# IS RADIOTHERAPY REQUIRED IN FIRST-LINE TREATMENT OF STAGE I DIFFUSE ANAPLASTIC WILMS TUMOUR? A REPORT OF SIOP RTSG, AIEOP, JWiTS AND UKCCSG

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| **Abbreviations** | |
|---|---|
| SIOP RTSG | International Society of Paediatric Oncology Renal Tumour Study Group |
| AIEOP | L'Associazone Italiana Ematologica Oncologia Pediatrica |
| JWiTS | Japan Wilms Tumor Study group |
| UKCCSG | United Kingdom Children's Cancer Study Group |
| DAWT | Diffuse Anaplasic Wilms Tumour |
| AVD | Actinomycin D, vincristine, doxorubicin |
| WT | Wilms tumour |
| OS | Overall survival |
| DA | Diffuse anaplasia |
| FA | Focal anaplasia |
| NWTS | National Wilms Tumor Study |
| EFS | Event-free survival |
| COG | Children's Oncology Group |
| SAS | Statistical Analysis Software |
| IQR | Interquartile range |
| CI | Confidence interval |
| Gy | Gray |

## ABSTRACT

### Background

Because a significant proportion of relapses occurred in the tumour bed or abdomen on NWTS-5 stage I anaplastic Wilms tumour patients, flank radiotherapy was added for stage I anaplastic Wilms tumour 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 pre-operative chemotherapy, such as in 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 DAWT stage I patients after induction chemotherapy.

**Methods** Retrospective data analysis of the pattern of relapse and survival of all stage I DAWT patients, included in recent SIOP, AIEOP, JWiTS group, UKCCSG renal tumour registries. Postoperative treatment consisted of AVD for 28 weeks without local irradiation.

**Results** One-hundred-nine cases with stage I DAWT were identified, of which 95 cases received pre-operative chemotherapy. Of these, seven patients underwent pre-operative 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% loco-regional relapse rate, an excellent rescue rate was achieved after salvage treatment, in stage I DAWT patients 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 pre-operative chemotherapy in stage I DAWT in the next SIOP protocol.

## INTRODUCTION

Outcome for children with Wilms Tumour (WT) has significantly improved over the past decades, as illustrated by overall survival (OS) rates of approximately 90% (1-4). Recognised 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 5-10% of all WT and, especially DA, is associated with adverse outcome (11-13). In the NWTS-5, 79% of all anaplastic tumours presented with DA, while 21% had focal anaplasia (FA) (11). This is concordant with 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 non-anaplastic tumours (14).

In general, DAWT is usually treated with more intensive regimens in order to improve cure rates. Interestingly, the results of the fifth National Wilms Tumor Study (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), as compared to 92% and 98%, respectively, for stage I favourable 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 stage I DAWT patients undergoing pre-operative chemotherapy such as in the SIOP setting has never been evaluated.

To address this question, we invited all non-COG national and multinational renal tumour study groups to provide available information on stage I DAWT patients who received pre-operative

chemotherapy and were registered in their recent studies in Europe and Japan (SIOP-RTSG (including Brazil), AIEOP, UKCCSG, and JWiTS), in order to find evidence for the use of adjuvant radiotherapy in this rare subset of patients.

## 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 International Society of Paediatric Oncology - Renal Tumour Study Group (SIOP 93-01/2001 studies), L'Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP TW-2003 study), the Japan Wilms Tumor Study group (JWiTS-1 and 2 studies) and the United Kingdom Children's Cancer Study Group (UKW3 trial). DAWT was confirmed based on the international definitions (12, 16). Briefly, DA was defined as: 1) non-localised anaplasia and/or anaplasia beyond the original tumour capsule; 2) anaplastic cells present in intra- or extra-renal vessels, renal sinus, extracapsular invasive sites, or metastatic deposits; 3) the anaplasia is focal but nuclear atypia approaching the criteria for anaplasia (so-called unrest nuclear change) is present elsewhere in the tumor; 4) anaplasia that is not clearly demarcated from non-anaplastic tumour; and 5) anaplasia, present in a biopsy or other incomplete tumour sample. In SIOP, all tumours 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; 2) tumor is present in the perirenal fat but is surrounded by a fibrous (pseudo) capsule. The (pseudo)capsule may be infiltrated by viable tumor which does not reach the outer surface; c) Tumor may show botrytoid/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 by tumor; e) Intrarenal vessel involvement may be present (Table 1) (8). Endpoints were 5-year event-free (EFS), overall survival (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 alive, without recurrence were censored at 60 months or at last follow-up date. The survival curves were constructed according to the Kaplan-Meier method. Statistical analysis was performed using the statistical software SAS (version 9.4) and R (version 3.5.1) (17).

**RESULTS**

In total, 109 patients diagnosed with stage I DAWT were identified. This included 14 patients who underwent primary nephrectomy (including all 5 AIEOP, 4 JWiTS and 5 UKW3 cases) (Figure 1) that were therefore excluded from the analysis. Of the 95 patients, 40 were males and 55 females. Median age at diagnosis was 49 months (IQR: 35-67) with a median follow-up 72 months.

Of the 95 eligible patients, 90 patients were treated according to SIOP 93-01/2001 protocols, thereby receiving, pre-operatively, 4 vincristine (1.5mg/$m^2$) and 2 actinomycin D (45µg/kg) administrations. Two of these patients had been biopsied. Five patients were registered in the UKW3 and treated with 7 vincristine (1.5mg/$m^2$), 2 actinomycin D (1.5mg/$m^2$) and 2 doxorubicin (30mg/$m^2$) doses after initial biopsy.

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

Sixteen out of the 95 patients relapsed (17%), i.e. six developed local relapse, four distant and six had a combined relapse (combined 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 two years after initial diagnosis. Salvage chemotherapy and radiotherapy was administered in all relapsed patients, as recommended by the SIOP 93-01/2001and 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.

## DISCUSSION

The current study aimed to obtain evidence in favour 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 the stage I DAWT patients treated with preoperative chemotherapy developed a relapse (75% local or combined) after doxorubicin based post-operative treatment, without radiotherapy in first-line. This is a higher relapse rate than the 5% relapse rate that is observed in stage I favourable histology group patients (18). This higher relapse rate has been acknowledged by the COG group who reported worse outcomes in anaplastic WT, compared to favourable histology stage I WT patients in directly nephrectomised 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 10.8Gy) was added to the treatment protocol, thereby intensifying local treatment for this group of patients following primary tumour nephrectomy, within the current setting of the AREN0321 protocol.

So far, a detailed analysis on outcome of chemotherapy pre-treated stage I DAWT patients had never been performed. Previous studies hamper such analysis as diffuse and focal anaplasia cases were not separately analysed (1). Of the 16 patients with stage I DAWT included in the SIOP-6 and 9 studies, 5 patients developed a relapse which 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 analysed, 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 pre-treated stage I DAWT patients, which is of benefit as radiotherapy exposure in WT patients can potentially lead to increased treatment-related long term toxicity (19-22).

It is conceivable that pre-operative chemotherapy together with a doxorubicin containing treatment after surgery, apparently, creates a situation in which general tumour 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 3 drug post-nephrectomy chemotherapy regimen, might be a more important component, rather then the benefit of using radiotherapy. A randomised 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 overall survival already has shown to be excellent, in the majority of chemotherapy pre-treated patients, in which RT is avoided during upfront treatment.

## CONCLUSION

We conclude that, despite a relatively high loco-regional relapse rate in patients with stage I DAWT, that receive pre-operative chemotherapy and a 3-drug postoperative regimen containing doxorubicin, an excellent overall survival 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.

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## Conflict of interest statement

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 conflicts of interests to declare.

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**Figure and Table Legends**

**Figure 1 Overall survival (OS) and event-free survival (EFS) for patients with stage I diffuse anaplasia (SIOP cohort)**

*Abbreviations:* OS: overall survival, CI: confidence interval, EFS: Event-free survival, n: number, SIOP: International Society of Paediatric Oncology

**Figure 2 Relapse pattern of patients with stage I DAWT**

*Abbreviations:* CHT: Chemotherapy, RT: Radiotherapy, *: pre-chemotherapy biopsy, OS: overall survival

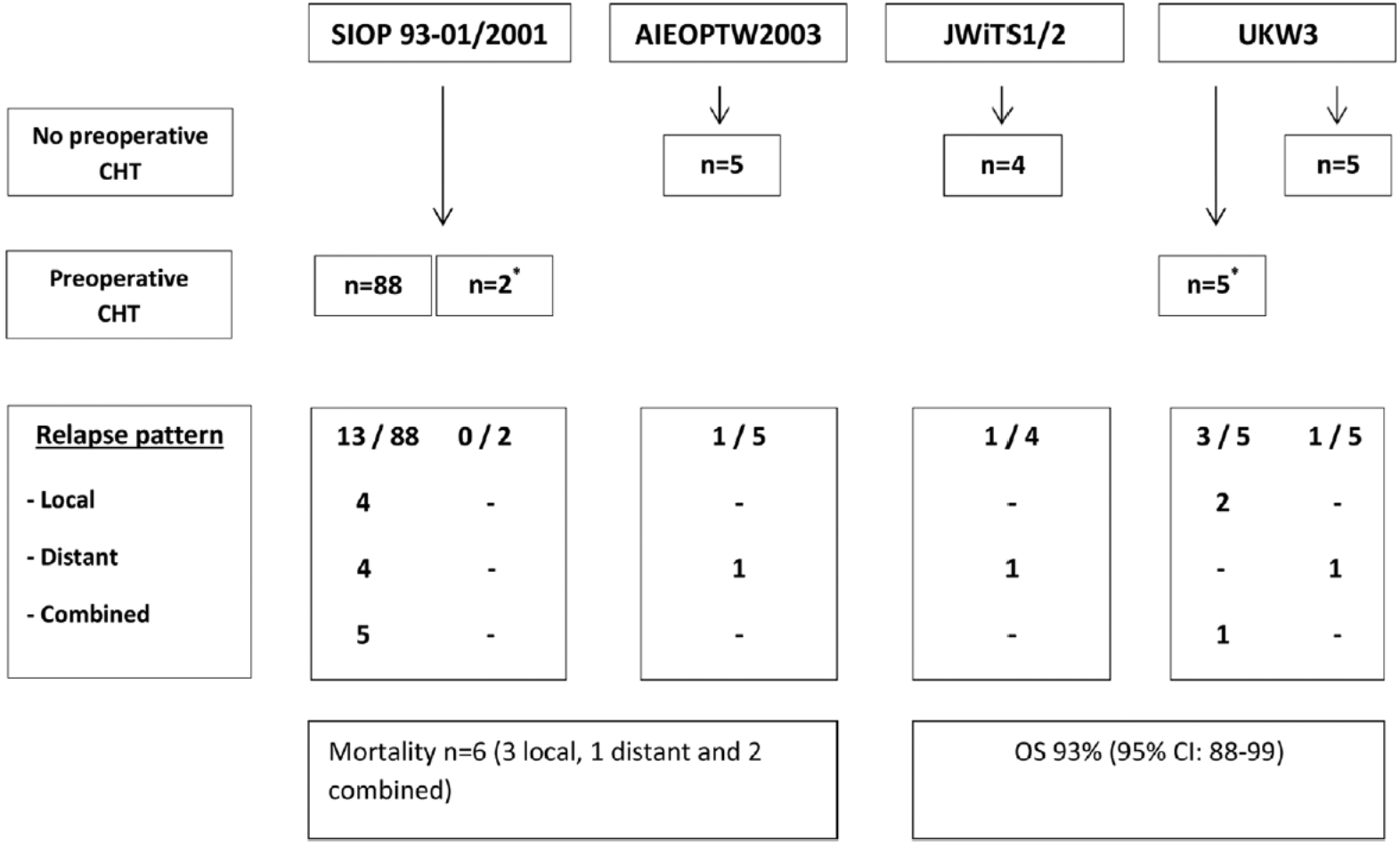
**Table 1 Characteristics of histological SIOP stage I vs NWTS-5 stage I criteria**

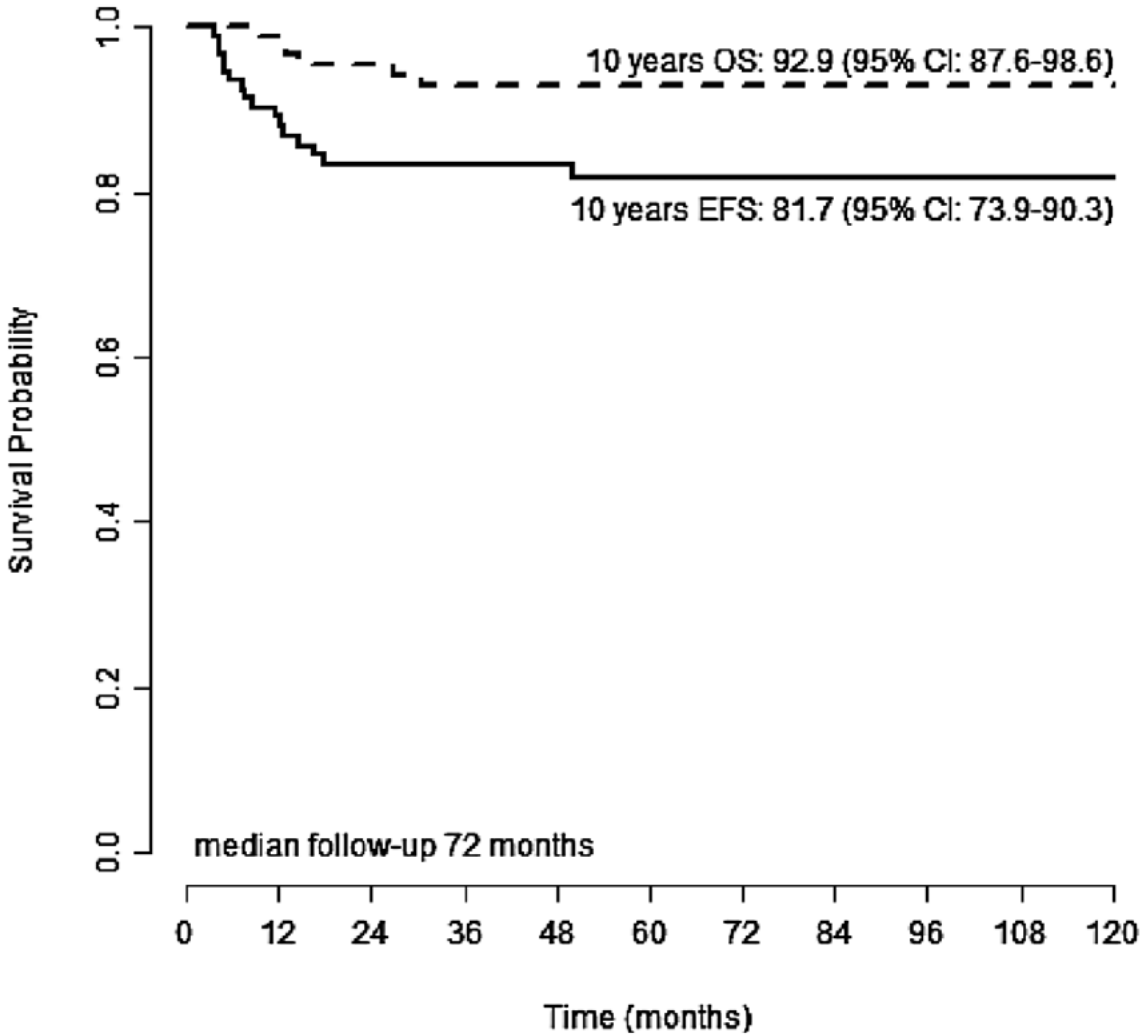
Histological SIOP stage I criteria according to Umbrella 2016 protocol (8); Histological NWTS-5 stage I criteria according to Children's Oncology Group staging system for Wilms tumor (23)

**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<br>• 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.<br>• Tumor may show botryoid/protruding growth into the renal pelvis or the ureter, but does not infiltrate their walls.<br>• The vessels or the soft tissues of the renal sinus are not involved by tumor.<br>• Intrarenal vessel involvement may be present.<br><br>Notes:<br>- 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.<br>- Fine needle aspiration or percutaneous cutting needle (true-cut) biopsy does not upstage the tumor.<br>- 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.<br>- 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.<br>- 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<br>• Tumor completely resected, renal capsule intact<br>• Tumor was not ruptured or biopsied prior to removal<br>• The vessels of the renal sinus are not involved<br>• There is no evidence of tumor at or beyond the margins of resections<br><br>Note:<br>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.


SIOP 93-01/2001
AIEOPTW2003
JWiTS1/2
UKW3
No preoperative CHT
n=5
n=4
n=5
Preoperative CHT
n=88
n=2*
n=5*
Relapse pattern
- Local
- Distant
- Combined
13 / 88
4
4
5
0 / 2
-
-
-
1 / 5
-
1
-
1 / 4
-
1
-
3 / 5
2
-
1
1 / 5
-
1
-
Mortality n=6 (3 local, 1 distant and 2 combined)
OS 93% (95% CI: 88-99)

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|---|---|---|---|---|---|---|---|---|---|---|---|
| EFS, n at risk: | 95 | 77 | 68 | 57 | 53 | 42 | | | | | 8 |
| OS, n at risk: | 95 | 86 | 79 | 66 | 62 | 52 | | | | | 13 |