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Outcomes of patients with Wilms' tumour stage III due to positive resection margins only: An analysis of patients treated on the SIOP-WT-2001 protocol in the UK-CCLG and GPOH studies

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Abstract

Stage III Wilms' tumour (WT) represents a heterogeneous group which includes different criteria, but all stage III patients are treated according to the same study regiment. The aim of the study was to retrospectively analyse outcomes in patients with stage III due to positive resection margins (RM) only, sub-grouped in RM with viable (RM-v) and nonviable (RM-nv) tumour. Patients were treated pre- and postoperatively according to the SIOP-WT-2001 protocol in the UK-CCLG and GPOH WT trials and studies (2001-2020). There were 197 patients, including 134 with localised, abdominal stage III and 63 with overall stage IV, but abdominal stage III. Stage III due to RM-v had 126 patients, and due to RM-nv 71 patients. The overall 5-year local-relapse-free survival (RFS), event-free (EFS) and overall survival (OS) estimates for all patients with abdominal stage III RM were 95.7% (±SE1.5%), 85.1 (±SE2.6%) and 90.3% (±SE2.2%), respectively. Patients with stage III RM-nv had significantly better

Abbreviations: AIEOP, Associazione Italiana di Ematologia e Oncologia Pediatrica; CCLG, Children's Cancer and Leukaemia Group; CIC, chemotherapy-induced changes; COG, Children's Oncology Group; EFS, event-free survival; GPOH, Gesellschaft für Pädiatrische Onkologie und Hämatologie; HR-WT, high-risk Wilms' tumour; IMPORT, Improving Population Outcomes for Renal Tumours of Childhood; IR-WT, intermediate-risk Wilms' tumour; LR-WT, low-risk Wilms' tumour; NWTS, National Wilms Tumour Study; OS, overall survival; RFS, relapse free survival; RM, resection margin; SIOP, International Society of Paediatric Oncology; WT, Wilms' tumour.

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RFS and EFS than patients with RM-v ($P = .027$ and $P = .003$, respectively). A multivariate analysis showed that RM-v remained a significant factor for EFS when adjusted for age, presence of metastasis at diagnosis, histological risk group and overall stage in Cox regression analysis ($P = .006$). Patients with stage III due to RM-nv only exhibited no local recurrence and have a significantly better RFS and EFS than patients with RM-v. The results suggest that exclusion of RM-nv as a stage III criterion in the UMBRELLA staging system and consequent treatment reduction is warranted.

KEYWORDS

outcomes, resection margins, stage III criteria, Wilms' tumour

What's new?

Criterion for abdominal stage III Wilms' tumour with positive resection margins is based on the finding of resection margin viable tumour (RM-v) or by evidence of chemotherapy-induced changes (CIC) at the resection margin (RM-nv). Previous studies indicate that RM-nv can be ignored for staging in different clinical situations. Here, comparison of outcomes among stage III Wilms' tumour patients staged by RM-v vs RM-nv shows that RM-nv patients fare better in terms of local-relapse-free and event-free survival compared to RM-v patients. Moreover, RM-nv patients experienced no local recurrence. Thus, RM-nv can be ignored as a stage III criterion, reducing patient treatment.

1 | INTRODUCTION

International Society of Paediatric Oncology (SIOP) trials/studies include preoperative chemotherapy as the first line of treatment of patients with Wilms' tumour (WT) and its purpose is to reduce surgical complications, down-stage tumours to reduce postoperative treatment and assess the histological response of the primary tumour and pulmonary metastases to determine postoperative treatment. With overall survival rates above 90%, the effort is now focused on identifying positive prognostic factors that can warrant therapy reduction to avoid long-term side effects in these young patients. A possible route is through identifying certain histological features which could create subgroups of WT requiring less treatment but maintaining the excellent outcomes.[1,2] Another is through staging, where certain criteria are revisited to assess whether they could be fine-tuned or changed.

In the early SIOP trials, the presence of chemotherapy-induced changes (CIC) in the renal sinus and its vessels, and in the perirenal fat was regarded as evidence of tumour expansion for staging purposes.[3,4] The SIOP 93-01 study showed that these changes could be ignored for staging,[5] and in the SIOP-WT-2001 trial and study the staging criteria were redefined accordingly, so only the finding of viable tumour in these sites was used as a criterion for stage II.[6] However, the finding of CIC at the resection margins or in the lymph nodes was kept as a criterion for stage III.

The aim of this retrospective study was to analyse the outcomes of patients with abdominal stage III due to positive resection margins alone, and to compare outcomes of those with stage III due to the finding of viable tumour (RM-v) vs CIC at the resection margins (RM-nv), to establish whether the latter could be removed as the criterion for stage III. The rationale for the study was the SIOP experience with excellent outcomes of patients in whom CIC was safely disregarded in other situations: (a) its presence in the renal sinus and its vessels, and in the perirenal fat was not a criterion for upstaging tumour to stage II[6]; (b) its presence in stage III completely necrotic WT (low-risk, LR-WT) was not indication for radiotherapy[7]; (c) in stage IV where complete remission of metastasis was achieved after preoperative chemotherapy, radiotherapy was not indicated for the metastatic site for LR-WT and IR-WT and (d) in patients with nonviable pulmonary metastases, radiotherapy was not indicated after complete surgical metastasectomy except for HR-WT.[8]

2 | PATIENTS AND METHODS

2.1 | Study population

Eligible patients were identified from the UK-SIOP-WT-2001 trial and study (2002-2011), UK-IMPORT study (2012-2020) and SIOP-WT-2001/GPOH trial and study (2002-2020). Eligibility criteria were (a) patients aged 6 months to 18 years, (b) with unilateral WT stage III at nephrectomy, both localised (abdominal) stage III and metastatic stage III (overall stage IV, but abdominal stage III), (c) treated with pre- and postoperative chemotherapy according to the SIOP-WT-2001 protocol and (d) submitted for central pathology review. Patients with bilateral WT were excluded since their preoperative treatment is prolonged and sometimes intensified.

TABLE 1 Staging criteria for stage III Wilms' tumour in the SIOP-WT-2001 study

Viable and nonviable tumour present at a resection margin
Abdominal lymph nodes contain viable or nonviable tumour
Viable or nonviable tumour thrombus present at resection margins of ureter, renal vein, or inferior vena cava
Viable or nonviable tumour thrombus in the inferior vena cava removed piecemeal by a surgeon
Preoperative or intraoperative tumour rupture
Wedge or open tumour biopsy before preoperative chemotherapy or surgery
Tumour implants (viable or nonviable) in the abdomen
Tumour (viable or nonviable) penetrated through the peritoneal surface

2.2 | Histological assessment

WT were classified and staged according to the SIOP-WT-2001 classification and staging criteria.[6] The criteria for stage III are listed in Table 1. Patients with WT from all three risk groups (low-risk: LR, intermediate-risk: IR, high-risk: HR) were included, although their postoperative treatment differed. We subclassified stage III WT due to positive resection margins where this was the only criterion for stage III into two groups: Group RM-nv and Group RM-v.

2.3 | Treatment

All patients were treated according to the SIOP-WT-2001 Trial protocol (Appendix S1). All patients with IR-WT and HR-WTs localised stage III and metastatic stage III were recommended to be treated with flank irradiation.

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 centres.

2.4 | Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 27). The overall survival (OS), event-free (EFS) and local (ie, operative bed and abdominal lymph nodes) relapse-free survival (RFS) rates were estimated according to the Kaplan-Meier method, the influence of presumed prognostic factors was determined with the log-rank test, Fisher-exact and Fisher-Freeman-Halton-exact-test. RFS was calculated as the time from the diagnosis to the first local or combined (local and metastatic) recurrence—since the aim of the study was to assess whether radiotherapy is necessary for prevention of local relapses, we did not take into consideration and analysed pure metastatic relapses. EFS as time from diagnosis to event and OS was calculated as time from the diagnosis to death for any reason or date of last follow-up. Death for any reasons and any relapse (local, combined, metachronous and metastatic) were regarded as event. Multivariate analysis of survival times was carried out applying the Cox regression model. 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 and pathological characteristics

There were 627 patients with abdominal stage III including 197 (31.4%) patients with stage III due to positive resection margins as the only criterion for stage III. This included 134/357 (37.5%) of all patients with localised stage III tumours, and 63/270 (23.3%) of all patients with metastatic stage III (Table 2). Group RM-nv comprised 71 patients, and Group RM-v 126 patients, and there were significantly more patients with RM-nv in the metastatic stage III group (38/132, 28.8% in localised stage III vs 33/63, 52.4% in metastatic stage III, $P = .001$) (Table 2).

3.2 | Patient outcomes

The median follow-up time at the last follow up was 7.06 years (range, 0.79 to 15.77 years). Two patients from Group RM-v were lost to follow-up. The overall 5-year RFS, EFS and OS estimates for all patients with abdominal stage III were 95.7% (±1.5% SE), 85.1 (±2.6% SE) and 90.3% (±2.2% SE), respectively.

The 5-year RFS estimate for any local (including combined) relapse was significantly better for patients from Group RM-nv than for patients from Group RM-v ($P = .027$) (Figure 1A). When subgrouped and analysed separately for localised and metastatic stage III, there was no statistically significant difference for local/combined relapse for Groups RM-nv vs Group RM-v for localised stage III ($P = .083$) (Figure 1B), and for metastatic stage III ($P = .294$) (Figure 1C). The 5-year EFS estimate for Group RM-nv patients was significantly superior to Group RM-v patients ($P = .003$) (Figure 2A); there was no significant difference in the 5-year EFS estimate between localised stage III Group RM-nv and Group RM-v patients ($P = .093$) (Figure 2B), and it was significant for metastatic stage III patients ($P = .004$) (Figure 2C).

There were 19/195 (9.7%) deaths (15 patients who relapsed and 4 who died without relapse). In univariate analysis, the 5-year OS estimate was significantly better for Group RM-nv patients in comparison to Group RM-v patients ($P = .047$) (Figure 3A). The difference was not significant between Group RM-nv and Group RM-v patients with localised WT stage III ($P = .379$) (Figure 3B), but only for metastatic stage III patients ($P = .016$) (Figure 3C).

A multivariate analysis showed that RM-v remained a significant factor for EFS when adjusted for age, presence of metastasis at diagnosis, histological risk group and overall stage in Cox regression analysis ($P = .006$, Table 3). Multivariate analysis was not reliably possible for RFS due to a small number of local/combined relapses (8 patients).

TABLE 2 Patients with Wilms' tumour stage III due to positive resection margins in the present study

Risk group (no. of pts)[a]	IR-WT (161 pts)		LR-WT (12 pts)		HR-WT (22 pts)		
Resection margins	RM-nv	RM-v	RM-nv	RM-v	RM-nv	RM-v	
Overall stage	III, IV	III, IV	III, IV	III, IV	III, IV	III, IV	Total
Without relapse	30, 21	70, 19	3, 9	0	2, 2	11, 2	169
Relapses							
Local relapse	0	2, 0	0	0	0	1, 0	3
Combined relapse	0	2, 0	0	0	0	2, 1	5
Metastatic relapse	3, 1	5, 8	0	0	0	1, 0	18

[a]Two patients with IR-WT localised stage III RM-v were lost to follow up.
Abbreviations: HR, high risk; IR, intermediate risk; LR, low risk; RM-nv, resection margins with nonviable tumour; RM-v, resection margins with viable tumour; WT, Wilms' tumour.

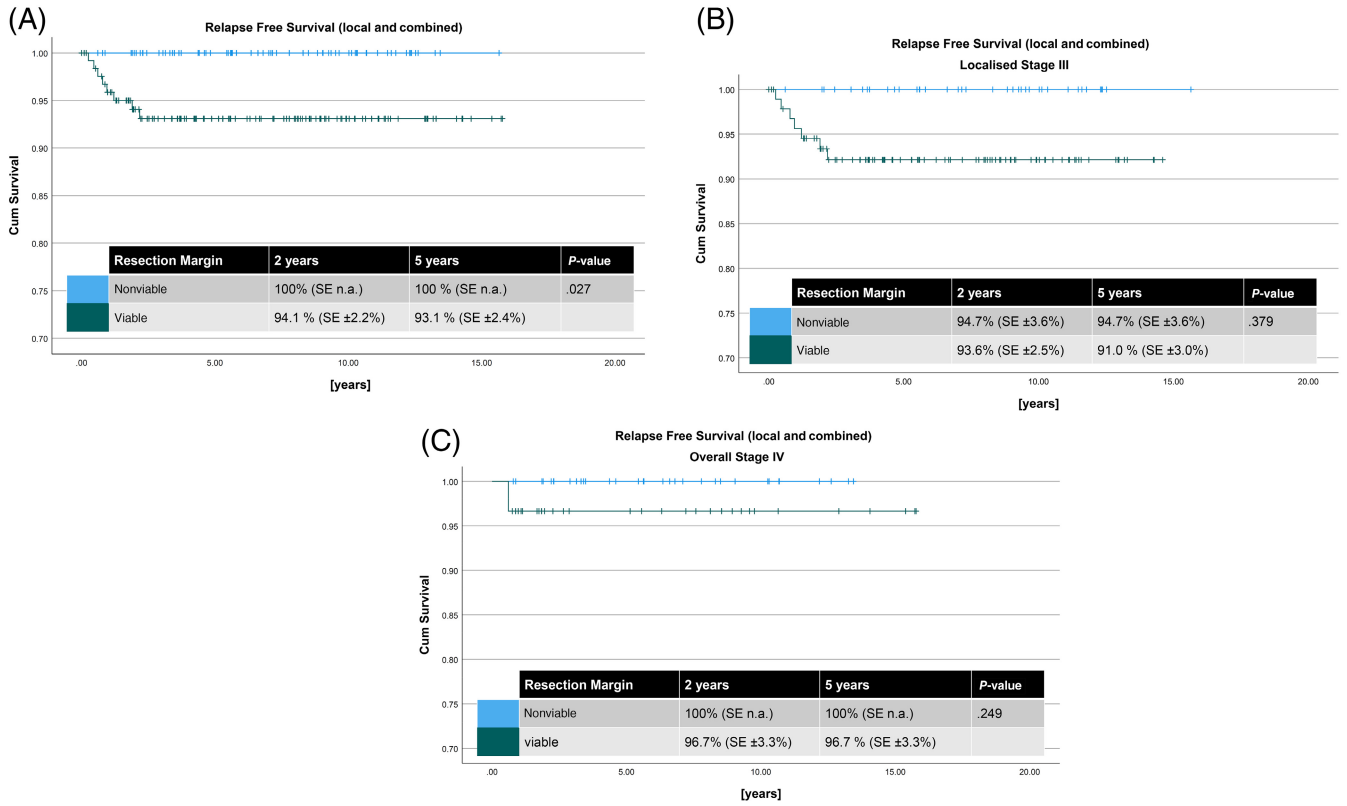

FIGURE 1 Estimated, (A), local relapse-free survival for all patients with Wilms' tumour stage III (localised stage III, and stage III, overall stage IV), (B), local relapse-free survival for patients with Wilms' tumour localised stage III, (C), local relapse-free survival for patients with Wilms' tumour stage III, overall stage IV

3.3 | Pattern of relapses

No relapses were observed in 169 out of 195 (86.7%) of patients, whereas 26 (13.3%) patients relapsed: 3 with local, 18 metastatic and 5 combined relapses (Table 2). One patient who developed a metachronous contralateral WT 8.84 years after the diagnosis was included in the metastatic relapse group. The median time to relapse among relapsing patients was 0.97 years from diagnosis (range 0.25-8.84 years), and 23/27 (81.5%) relapsed within 2 years after the diagnosis. In Group RM-nv, 4/71 (4.2%) patients developed metastatic relapses, and no patient developed local or combined relapse. In Group RM-v, 22/124 (17.7%) patients relapsed, including 8 with local/combined, and 14 with metastatic relapses (Table 2).

3.4 | Radiotherapy treatment

Information about flank radiotherapy was available for 183 patients. Radiotherapy was given to 162 patients: 21/21 patients with HR-WT, 6/12 with LR-WT and 135/150 with IR-WT. It was not given to 6/12

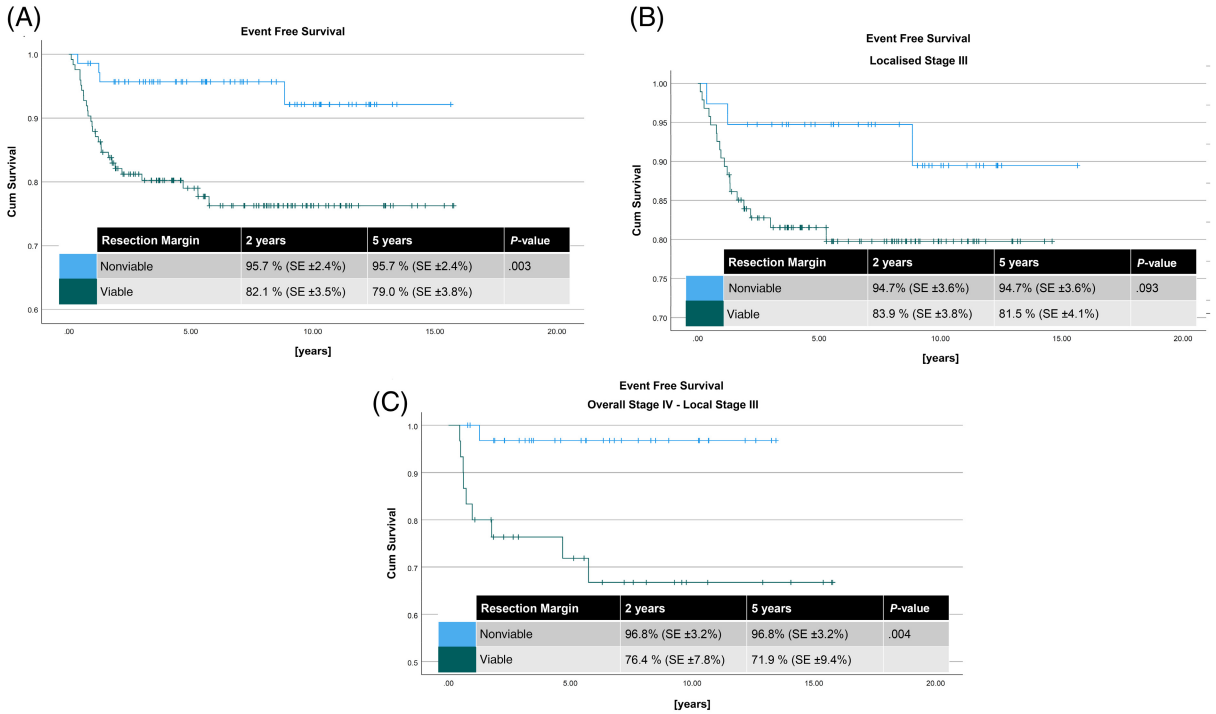

FIGURE 2 Estimated, (A), event-free survival for all patients with Wilms' tumour stage III (localised stage III, and stage III, overall stage IV), (B), event-free survival for patients with Wilms' tumour localised stage III, (C), event-free survival for patients with Wilms' tumour stage III, overall stage IV

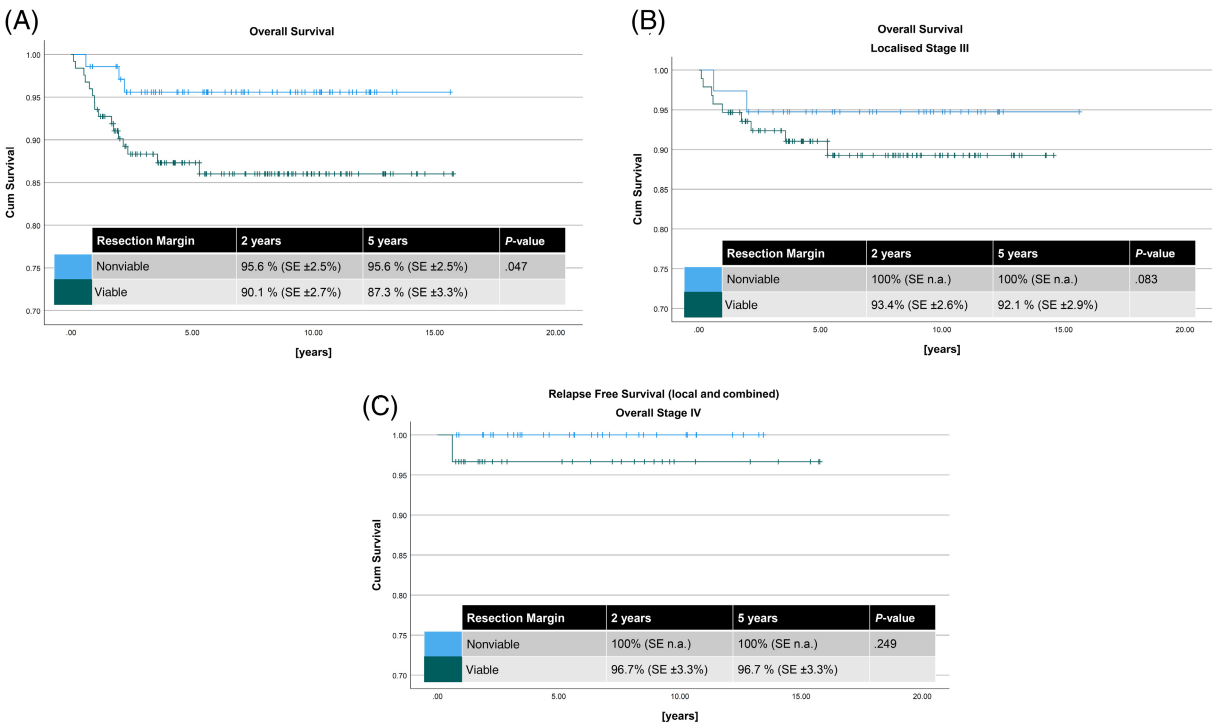

FIGURE 3 Estimated, (A), overall survival for all patients with stage III (localised and metastatic), (B), overall survival for patients with localised stage III, (C), overall survival for patients with Wilms' tumour stage III, overall stage IV

patients with LR-WT, and to 15/150 (10.0%) patients with IR-WT (nine Group RM-nv patients, and six Group RM-v patients). One patient who received no radiotherapy from Group RM-v (IR-WT mixed type) developed a combined relapse 1.90 years after the diagnosis but was alive and with no disease 10.51 years after the diagnosis. All 26 patients who relapsed were treated with flank irradiation.

TABLE 3 Multivariate analysis of EFS by the status of resection margins, WT risk group, age at diagnosis and overall stage

	Exp (B)	95% CI for exp (B)		
	(Hazard ratio)	Lower	Upper	*P*-value
Viable vs nonviable resection margins	4.413	1.517	12.839	.006
HR-WT vs IR-WT + LR-WT	1.375	0.498	3.794	.539
Age at diagnosis (per unit)	1.089	0.956	1.241	.198
Overall stage IV vs localised Stage III	1.297	0.591	2.846	.517

Abbreviations: EFS, event-free survival; HR-WT, high risk; IR-WT, intermediate risk; LR-WT, low risk; WT, Wilms' tumour.

4 | DISCUSSION

Since the outcomes for patients with WT are generally excellent, side effects of treatment are relevant in respect to long-term survival. Therefore, new strategies have been developed to reduce treatment and maintain the excellent outcome. The SIOP-WT-2001 trial has demonstrated that it is safe to omit doxorubicin in treatment of patients with stage II and stage III IR-WT, which has been now implemented in the SIOP-RTSG UMBRELLA 2016 study,[9,10] except for patients with large (>500 mL) IR-WT (excluding stromal and epithelial WT) who still receive doxorubicin. Previously, the SIOP 93-01 trial showed that postoperative treatment for patients with IR-WT stage I can be safely reduced from 18 to 4 weeks.[4]

We expanded our preliminary study on stage III patients[11] by adding the UK-CCLG patients, and showed that 5-year estimates RFS, EFS and OS for patients with both localised and metastatic stage III due to positive RM only were excellent. In particular, there were no local or combined relapses in Group RM-nv patients, not even in those nine patients who received no flank radiotherapy. There was a trend for the superior 5-year RFS estimate for local/combined relapse for Groups RM-nv vs Group RM-v for localised stage III, and no significant difference in metastatic stage III, probably because the subgroups ran out of power due to few events. These results led to the decision that in the SIOP-RTSG UMBRELLA 2016 Study RM-nv criterion should not be used for stage III, but patients should be staged based on other findings, and patients with IR-WT should not be treated with flank radiotherapy.[10]

In the UKW3 study of patients with nonanaplastic and "inoperable" stage III WT, in 22 patients the presence of CIC at resection margins was discounted for staging purpose, and they were not treated with flank irradiation, despite the protocol recommendations. Their 4-year EFS and OS were not significantly worse than in those who were treated with flank radiotherapy: EFS 82.1% (95% CI: 72.8-88.5) vs 78.4% (95% CI: 61.4%-88.6%), and OS 90.5 (95% CI: 82.5-94.9) vs 83.8% (95% CI: 67.4-92.4), respectively.[12] However, no comparison to our groups was possible since in Irtan et al study it is not clear from which "subgroup" of stage III the patients who received no radiotherapy were. Interestingly, they were significantly younger than the group that received radiotherapy.

Stage III comprised 20.1% of all WT in the SIOP-WT-2001 trial and study[13] and 29.9% of favourable-histology WT in the NWTS-5 study.[14] It is a heterogeneous group which includes different criteria, some related to tumour biology (eg, lymph node metastases), others related to "human" factors (eg, open biopsy, intraoperative rupture) and some dependent on the tumour history (preoperative tumour rupture). Therefore, it is important to analyse and stratify them more carefully as they may not require the same treatment. Although stage III criteria and terminology differ between the studies,[15] a significant proportion of stage III were due to either positive resection margins alone (26.1% in the AIEOP study),[16] or combined with other stage III criteria (48% in the NWTS-5 study, and 32.1% in the COG AREN0532 study, respectively).[17,18] In our cohort, positive resection margins as the only criterion comprised 32.5% of stage III, but included localised and metastatic stage III. Other studies have used the NWTS/COG staging criteria, which are different from the SIOP staging criteria,[15-18] or defined subgroups differently ("microscopic stage III," "macroscopic stage III"),[16] or "lumped" both cases treated with primary surgery and preoperative chemotherapy together.[16,17] The advantage of our study is that all included patients were treated according to the standardised SIOP-WT-2001 protocol which included preoperative chemotherapy and postoperative treatment.

Previous studies have analysed outcomes of patients with stage III WT, looking for subgroups with better or worse outcomes, and considering whether they might need different treatment.[12,16-18] However, none of these studies analysed separately outcomes for patients with stage III due to RM-v vs RM-nv, although they included patients treated with preoperative chemotherapy. In the AREN0532 study,[17] patients with stage III had excellent 4-year EFS and OS estimates of 88% (95% CI: 85%-91%) and 97% (95% CI: 95%-98%), respectively, but their stage III group included 116/588 (19.7%) patients who were stage III only due to preoperative chemotherapy received, and many of them would have been lower stages in the SIOP study where staging is based on pathological findings at nephrectomy rather than on the fact that they have received preoperative chemotherapy.[15]

In the AIEOP study, patients with stage III due to positive lymph nodes had the worst outcomes—the 4-year disease-free survival was 73% ± 7% vs 98% ± 2% for patients with negative lymph nodes ($P = .001$).[16] Similarly, the multivariate analysis of stage III patients in the NWTS-5 study showed that patients with lymph node metastases, and patients with "microscopic residual disease" had worse 8-year EFS in comparison to other stage III patients ($P = .005$ and .007, respectively).[18] The same studies showed that patients with negative "microscopic residual disease" had excellent 8-year overall survival of

92%.[18] The AREN0532 study also showed that patients with positive lymph nodes had a poorer 4-year EFS (82%, 95% CI: 74.9%-89%) compared to those with negative lymph nodes (95%, 95% CI: 90.2%-97.4%), but there was no significant difference for OS. The same study showed no difference between patients with and without "gross residual disease" ($P = .30$).[17]

Relapses have been reported in 14.1% to 24.1% of patients with localised WT stage III,[16-18] but it is difficult to compare different studies because of the above-mentioned differences in subgrouping and definitions. Like the present study, in other studies, in about 85% of patients who relapsed, relapses developed within 2 years after diagnosis. In the present study, there were no local/combined relapses in Group RM-nv patients, including patients who received no flank radiotherapy. As mentioned above, in the UKW3 study patients with (differently defined) stage III WT who received no flank radiotherapy did not have worse EFS and OS than patients treated with flank radiotherapy.[12] Interestingly, the recent COG study showed that genetic changes were associated with relapse in patients with WT,[19] opening a new avenue of investigation for patients who relapse.

The weakness of our study is a relatively small number of patients and events that made detailed multivariate analyses impossible. Also, patients with localised stage III tumours, and those with metastatic stage III disease at diagnosis, received different intensities of chemotherapy, both preoperatively and postoperatively.

In summary, patients with WT stage III comprise 20% to 30% of patients in the SIOP and COG studies, and patients with stage III due to positive RM alone represent a significant proportion of stage III group. Group RM-nv stage III patients have a significantly better RFS than patients with RM-v stage III. In the SIOP-RTSG UMBRELLA 2016 Study RM-nv as a stage III criterion was excluded, leading to down-staging and no radiotherapy treatment of such patients with close follow up and careful analysis of treatment received and outcome.[10,20]

AUTHOR CONTRIBUTIONS

Gordan M. Vujanić: Conceived the study, reviewed the cases included in the study, performed analyses, wrote the article and reviewed and edited the final article drafts. **Norbert Graf:** Provided the clinical data for the study, reviewed and edited the final article drafts. **Ellen D'Hooghe:** Conceived the study, reviewed, and edited the final article drafts. **Tanzina Chowdhury:** Provided the clinical data for the study, reviewed, and edited the final article drafts. **Christian Vokuhl:** reviewed the pathology of cases included in the study, reviewed, and edited the final article drafts. **Reem Al-Saadi:** Collected and assembled the UK data, reviewed, and edited the final article drafts, **Kathy Pritchard-Jones:** Provided the clinical data for the study, reviewed, and edited the final article drafts. **Patrick Melchior:** Provided the clinical data for the study, reviewed and edited the final article drafts. **Rhoikos Furtwängler:** Conceived the study, provided the clinical data for the study, performed analyses, reviewed, and edited the final article drafts. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

DATA AVAILABILITY STATEMENT

The data will be made available upon reasonable request.

ETHICS STATEMENT

Ethical approval for the UK-CCLG-SIOP-WT-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 January 17, 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 September 20, 2002). Informed consent was provided for all participants.

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SUPPORTING INFORMATION

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

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