Received: 10 March 2019 | Revised: 5 September 2019 | Accepted: 23 September 2019

DOI: 10.1002/pbc.28039

Pediatric Blood & Cancer | SIOP International Society of Paediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology | WILEY

RESEARCH ARTICLE

Is radiotherapy required in first-line treatment of stage I diffuse anaplastic Wilms tumor? A report of SIOP-RTSG, AIEOP, JWiTS, and UKCCSG

Raquel Dávila Fajardo[1,2] | Marry M. van den Heuvel-Eibrink[2] | Harm van Tinteren[4] | Filippo Spreafico[3] | Thomas Acha[5] | Christophe Bergeron[6] | Beatriz de Camargo[7] | Foppe Oldenburger[8] | Christian Rübe[9] | Takaharu Oue[10] | Christian Vokuhl[11] | Ronald R. de Krijger[2] | Gordan Vujanic[12] | Neil Sebire[13] | Aurore Coulomb-L'Hermine[14] | Paola Collini[15] | Lorenza Gandola[16] | Kathy Pritchard-Jones[17] | Norbert Graf[18] | Geert O. Janssens[1,2] | Martine van Grotel[2]

[1]Department of Radiation Oncology, University Medical Centre Utrecht, Utrecht, The Netherlands
[2]Department of Pediatric Oncology, Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands
[3]Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[4]Department of Statistics, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[5]Department of Pediatric Oncology, Hospital Materno-Infantil, Málaga, Spain
[6]Department of Pediatric Oncology, Centre Leon Berard, Lyon, France
[7]Department of Pediatric Hematology and Oncology, Instituto Nacional Do Cancer (INCA), Rio de Janeiro, Brazil
[8]Department of Radiation Oncology, Academic Medical Center, Amsterdam, The Netherlands
[9]Department of Radio-Oncology, University Hospital of Saarland, Homburg, Germany
[10]Department of Pediatric Surgery, Hyogo College of Medicine, Nishinomiya City, Hyogo Prefecture, Osaka, Japan
[11]Institute of Pediatric Pathology, University of Kiel, Kiel, Germany
[12]Department of Pathology, Sidra Medicine, Doha, Qatar
[13]Department of Histopathology, Great Ormond Street Hospital, London, UK
[14]Department of Pathology, Hopitaux Universitaires Est Parisien, Paris, France
[15]Department of Pathology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[16]Department of Radiation Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[17]Institute of Child Health, University College London, London, UK
[18]Department of Pediatric Oncology, University Hospital of Saarland, Homburg, Germany

Correspondence
Martine van Grotel, Princess Máxima Center for Pediatric Oncology, Heidelberglaan 25, 3584 CS Utrecht, The Netherlands.
Email: m.vangrotel@prinsesmaximacentrum.nl

Abstract

Background: As a significant proportion of relapses occurred in the tumor bed or abdomen on patients with the fifth National Wilms Tumor Study stage I anaplastic Wilms tumor (WT), flank radiotherapy was added for stage I anaplastic WT in the subsequent study of the Children's Oncology Group (AREN0321). Preliminary results revealed reduction of relapse rate and improved survival. In cases treated with preoperative chemotherapy, such as in International Society of

Abbreviations: AIEOP, L'Associazone Italiana Ematologica Oncologia Pediatrica; CI, confidence interval; COG, Children's Oncology Group; DA, diffuse anaplasia; DAWT, diffuse anaplastic Wilms tumor; EFS, event-free survival; FA, focal anaplasia; JWiTS, Japan Wilms Tumor Study group; NWTS, National Wilms Tumor Study; OS, overall survival; SIOP-RTSG, International Society of Pediatric Oncology-Renal Tumor Study Group; WT, Wilms tumor.

Pediatric Oncology (SIOP), the value of radiotherapy has never been studied. The aim of this observational study is to describe the pattern of recurrence and survival of patients with stage I diffuse anaplastic WT (DAWT) after induction chemotherapy.

Methods: Retrospective data analysis of the pattern of relapse and survival of all patients with stage I DAWT were included in recent SIOP, L'Associazone Italiana Ematologica Oncologia Pediatrica (AIEOP), Japan Wilms Tumor Study Group (JWiTS), United Kingdom Children's Cancer Study Group (UKCCSG) renal tumor registries. Postoperative treatment consisted of actinomycin D, vincristine, and doxorubicin for 28 weeks without local irradiation.

Results: One hundred nine cases with stage I DAWT were identified, of which 95 cases received preoperative chemotherapy. Of these, seven patients underwent preoperative true-cut biopsy. Sixteen of the 95 patients relapsed (17%), six locally, four at distant site, and six combined, and all treated according to SIOP 2001 relapse protocol, which resulted in a 5-year overall survival of 93%.

Conclusion: Despite 13% locoregional relapse rate, an excellent rescue rate was achieved after salvage treatment, in patients with stage I DAWT whose first-line treatment comprised three-drug chemotherapy (including doxorubicin), without flank irradiation. Therefore, we continue not to advocate the use of radiotherapy in first-line treatment after preoperative chemotherapy in stage I DAWT in the next SIOP protocol.

KEYWORDS
diffuse anaplasia, radiotherapy, stage I, Wilms tumor

1 | INTRODUCTION

Outcome for children with Wilms tumor (WT) has significantly improved over the past decades, as illustrated by overall survival (OS) rates of approximately 90%.[1–4] Recognized prognostic factors for survival include age, stage, gender, and histology.[2,5–10] Among the high-risk cases that can be identified based on histology, there is a subgroup characterized by diffuse anaplasia (DA).[1,11,12] Presence of anaplasia is observed in 5% to 10% of all WT and, especially DA, is associated with adverse outcome.[11–13] In the fifth National Wilms Tumor Study (NWTS-5), 79% of all anaplastic tumors presented with DA, while 21% had focal anaplasia (FA).[11] This is concordant with International Society of Pediatric Oncology (SIOP) data that showed 81% DA and 19% FA.[12] Five-year OS for all stages of diffuse anaplastic WT (DAWT) does not exceed 60%, in contrast to the higher than 90% OS that is observed in nonanaplastic tumors.[14]

In general, DAWT is usually treated with more intensive regimens in order to improve cure rates. Interestingly, the results of the NWTS-5 revealed a significantly lower 4-year event-free survival (EFS) and OS for stage I DAWT after initial nephrectomy (68% and 78%, respectively) compared to 92% and 98%, respectively, for stage I favorable histology patients.[11] The relatively high proportion of local and combined relapses in stage I anaplastic WT observed in NWTS-5 advocates for the use of doxorubicin as well as adjuvant radiotherapy in this specific group of patients in the subsequent AREN0321 protocol. Preliminary data showed an improvement in EFS and OS in patients treated according to the more intensive study regimen including radiotherapy in stage I.[15] Whether flank radiotherapy also benefits patients with stage I DAWT undergoing preoperative chemotherapy, such as in the SIOP setting, has never been evaluated.

To address this question, we invited all non-COG (Children's Oncology Group) national and multinational renal tumor study groups to provide available information on patients with stage I DAWT who received preoperative chemotherapy and were registered in their recent studies in Europe and Japan (International Society of Pediatric Oncology-Renal Tumor Study Group [SIOP-RTSG; including Brazil], L'Associazone Italiana Ematologica Oncologia Pediatrica [AIEOP], United Kingdom Children's Cancer Study Group (UKCCSG), and Japan Wilms Tumor Study group [JWiTS]), in order to find evidence for the use of adjuvant radiotherapy in this rare subset of patients.

2 | PATIENTS AND METHODS

This observational study selected prospectively registered data of all patients with stage I DAWT included until 2015, in the most recent renal studies of the SIOP-RTSG 93-01/2001 studies, AIEOP TW-2003 study, JWiTS-1 and 2 studies, and the UKCCSG (UKW3 trial).

DAWT was confirmed based on the international definitions.[12,16] Briefly, DA was defined as (a) nonlocalized anaplasia and/or anaplasia beyond the original tumor capsule; (b) anaplastic cells present in intra- or extrarenal vessels, renal sinus, extracapsular invasive sites, or metastatic deposits; (c) the anaplasia is focal but nuclear atypia approaching the criteria for anaplasia (so-called unrest nuclear change) is present elsewhere in the tumor; (d) anaplasia that is not clearly demarcated from nonanaplastic tumor; and (e) anaplasia present in a

TABLE 1 Characteristics of histological SIOP stage I versus NWTS-5 stage I criteria

SIOP stage I	NWTS-5 stage I
• The tumor is limited to the kidney • Tumor is present in the perirenal fat but is surrounded by a fibrous (pseudo)capsule. The (pseudo)capsule may be infiltrated by viable tumor that does not reach the outer surface. • Tumor may show botryoid/protruding growth into the renal pelvis or the ureter, but does not infiltrate their walls. • The vessels or the soft tissues of the renal sinus are not involved by tumor. • Intrarenal vessel involvement may be present. Notes: - Be aware of mature tubules within the sinus or hilar region, which usually represent nephrogenic rests. Genuine infiltration of the sinus/hilar structures is usually seen as blastemal foci closely related to nerves. - Fine needle aspiration or percutaneous cutting needle (true-cut) biopsy does not upstage the tumor. - The presence of necrotic tumor or chemotherapy-induced change in the renal sinus, renal veins, and/or within the perirenal fat should not be regarded as a reason for upstaging the tumor. - Viable tumor infiltration of fat between the kidney and the adrenal gland, or of the adrenal gland itself, does not upstage the tumor, if the tumor is contained within the (pseudo)capsule. - Liver: tumor might be attached to the liver capsule and this should not be regarded as infiltration of the adjacent organ; only if clear infiltration of the liver parenchyma is present, tumor should be regarded as stage II (if completely resected) or stage III (if incompletely resected).	• Tumor limited to the kidney • Tumor completely resected, renal capsule intact • Tumor was not ruptured or biopsied prior to removal • The vessels of the renal sinus are not involved • There is no evidence of tumor at or beyond the margins of resections Note: For a tumor to qualify for certain therapeutic protocols as stage I, regional lymph nodes must be examined microscopically

Note: Histological SIOP stage I criteria according to Umbrella 2016 protocol[8]; histological NWTS-5 stage I criteria according to Children's Oncology Group staging system for Wilms tumor.[23]Abbreviations: NWTS-5, fifth National Wilms Tumor Study; SIOP, International Society of Paediatric Oncology.

biopsy or other incomplete tumor sample. In SIOP, all tumors were histologically classified and reviewed by the SIOP review panel of pathologists. Histological stage I was defined according to the SIOP Umbrella 2016 criteria. (a) The tumor is limited to the kidney. (b) Tumor is present in the perirenal fat but is surrounded by a fibrous (pseudo)capsule. The (pseudo)capsule may be infiltrated by viable tumor that does not reach the outer surface. (c) Tumor may show botryoid/protruding growth into the renal pelvis or the ureter, but does not infiltrate their walls. (d) The vessels or the soft tissue of the renal sinus are not involved in tumor. (e) Intrarenal vessel involvement may be present (Table 1).[8] Endpoints were 5-year EFS, OS, and pattern of relapse (local, distant, or combined). Survival rates were calculated from the date of diagnosis to the date of recurrence or death, whichever happened first. Patients

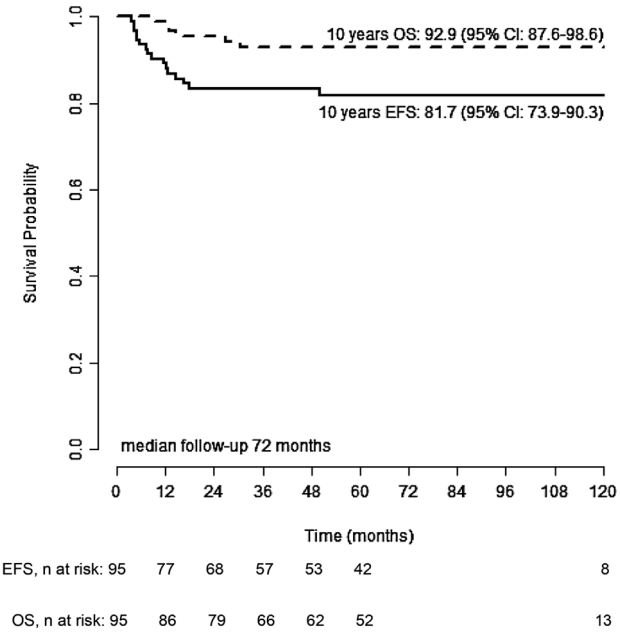

FIGURE 1 Overall survival (OS) and event-free survival (EFS) for patients with stage I diffuse anaplasia (SIOP cohort)
Abbreviations: CI, confidence interval; EFS, event-free survival; *n*:, number; OS, overall survival; SIOP, International Society of Paediatric Oncology

alive, without recurrence, were censored at 60 months or at the last follow-up date. The survival curves were constructed according to the Kaplan-Meier method. Statistical analysis was performed using the Statistical Analysis Software (version 9.4) and R (version 3.5.1).[17]

3 | RESULTS

In total, 109 patients diagnosed with stage I DAWT were identified. This included 14 patients who underwent primary nephrectomy (including all five AIEOP, four JWiTS, and five UKW3 cases) (Figure 1), and were therefore excluded from the analysis. Of the 95 patients, 40 were males and 55 were females. Median age at diagnosis was 49 months (interquartile range: 35-67) with a median follow-up of 72 months.

Of the 95 eligible patients, 90 patients were treated according to SIOP 93-01/2001 protocols, thereby receiving, preoperatively, four vincristine (1.5 mg/m^2) and two actinomycin D (45 μg/kg) administrations. Two of these patients had been biopsied. Five patients were registered in the UKW3 and treated with seven vincristine (1.5 mg/m^2), two actinomycin D (1.5 mg/m^2), and two doxorubicin (30 mg/m^2) doses after initial biopsy.

None of the 95 patients received postoperative radiotherapy as first-line treatment. The postoperative chemotherapy regimen in both SIOP and UKW3 contained doxorubicin (actinomycin D, vincristine, doxorubicin). The 5-year EFS and OS was 82% (95% confidence interval [CI]: 74-90) and 93% (95% CI: 88-99), respectively (Figure 1).

Sixteen of the 95 patients relapsed (17%), that is, 6 developed local relapse, 4 distant relapse, and 6 had a combined relapse (combined

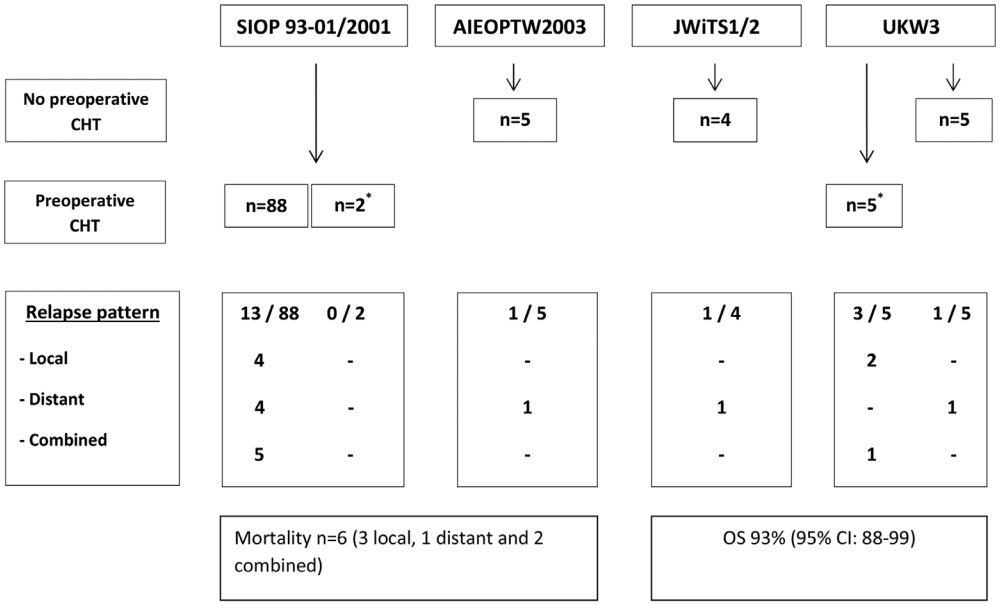

FIGURE 2 Relapse pattern of patients with stage I DAWT
Abbreviations: CHT, chemotherapy; OS, overall survival.
*Prechemotherapy biopsy

relapse = primary site + lung [n = 3], primary site + lung + lymphnode [n = 1], primary site + liver [n = 1], primary site + elsewhere in abdomen [n = 1]) (Figure 2). All but two of the relapses occurred within 2 years after initial diagnosis. Salvage chemotherapy and radiotherapy was administered in all relapsed patients, as recommended by the SIOP 93-01/2001 and UKW3 protocols, resulting in complete remission in 10 cases. Six patients died. Of them, three had developed local relapse, two combined relapse, and one distant relapse.

4 | DISCUSSION

The current study aimed to obtain evidence in favor or against administration of flank radiotherapy in patients with stage I DAWT that had been treated with chemotherapy before surgery. We show that 17% of patients with stage I DAWT treated with preoperative chemotherapy developed a relapse (75% local or combined) after doxorubicin-based postoperative treatment, without radiotherapy in first-line treatment. This is a higher relapse rate than the 5% relapse rate that is observed in stage I favorable histology group patients.[18] This higher relapse rate has been acknowledged by the COG group that reported worse outcomes in anaplastic WT compared to patients with favorable histology stage I WT in directly nephrectomized cases within the NWTS-5 study.[11] Because of a significant proportion of recurrences (37.5%) occurred in the abdomen or operative bed,[11] flank radiation (at a total dose of 10.8 Gy) was added to the treatment protocol, thereby intensifying local treatment for this group of patients following primary tumor nephrectomy, within the current setting of the AREN0321 protocol.

So far, a detailed analysis on outcome of patients with chemotherapy pretreated stage I DAWT had never been performed. Previous studies hamper such analysis, as diffuse and FA cases were not separately analyzed.[1] Of the 16 patients with stage I DAWT included in the SIOP-6 and SIOP-9 studies, 5 patients developed a relapse that translated into a 4-year EFS and OS of 69% and 75%, respectively.[12] In the current report, where all stage I DA from recent non-COG registries were analyzed, the number of patients with a local relapse was relatively high (12/16), but most patients could be rescued with second-line chemotherapy and radiotherapy. This suggests that radiotherapy could be avoided in the vast majority of pretreated patients with stage I DAWT, which is of benefit as radiotherapy exposure in patients with WT can potentially lead to increased treatment-related long-term toxicity.[19–22]

It is conceivable that preoperative chemotherapy together with a doxorubicin-containing treatment after surgery, apparently, creates a situation in which general tumor control is achieved, thereby benefitting the majority of the children in which radiotherapy can be omitted. Therefore in the COG approach, the use of a three-drug postnephrectomy chemotherapy regimen might be a more important component rather than the benefit of using radiotherapy. A randomized controlled trial would obviously offer the best evidence to prove the relative value of radiotherapy, however, numbers of stage I DAWT are extremely small. In addition, such a randomization may be difficult to pursue, as OS already has shown to be excellent in the majority of chemotherapy pretreated patients, in which renal tumor is avoided during upfront treatment.

5 | CONCLUSION

We conclude that despite a relatively high locoregional relapse rate in patients with stage I DAWT that receive preoperative chemotherapy and a three-drug postoperative regimen containing doxorubicin,

an excellent OS is achieved with most cases rescued after salvage approach. Therefore, we advise against the use of radiotherapy in first-line treatment for this group in the next SIOP protocol.

ACKNOWLEDGMENTS

We dedicate this work to Prof. I. Leuschner who has contributed tremendously to the development and activities of the pathology review group of the SIOP-RTSG. Prof. I. Leuschner unfortunately passed away on January 29, 2017.

The SIOP WT 2001 study was funded by Cancer Research UK (grant C1188/A8687), the UK National Cancer Research Network and Children's Cancer and Leukemia Group (which supported the UK section), Société Française des Cancers de l'Enfant and Association Leon Berard Enfant Cancéreux and Enfant et Santé (which supported the French section), Gesellschaft für Pädiatrische Onkologie und Hämatologie and Deutsche Krebschilfe (grant 50-2709-Gr2, which supported the German section), Grupo Cooperativo Brasileiro para o Tratamento do Tumor de Wilms and Sociedade Brasileira de Oncologia Pediátrica (which supported the Brazilian section), the Spanish Society of Pediatric Haematology and Oncology and the Spanish Association Against Cancer (which supported the Spanish section), and SIOP-NL. KP-J is partly supported by the National Institute for Health Research Biomedical Research Centre Funding Scheme. We acknowledge the enormous efforts made by more than 1000 clinicians working at the 251 childhood cancer treatment centers in this study from 28 countries who enrolled and followed up patients in this study, and the patients and their families for their participation.

CONFLICT OF INTEREST

We confirm that this manuscript has not been published elsewhere and is not under consideration by any other journal. All authors agree with submission to Pediatric Blood and Cancer. We have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Author elects to not share data Research data are not shared.

ORCID

Raquel Dávila Fajardo https://orcid.org/0000-0002-4729-825X
Filippo Spreafico https://orcid.org/0000-0002-5587-3509
Beatriz de Camargo https://orcid.org/0000-0002-5794-1042
Christian Vokuhl https://orcid.org/0000-0002-4138-4536
Gordan Vujanic https://orcid.org/0000-0003-0726-6939
Martine van Grotel https://orcid.org/0000-0002-8849-8573

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How to cite this article: Fajardo RD, van den Heuvel-Eibrink MM, van Tinteren H, et al. Is radiotherapy required in first-line treatment of stage I diffuse anaplastic Wilms tumor? A report of SIOP RTSG, AIEOP, JWiTS, and UKCCSG. *Pediatr Blood Cancer*. 2020;67:e28039. https://doi.org/10.1002/pbc.28039