groups are presented in Table 2 and Figures 1 and 2.

There was significant difference between the CN-WT and RT-WT groups for EFS (*P* = .004) but not for OS (*P* = .645) (Table 2, Figure 1A,B). The 5-year EFS estimates were significantly superior for the CN-WT (*P* = .002) and STN-WT96-99 (*P* = .02) groups when compared to the RR-WT67-95 group (Table 2, Figure 2A). STN-WT96-99 protective impact on survival remained significant when adjusted for the established risk factors including local stage, metastases and age (Table 3, *P* = .011). The 5-year OS estimates showed no significant differences between the three groups (Table 2, Figure 2B). The 5-year EFS estimates for localized CN-WT were significantly better than for RR-WT67-95 (*P* = .01), and showed a trend, but not statistically significant, to superior survival for the STN-WT96-99 compared to RR-WT67-95 groups (*P* = .16, Table 2, Figure 2C). The

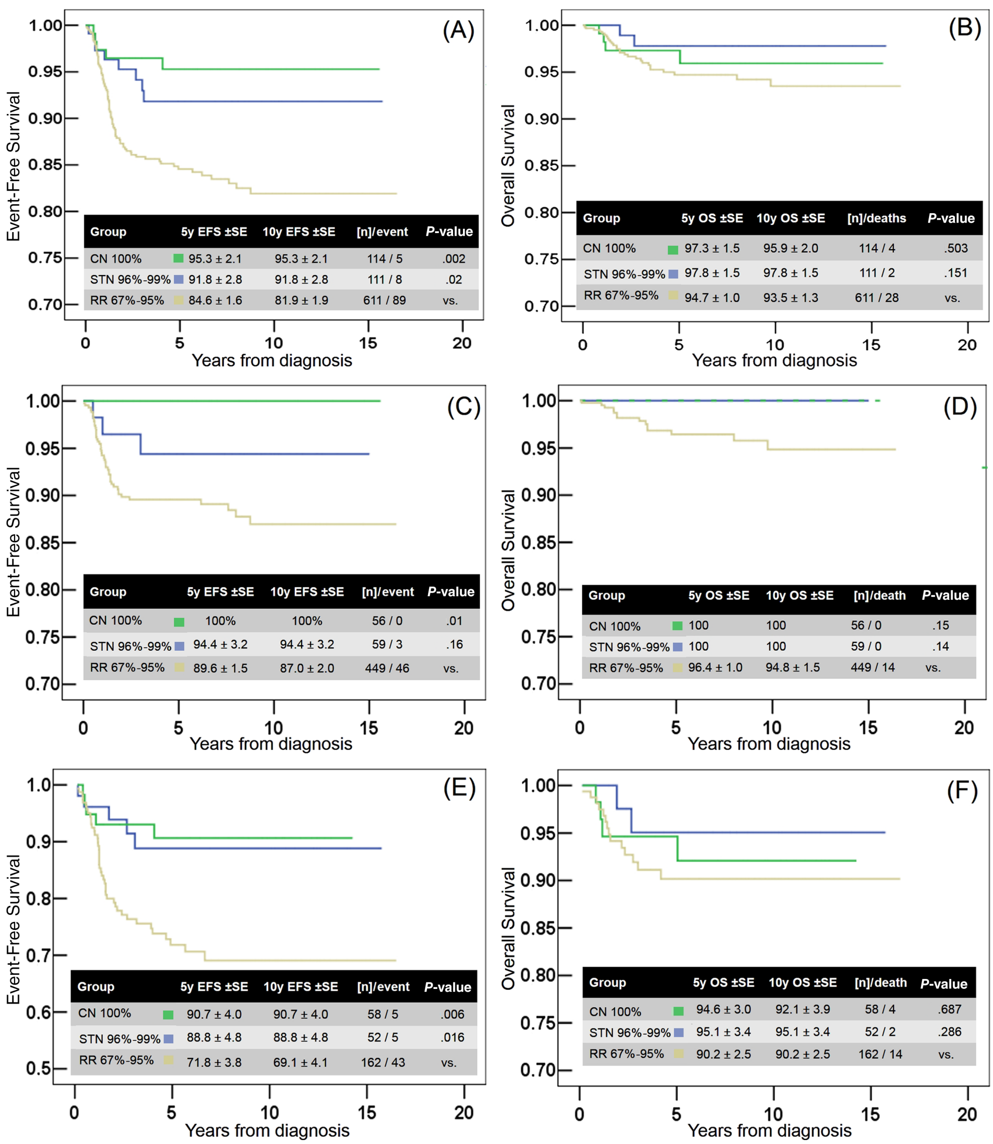

FIGURE 2 Estimated, (A) event-free survival for patients with localized and metastatic tumors, (B) overall survival for patients with localized and metastatic tumors, (C) event-free survival for patients with localized tumors only, (D) overall survival for patients with localized tumors only, (E) event-free survival for patients with metastatic tumors, (F) overall survival for patients with metastatic tumors [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Cox regression analysis of EFS comparing CN-WT and STN-WT96-99 and RR-WT67-89 adjusted for age, metastases at diagnosis and local stage

			95% CI for hazard ratio	
	P value	Hazard ratio	Lower	Upper
CN-WT (vs RR-WT67-95)	.001	0.205	0.083	0.51
STN-WT96-99 (vs RR-WT67-95)	.011	0.389	0.188	0.805
Age	.000	1.009	1.005	1.014
Metastasis at diagnosis	.000	1.326	1.16	1.54
Local stage	.791	0.969	0.767	1.224

Abbreviations: CI, confidence interval; CN-WT, completely necrotic Wilms' tumor; RR-WT, rest of regressive type Wilms' tumor; STN-WT, subtotally necrotic Wilms' tumor.

TABLE 4 Types of relapses per groups and stages of Wilms' tumors included in the study

		Stage (n, %)							
Group	Type of relapse	I		II		III		IV	
CN-WT (N = 114)	Local	—	—	—	—	—	—	1	2
(100% CIC)	Distant	—	—	—	—	—	—	2	3
	Combined	—	—	—	—	—	—	2	3
	No relapse	44	100	—	—	12	100	53	91
STN-WT (N = 111)	Local	2	5	—	—	—	—	—	—
(96%-99% CIC)	Distant	1	3	—	—	—	—	2	4
	Combined	—	—	—	—	—	—	2	4
	No relapse	34	92	10	100	12	100	48	92
RR-WT (N = 611)	Local	5	2	3	3	5	5	4	3
(67%-95% CIC)	Distant	12	5	5	5	7	7	30	19
	Combined	4	2	1	1	1	1	7	4
	No relapse	217	91	98	92	91	88	121	75

Abbreviations: CIC, chemotherapy-induced changes; CN-WT, completely necrotic Wilms' tumor; RR-WT, rest of regressive type Wilms' tumor; STN-WT, subtotally necrotic Wilms' tumor.

5-year OS estimates for localized CN-WT, STN-WT96-99 and RR-WT67-95 showed no significant differences (Table 2, Figure 2D). For metastatic tumors, both CN-WT and STN-WT96-99 showed significantly superior EFS from RR-WT67-95 ($P = .006$ and $P = .016$, respectively, Table 2, Figure 2E), but not OS ($P = .687$ and $P = .286$, respectively, Table 2, Figure 2F). There were no significant differences between CN-WT and STN-WT96-99 groups in any of the above-analyzed categories.

There was no significant difference in OS of patients from all groups who relapsed with localized or metastatic WTs ($P = .3$).

Six patients without relapse died: two due surgery-related post-operative complications, one patient developed glioblastoma, one due to acute myeloid leukemia, one died during stem cell transplantation, and one patient died 32 months after the diagnosis, recorded only as "tumor-related death, with no relapse."

3.3 | Patterns of recurrence

The types of relapses in all groups and stages are presented in Table 4. Distant relapses were more common than local relapses ($P < .00001$).

In the CN-WT group, no relapses occurred in 56 patients with localized WT, whereas 5/58 (8.6%) stage IV patients relapsed.

In the RT-WT group, 91/722 (13%) patients relapsed, including 44/506 (9%) patients with localized tumor and 47/216 (22%) with metastatic tumor ($P < .00001$). In the STN-WT96-99 group, 7/111 (6%) patients relapsed, including 3/59 (5%) with localized and 4/52 (8%) with metastatic WT ($P = .6$). In the RR-WT67-95 group, 84/611 (14%) patients relapsed, including 43/449 (10%) patients with localized and 41/162 (25%) with metastatic WTs ($P < .00001$). We further substratified RR-WT67-95 group into RR-WT67-89 and RR-WT90-95 groups, but there were no differences between them, so they were not further analyzed separately (Table S2).

Relapses were significantly more common in the RT-WT group than in the CN-WT group (91/722, 13% vs 5/114, 4%, respectively, $P = .01$). There was no difference in relapses between the CN-WT group and the STN-WT96-99 group (5/114, 4% vs 7/111, 6%, respectively, $P = .52$), including localized ($P = .24$) and metastatic ($P = 1$) WTs, but only between the CN-WT and the RR-WT67-95 groups, for both localized ($P = .009$) and metastatic tumors ($P = .008$). A significant difference existed between the STN-WT96-99 and RR-WT67-95 groups (7/111, 6% vs 84/611, 14%, $P = .03$), but only for metastatic (4/52, 8% vs 41/162, 25%, $P = .01$) and not for localized tumors (3/59, 5% vs 43/449, 10%, $P = .2$).

Lymph nodes were sampled and examined in 86/96 (90%) patients who relapsed and in 637/740 (86%) who did not relapse ($P = .4$).

4 | DISCUSSION

Responsiveness of WTs to neoadjuvant chemotherapy is considered for risk and treatment stratification in the SIOP studies, with CN-WT classified as low-risk and RT-WT as intermediate-risk tumors. However, RT-WTs with 67% CIC and RT-WTs with 99% CIC are currently treated the same. In the SIOP 93-01 trial "WT with some features left"—defined as tumors showing <10% of viable tumor cells—were monitored as a possible candidate for the low-risk tumor group,[7,21] but in the subsequent SIOP classification they were included into the RT-WT group.[8] The present study readdressed the question of whether there were patients within the RT-WTs group who showed outcomes comparable to CN-WTs, so they could be candidates for treatment reduction.

The prevalence of CN-WT in our study was 6.0%, which was significantly lower than in the SIOP 9 study (10%) ($P = .0002$).[6] But, since the SIOP 9 study, subsequent studies have shown that only 4%-6% of WT were completely necrotic type.[22-24] Although in the SIOP 9 trial patients with localized WTs were randomized to receive 4 vs 8 weeks of preoperative chemotherapy, only 10/37 (27%) patients with CN-WTs received treatment for 8 weeks, which cannot fully explain the higher prevalence of CN-WT. However, the SIOP 9 study was based on the material that would be regarded as suboptimal for review by the current standard, with a small number of slides examined per tumor (2-16, mean 5). Thus, it is likely that their CN-WT group included WTs that were not totally necrotic but were not detected as such due to substandard material. In the present study, the prevalence of STN-WT96-99 was identical to the prevalence of CN-WT, and these results were based on superior material, with a median number of 29 slides per case. On the other hand, in all SIOP studies, RT-WT is the most common tumor type, representing, as also found in our series, 35%-40% of all WTs.[22,23,25]

The proportion of metastatic cases in the CN-WT group in the present study was significantly higher than in the overall unilateral WT cohort in the SIOP-2001 Study[26] (66/126, 52% vs 472/3176, 15%, respectively, $P < .00001$), but not when compared to the STN-WT96-99 group ($P = .53$). Similarly, in the current study, the STN-WT96-99 group included significantly more metastatic cases than the RR-WT67-95 group ($P < .00001$). This may be explained by the fact that patients with metastatic WTs received longer and more intensive preoperative treatment than patients with localized tumors, resulting more frequently in extensive CIC.

The prognosis for patients with CN-WTs in the SIOP 9 study was excellent, with OS of 97% for patients with localized and 100% for patients with metastatic WT,[6] and it was confirmed in the present study, with 100% EFS and OS for localized, and 90.7% and 94.6% for metastatic CN-WT, respectively.

The EFS of patients with RT-WTs was significantly worse than for patients with CN-WTs, for both localized and metastatic tumors. However, there were no significant differences in EFS and OS between patients with CN-WT and STN-WT96-99. When the RR-WT67-95 group was subdivided into a subset of patients with RT-WT90-95 and RT-WT67-89, the proportion of relapses remained the same and the survivals superimposable. Patients with STN-WT96-99 had significantly better EFS than patients with RR-WT67-95, whereas the OS for both groups was excellent and not significantly different. EFS for STN-WT96-99 group remained significantly superior when adjusted for age, metastasis at diagnosis and local stage in a multivariate analysis.

In all analyzed groups (CN-WT, STN-WT96-99, RR-WT67-95), distant relapses were more common than local relapses. No relapses occurred in the localized CN-WT, confirming its current treatment is adequate for disease control. Although there were 3/59 relapses in the localized STN-WT96-99 group, the difference between STN-WT96-99 and CN-WT was not statistically significant. Also, no significant difference in relapses was observed between metastatic CN-WT and STN-WT96-99 groups. OS of patients who relapsed in all three groups with localized and metastatic WTs was not significantly different, clearly indicating that even patients with relapses can be successfully cured with additional therapy.

Lymph nodes were sampled in nearly 90% of patients, which is similar to other studies.[27] Some studies have shown that patients with WTs who had no lymph nodes sampled were more likely to experience relapses,[27,28] but our study showed no significant difference between the two groups. In two patients with stage I STN-WT96-99 who had a local relapse, the lymph nodes were examined and were negative.

Another point that we took into consideration was the impact of the percentage of viable tumor on the blastemal volume, which is being prospectively studied in the current SIOP-UMBRELLA-2016 study, as potentially prognostically important.[2,29] However, no STN-WT96-99 had a blastemal volume near the cut-off point considered to be significant for risk stratification (>20 mL for unilateral and >10 mL for metastatic WTs).[1]

The results of the present study clearly demonstrated that EFS and OS for patients with CN-WT and STN-WT96-99 were not significantly different, indicating that a reduction in postoperative treatment of patients with STN-WT96-99 should be considered. While, ideally, any reduction in treatment should be confirmed in a randomized controlled clinical trial or carefully monitored prospective cohort study,[21,22] the numbers of patients in smaller subsets of WT do not permit a prospective randomized trial in a realistic timeframe,[30] and in WT studies reduction in treatment was often based on previous studies which showed results justifying treatment reduction. For example, CN-WTs were moved from the intermediate to low-risk group based on the SIOP 9 study, in which CN-WTs had been treated as other WT types,[6] but in the subsequent SIOP 93-01 and SIOP-WT-2001 studies, these patients were successfully treated significantly less. The results of the present study confirmed that their EFS and OS remained excellent despite this reduction in treatment. Similarly, when COG introduced "a very-low risk tumor group"—stage 1 WT patients who were to be treated with surgery only[31]—it was based on the results of previously treated stage I WTs.[4] But, again, it proved to be safe and therefore became a standard of care for patients with WTs fulfilling the criteria for surgery only treatment.[5] Equally, epithelial predominant WT stage I has been added to the COG "surgery-only" group, based on the results of previously treated tumors.[32]

We acknowledge that the limitations of our study are that excellent outcomes in patients with STN-WT96-99 were achieved by treating them more than patients with CN-WT, including radiotherapy in patients with stage III, and that the study was not randomized. However, in the studies where reduction of treatment was introduced without previous trials and randomization, there were rigorous stopping rules in place which ensured that the studies would be stopped if EFS fell below the expected level. The same principle should be followed in treatment of patients with STN-WT96-99 since our study showed that many of them probably do not need the treatment intensity they have been receiving and could maintain excellent EFS and OS with treatment given to patients with CN-WT.

The SIOP-UMBRELLA-2016 Study is set up to determine, in a prospective fashion, the independent additional adverse prognostic value of molecular features (such as 1q gain)[33,34] and residual blastemal volume which would be more specific and sensitive predictive markers to tailor therapy are warranted.[2] However, other prognostic factors, one of them being the response to preoperative chemotherapy, should be also searched for and used.

In summary, we demonstrated that patients with STN-WT96-99 had comparable 5-year EFS and OS to patients with CN-WT. Overall STN-WT96-99 showed a significant difference in EFS from RR-WT67-95. However, this difference was significant only for metastatic cases, but not for localized cases, because they have excellent EFS in general. For all three groups, CN-WT, STN-WT96-99 and RR-WT67-95, OS is excellent and superimposable. Given the uniformly high OS estimates in all groups, we suggest considering reduction in treatment of localized and metastatic STN-WT96-99 (with a stopping rule) and expect to rescue any excess in relapses, as OS is not significantly different between all three groups. We also revealed that STN-WT96-99 had a very low volume of residual blastema and fit into the current SIOP-RTSG philosophy. By moving patients with STN-WT96-99 into the low-risk group, the number of stage I patients eligible for no further treatment postoperatively would double. In total, 16% of patients with RT-WT would benefit from reduction in total duration of treatment, exclusion of radiotherapy for stage III patients, improvement of quality of life of patients and less access to the hospital.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethical approval for the UK-CCLG-SIOP-2001 study was given by East Midlands—Derby Research Ethics Committee (National Research Ethics Service [NRES] in the UK) (reference approval number MREC/01/4/086, from 17.01.2002). For the IMPORT study, the approval was given by the London Bridge REC (reference 12/LO/0101, IRAS ID 62637, from 02.05.2012), and for the SIOP/GPOH study by the Ärztekammer des Saarlandes (No. 136/01 from 20.09.2002). Informed consent was provided for all participants.

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REFERENCES

1. Dome JS, Perlman EJ, Graf N. Risk stratification for Wilms tumor: current approach and future directions. *Am Soc Clin Oncol Edu Book*. 2014;34:215-223.
2. van den Heuvel-Eibrink MM, Hol JA, Pritchard-Jones K, et al. Position paper: rationale for the treatment of Wilms tumor in the UMBRELLA SIOP–RTSG 2016 protocol. *Nat Rev Urol*. 2017;14:743-752.
3. Verschuur A, Tinteren HV, Graf N, Bergeron C, Sandstedt B, de Kraker J. Treatment of pulmonary metastases in children with stage IV nephroblastoma with risk-based use of pulmonary radiotherapy. *J Clin Oncol*. 2012;30:3533-3539.
4. Green DM, Breslow NE, Beckwith JB, Takashima J, Kelalis P, D'Angio GJ. Treatment outcomes in patients less than 2 years of age with small, stage I, favorable histology Wilms' tumors: a report from the National Wilms' Tumor Study. *J Clin Oncol*. 1993;11:91-95.

5. Fernandez CV, Perlman EJ, Mullen EA, et al. Clinical outcome and biological predictors of relapse after nephrectomy only for very low-risk Wilms tumor: a report from Children's Oncology Group AREN0532. *Ann Surg*. 2017;265:835-840.
6. Boccon-Gibod L, Rey A, Sandstedt B, et al. Complete necrosis induced by preoperative chemotherapy in Wilms tumor as an indicator of low risk: report of the International Society of Paediatric Oncology (SIOP) nephroblastoma trial and study 9. *Med Pediatr Oncol*. 2000;34:183-190.
7. Delemarre JF, Sandstedt B, Harms D, Boccon-Gibod L, Vujanic GM. The new SIOP (Stockholm) working classification of renal tumors of childhood. *Med Pediatr Oncol*. 1996;26:145-146.
8. Vujanic GM, Sandstedt B, Harms D, Kelsey A, Leuschner I, de Kraker J. Revised International Society of Paediatric Oncology (SIOP) working classification of renal tumors of childhood. *Med Pediatr Oncol*. 2002;38:79-82.
9. Huvos AG, Rosen G, Marcove RC. Primary osteogenic sarcoma: pathologic aspects in 20 patients after treatment with chemotherapy en bloc resection, and prosthetic bone replacement. *Arch Pathol Lab Med*. 1977;101:14-18.
10. Picci P, Rougraff BT, Bacci G, et al. Prognostic significance of histopathologic response to chemotherapy in nonmetastatic Ewing's sarcoma of the extremities. *J Clin Oncol*. 1993;11:1763-1769.
11. van der Woude HJ, Bloem JL, Taminiau AH, Nooy MA, Hogendoorn PC. Classification of histopathologic changes following chemotherapy in Ewing's sarcoma of bone. *Skeletal Radiol*. 1994;23:5071-5077.
12. Bielack SS, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. *J Clin Oncol*. 2002;20:776-790.
13. Wardelmann E, Haas RL, Bovée JV, et al. Evaluation of response after neoadjuvant treatment in soft tissue sarcomas; the European Organization for Research and Treatment of Cancer–Soft Tissue and Bone Sarcoma Group (EORTC–STBSG) recommendations for pathological examination and reporting. *Eur J Cancer*. 2016;53:84-95.
14. Eilber FC, Rosen G, Eckardt J. Treatment-induced pathologic necrosis: a predictor of local recurrence and survival in patients receiving neoadjuvant therapy for high-grade extremity soft tissue sarcomas. *J Clin Oncol*. 2001;19:3203-3209.
15. Shah D, Borys D, Martinez SR, et al. Complete pathologic response to neoadjuvant radiotherapy is predictive of oncological outcome in patients with soft tissue sarcoma. *Anticancer Res*. 2012;32:3911-3915.
16. Donahue TR, Kattan MW, Nelson SD, Tap WD, Eiber FR, Eiber FC. Evaluation of neoadjuvant therapy and histopathological response in primary, high-grade retroperitoneal sarcomas using sarcoma nomogram. *Cancer*. 2010;116:3883-3891.
17. Look Hong NJ, Hornicek FJ, Harmon DC, et al. Neoadjuvant chemoradiotherapy for patients with high-risk extremity and truncal sarcomas: a 10-year single institution retrospective study. *Eur J Cancer*. 2013;49:875-883.
18. Schaefer IM, Hornick JL, Barysauskas CM, et al. Histologic appearance after preoperative radiation therapy for soft tissue sarcoma: assessment of the European Organization for Research and Treatment of Cancer–Soft Tissue and Bone Sarcoma Group Response Score. *Int J Radiat Oncol Biol Phys*. 2017;98:375-383.
19. Vujanić GM, Sandstedt B, Kelsey A, Sebire NJ. Central pathology review in multicenter trials and studies: lessons from the nephroblastoma trials. *Cancer*. 2009;115:1977-1983.
20. Vujanić GM, Sandstedt B. The pathology of Wilms' tumor (nephroblastoma): the International Society of Paediatric Oncology approach. *J Clin Pathol*. 2010;63:102-109.
21. de Kraker J, Graf N, van Tinteren H, et al. Reduction of postoperative chemotherapy in children with stage I intermediate-risk and anaplastic Wilms' tumor (SIOP 93-01 trial): a randomised controlled trial. *Lancet*. 2004;364:1229-1235.
22. Pritchard-Jones K, Bergeron C, de Camargo B, et al. Omission of doxorubicin from the treatment of stage II–III, intermediate-risk Wilms' tumor (SIOP WT 2001): an open-label, non-inferiority, randomised controlled trial. *Lancet*. 2015;386:1156-1164.
23. Weirich A, Leuschner I, Harms D, et al. Clinical impact of histologic subtypes in localized non-anaplastic nephroblastoma treated according to the trial and study SIOP-9/GPOH. *Ann Oncol*. 2001;12:311-319.
24. Vujanić GM, Apps JR, Moroz V, et al. Nephrogenic rests in Wilms tumors treated with preoperative chemotherapy: the UKSIOP Wilms Tumor 2001 Trial experience. *Pediatr Blood Cancer*. 2017;64:e26547.
25. Vujanić GM, D'Hooghe E, Popov SD, Sebire NJ, Kelsey A. The effect of preoperative chemotherapy on histological subtyping and staging of Wilms tumors: the United Kingdom Children's Cancer Study Group (UKCCSG) Wilms tumor trial 3 (UKW3) experience. *Pediatr Blood Cancer*. 2019;66:e27549.
26. van Tinteren H. SIOP-RTSG 2001 Study – international benchmarking study – comparison of characteristics and survivals estimates among countries. Statistical report 2019.
27. Zhuge Y, Cheung MC, Yang R, Koniaris LG, Neville HL, Sola JE. Improved survival with lymph node sampling in Wilms tumor. *J Surg Res*. 2011;167:e199-e203.
28. Kieran K, Anderson JR, Dome JS, et al. Lymph node involvement in Wilms tumor: results from National Wilms Tumor Studies 4 and 5. *J Pediatr Surg*. 2012;47:700-706.
29. Spreafico F, van den Heuvel-Eibrink MM, Pritchard-Jones K, et al. Paediatric renal tumors: perspectives from the SIOP–RTSG. *Nat Rev Urol*. 2016;14:3.
30. Mathoulin-Pélisster S, Pritchard-Jones K. Evidence-based data and rare cancers: the need for a new methodological approach in research and investigation. *Eur J Surg Oncol*. 2019;45:22-30.
31. Green DM, Breslow NE, Beckwith JB, et al. Treatment with nephrectomy only for small, stage I/favorable histology Wilms' tumor: a report from the National Wilms' Tumor Study Group. *J Clin Oncol*. 2001;19:3719-3724.
32. Parsons LN, Mullen EA, Geller JI, et al. Outcome analysis of stage I epithelial-predominant favorable-histology Wilms tumors: a report from Children's Oncology Group study AREN03B2. *Cancer*. 2020;126:2866-2871.
33. Chagtai T, Zill C, Dainese L, et al. Gain of 1q as a prognostic biomarker in Wilms tumors (WTs) treated with preoperative chemotherapy in the International Society of Paediatric Oncology (SIOP) WT 2001 trial: a SIOP renal tumors biology consortium study. *J Clin Oncol*. 2016;34:3195-3203.
34. Gratias EJ, Dome JS, Jennings LJ, et al. Association of chromosome 1q gain with inferior survival in favorable-histology Wilms tumor: a report from the Children's Oncology Group. *J Clin Oncol*. 2016;34:3189-3194.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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