EVALUATION OF BOOST IRRADIATION IN PATIENTS WITH INTERMEDIATE-RISK STAGE III WILMS TUMOUR WITH POSITIVE LYMPH NODES ONLY: RESULTS FROM THE SIOP-WT-2001 REGISTRY

Raquel Dávila Fajardo [a1] and Eva Oldenburger [b1], Christian Rübe [c], Marta López-Yurda [d], Kathy Pritchard-Jones [e], Christophe Bergeron [f], Norbert Graf [g], Martine van Grotel [h], Harm van Tinteren [d], Daniel Saunders[i], Marry M. van den Heuvel-Eibrink [h], Geert O. Janssens [a2] and Foppe Oldenburger [j2]

[a] Department of Radiation Oncology, University Medical Center Utrecht and Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands
[b] Radiation Oncology Department, Leuven Cancer Center, Leuven, Belgium
[c] Department of Radio-Oncology, University Hospital of Saarland, Homburg, Germany
[d] Department of Statistics, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[e] Cancer Section, University College London Institute of Child Health, London, UK
[f] Department of Paediatric Oncology, Centre Leon Berard, Lyon, France
[g] Department of Paediatric Oncology, University Hospital of Saarland, Homburg, Germany
[h] Princess Máxima Center for Paediatric Oncology, Utrecht, The Netherlands
[i] The Christie NHS Foundation Trust, Manchester, UK
[j] Department of Radiation Oncology, Academic Medical Center, Amsterdam, The Netherlands

(1,2) These authors contributed equally to the work

*Corresponding author:
Prof. Dr. M.M. van den Heuvel-Eibrink, MD PhD
Professor Paediatric Oncology
Princess Máxima Center for Pediatric Oncology
Room Q05.2.302
Lundlaan 6, 3508 AB Utrecht
The Netherlands
Phone: +31-88-9727272
Email: m.m.vandenheuvel-eibrink@prinsesmaximacentrum.nl

Abstract word count: 237

Manuscript word count: 2507

Number of tables: 2

Number of figures: 2 (1 of them is composite)

Number of supplemental files: 1

Running title: Omission of boost for IR-WT stage III-LN positive

Key words: Wilms tumour, Intermediate-risk, Lymph node, Radiotherapy, Boost

Abbreviations:

CCLG	Children's Cancer and Leukaemia Group
COG	Children's Oncology Group
CTV	clinical target volume
EFS	event-free survival
Gy	Gray
ICRU	International Commission on Radiation Units & Measurements
IGRT	image-guided radiotherapy
IR	intermediate risk
iv	intravenous
LN	lymph nodes
LRC	loco-regional control
NWTS	National Wilms Tumor Study Group
OS	overall survival
PTV	planning target volume
RT	radiotherapy
SAS	statistical analysis software
SIOP	International Society of Paediatric Oncology
WT	Wilms tumour

ABSTRACT

Objective

To evaluate the value of radiotherapy boost omission in patients with intermediate-risk, stage III Wilms tumours (WT) with positive lymph nodes (LN).

Methods and materials

All patients with intermediate-risk, stage III (LN positive) WT consecutively registered in the SIOP-WT-2001 study were included in this analysis. Endpoints were 5-year event-free survival (EFS), loco-regional control (LRC) and overall survival (OS).

Results

Between June 2001 and May 2015, 2,569 patients with stage I to III WT after preoperative chemotherapy were registered in the SIOP-WT-2001 study. Five hundred twenty-three (20%) had stage III disease, of which 113 patients had stage III due to positive LN only. Of those, 101 (89%) received radiotherapy, 36 out of them (36%) received, apart from flank irradiation, a boost dose to the LN positive area. Four patients (4%) did not receive any adjuvant radiotherapy. In eight patients information on radiotherapy was not available.

With a median follow-up of 71 months, no difference in 5-year EFS (84% vs. 83%, p=0.77) and LRC (96% vs. 97%, p=0.91) was observed between patients receiving a radiotherapy boost and those without boost, respectively. The 5-year OS, including salvage therapy was excellent (boost vs. no boost: 97% vs. 95%, p=0.58).

Conclusions

Outcome data demonstrate that omission of the radiotherapy boost to the loco-regional positive lymph nodes in intermediate-risk, stage III WT patients who receive

preoperative chemotherapy and postoperative flank irradiation (14.4Gy) can be considered a safe approach for future SIOP protocols.

INTRODUCTION

Wilms tumour (WT) or nephroblastoma is the most common malignant tumour of the kidney in children, with 90% of cases occurring before the age of 7 years [1,2]. The International Society of Paediatric Oncology (SIOP) in Europe and the National Wilms Tumor Study Group (NWTS), now Children's Oncology Group (COG), in the United States, have conducted different clinical trials on treatment optimization for children with WT. While outcome for children with WT is highly successful across both groups, there is a difference in treatment philosophies [3-8,2]. In contrast to the COG-approach that recommends primary surgery followed by adjuvant treatment, children treated within recent SIOP protocols receive upfront chemotherapy followed by surgery. Over the past decades, excellent outcome allowed efforts to reduce toxicity and burden of the treatment sustaining effectiveness [5,9].

Stage and histology are considered to be the most important clinical prognostic factors so far [2,7,10-12]. Around 20% of all WT present as stage III, of which 30% is based on lymph node involvement, as assessed at time of surgery. Previous studies from SIOP and COG have shown that stage III WTs carry an increased risk of abdominal recurrence [13,14]. Therefore, the radiotherapy boost dose in addition to flank irradiation (14.4Gy + 10.8Gy) has been common practice in such patients within previous SIOP protocols [15-20,21]. Over the past two decades a rising tendency occurred to omit the radiotherapy boost to the positive lymph nodes in order to avoid late sequelae. Whether the omission of radiotherapy boost impacts loco-regional control and event-free survival has, however, never been demonstrated.

The purpose of the current study is to evaluate the contribution of the radiotherapy boost dose in patients with stage III, intermediate-risk, LN positive WT participating in the prospective SIOP-WT-2001 study.

PATIENTS AND METHODS

Study design

SIOP-WT-2001 included an open-label, non-inferiority, phase-3 trial for children aged 6 months to 18 years at the time of diagnosis, with a primary intermediate-risk, stage II/III WT (Eudra-CT 2007-004591-39) [5]. Treatment consisted of preoperative chemotherapy followed by nephrectomy with para-aortic lymph node sampling. Subsequently, the tumour was classified based on the revised SIOP working classification of renal tumours of the childhood, combining tumour staging system and histological risk classification [12]. Afterwards, patients were randomised to receive postoperative chemotherapy either with or without doxorubicin (Appendix). Postoperative flank irradiation was recommended in children with stage III. Details of the protocol are available online (www.siop-rtsg.eu). Two hundred fifty-one hospitals from 26 countries participated in this study. National and local regulatory and ethical approvals were obtained according to the national regulations.

In the current analysis only patients with intermediate-risk, stage III tumour, based on lymph node involvement (presence of vital or necrotic tumour cells after pre-operative chemotherapy), were included [12].

Systemic treatment

According to the SIOP protocol, all newly diagnosed patients with a local intra-renal tumour received preoperative chemotherapy (weekly iv. vincristine (1.5mg/m^2) combined with actinomycin-D (45µg/kg) every 2 weeks for 4 weeks), followed by an ipsilateral nephrectomy including standard lymph nodes sampling. Intermediate-risk, stage III WT patients received postoperative chemotherapy for 27 weeks (iv.

vincristine combined with actinomycin-D every 3 weeks, and five additional doxorubicin doses, depending on the allocated randomisation) [5] (Appendix).

Radiotherapy

Radiotherapy was administered during week 2 to 4 of postoperative chemotherapy according to the radiotherapy guidelines of SIOP 2001 protocol, i.e. patients with intermediate-risk, stage III WT and LN positive received radiotherapy to the flank (14.4 Gy in 8 fractions of 1.8 Gy). A boost dose of 10.8 Gy in 6 fractions of 1.8 Gy was recommended to loco-regional lymph nodes with microscopic tumour involvement, as well as necrotic lymph nodes at time of surgery.

After a preliminary analysis in 107 patients with intermediate-risk, stage III WT, by consensus of the radiotherapy panel and the SIOP steering committee, omission of the radiotherapy boost was allowed [22].

Target volume definition was according to the ICRU 50 and ICRU 62 recommendation guidelines. The target volume of the tumour bed and involved lymph nodes encompassed the post-chemotherapy/preoperative macroscopic tumour extent according to pre-operative imaging (CT-scan or ultrasound) as well as to the surgical and histological reports. In the absence of pre-operative imaging, the target volume was delineated based on surgical clips. A margin of 1.0 cm was added for clinical target volume (CTV). Margins for the planning target volume (PTV) were dependant on department policy. The treated volume should extend across the midline to achieve homogenous irradiation of the full width of the vertebral bodies. Target boost volume was restricted to the nodal chain. Cranial and caudal borders of the para-aortic lymph nodes were defined at the vertebral interspace of T10/11, and the bifurcation of the aorta into common iliac arteries (generally including the lower plate of the fourth

lumbar vertebrae), respectively. Lateral borders included the transverse processes of the vertebrae at each level and the ipsilateral renal hilus.

Statistical analysis

Event-free survival (time to loco-regional or distant recurrence, or death form any cause), loco-regional disease control (time to loco-regional recurrence) and overall survival (time to death from any cause) were calculated from the date of diagnosis. Patients who were event-free at the end of follow-up were censored at that time. For the current study, 5-year event-free survival (EFS), loco-regional control (LRC) and overall survival (OS) were used as endpoints.

The survival curves were constructed according to the Kaplan-Meier method. The log-rank test was used to compare survival between subgroups. The median follow-up was calculated using the reverse Kaplan-Meier method. Comparison of categorical variables was based on Fisher's 2-tailed exact test. Continuous variables were compared using the Wilcoxon rank-sum test. Statistical analysis was performed using the statistical software SAS version 9.2 and R version 3.01 [23].

RESULTS

Patient characteristics

Between June 2001 and May 2015, 2,569 patients with stage I to III WT after preoperative chemotherapy and overall treated as "per-protocol" with relevant stage-adapted therapy, were registered in the SIOP-WT-2001. Of these, 1397 (55%) had stage I, 649 (25%) had stage II and 523 (20%) had stage III disease. Presence of positive LN as reason for stage III was described in 171 (33%) patients, 113 of them had positive LN only while 58 patients had positive LN combined with major rupture or positive margin.

Stage III, positive lymph nodes only

Patient, tumour and treatment characteristics of the patient subset with stage III disease due to LN positive only, are listed in Table 1. Information on radiotherapy was missing in 8 patients (7%).

Of the 105 LN positive, intermediate-risk, stage III WT patients with available radiotherapy data, 101 patients (96%) received radiotherapy, 36 of them (36%) received also a boost dose to the lymph nodes. Both groups, with and without boost, were equally balanced in their clinical characteristics (Table 1). Four patients (4%) did not receive adjuvant radiotherapy based on physician choice. Reasons for omitting radiotherapy, a deviation from the protocol recommendations, were not recorded.

Disease control

With a median follow-up of 71 months (range 35-100) similar EFS was observed in patients receiving radiotherapy with boost and those without boost (p=0.77) (Figure 1A). The 5-year EFS rate was 84% (95% CI 73% to 98%) for patients receiving

radiotherapy with boost vs. 83% (95% CI 74% to 93%) for those without boost. Omission of the radiotherapy boost did not impact LRC (p=0.91). The 5-year LRC rate was 96% (95% CI 90% to 100%) for patients receiving radiotherapy with boost vs. 97% (95% CI 92% to 100%) for those without boost (Figure 1B). Loco-regional relapses occurred in one out of 36 (3%) patients who received the boost and two out of 65 (3%) patients without boost. Distant metastasis was the main reason for failure in patients undergoing radiotherapy (n=11/101; 11%; Table 2).

Survival

Fifteen (15%) out of 101 patients relapsed. Salvage treatment was administered in all of them. As recommended by the SIOP-WT-2001 protocol salvage procedures, depending on the previously administered treatment, were applied resulting in an excellent 5-year overall survival for both categories of patients (boost vs. no boost: 97% [95% CI 90% to 100%] vs. 95% [95% CI 89% to 100%], p=0.58) (Figure 2).

DISCUSSION

In SIOP-2001 radiotherapy to the flank and para-aortic lymph nodes, followed by a boost dose of 10.8 Gy to the involved lymph node area was advised for all WT patients with stage III, intermediate-risk disease with positive or necrotic lymph nodes at the time of surgery. After a preliminary analysis in 2011, omission of the radiotherapy boost was pursued in a significant number of patients [22]. Our study suggests that such a post-operative radiotherapy dose reduction by omitting boost does not alter loco-regional control and survival rates.

Since SIOP-1, in the nineteen seventies, radiotherapy has been considered to be a potent component of the treatment to obtain loco-regional control in patients with nephroblastoma [17]. A better understanding of the biology of the disease, associated with advances in imaging and pathology, has allowed risk-stratification. By tailoring systemic agents, sequential SIOP trials demonstrated that dose de-escalation and even omission of radiotherapy was proven safe, depending on stage, histology, and response to pre-operative chemotherapy [5,9,17-20]. Based on available evidence, the total radiotherapy dose for patients with involved lymph nodes (stages II-N^+ and III), stepwise decreased from 35 Gy in SIOP-1 to 30 Gy in SIOP-9 and SIOP 93-01, ending up with 25.2 Gy in the SIOP-2001 protocol. In the same period, disease-free survival rates of patients with residual disease, usually microscopic only, increased from roughly 50% in SIOP-1 to 90% in SIOP-2001 [5,17,24]. In parallel with SIOP, the NWTS-group tried to reduce the radiotherapy-associated morbidity by radiotherapy dose de-escalation. The results of NWTS-3 and NWTS-4 permitted to decrease the dose from 20 Gy to 10.8 Gy in stage III, favourable histology (FH) without jeopardizing loco-regional control and survival [14,25].

Our results suggest that in the SIOP setting further radiotherapy dose de-escalation can be applied in the specific subset of patients with intermediate-risk, stage III WT due to positive LN. A reduction in radiotherapy dose can result in a potential benefit in terms of toxicity. **Late sequelae** of cancer treatment have become an important issue, as overall survival of WT has been consistently high over the last decades. Although multifactorial, children undergoing abdominal radiotherapy are at increased risk of developing orthopaedic-, renal-, metabolic-, hepatic-, gonadal-, and vascular problems in addition to an increased risk of treatment induced neoplasms [26-29].

Different studies on late effects show that the extent of damage is related to the total radiotherapy dose, dose per fraction, radiation field and age of the child [26-28]. Omission of the radiotherapy boost dose to the area of involved lymph nodes can benefit patients who are more susceptible for musculoskeletal-, renal function-, and vascular problems. Musculoskeletal problems include loss of growth potential, spinal deformities, and soft-tissue hypoplasia. Hogeboom et al. demonstrated a deficit in height ranging from 0.8 to 7.2 cm following flank irradiation at selected ages and doses [30]. Therefore, a reduction of the radiotherapy dose from 25.2 Gy to 14.4 Gy by omission of the boost to the para-aortic lymph nodes may result in a significant benefit in ultimate sitting height [30]. Impaired creatinine clearance is observed in 19%, 32% and 73% of patients after mean doses to the kidney of <12 Gy, 12-24 Gy and >24 Gy, respectively [26,31,32]. After omission of the boost, it is expected that administration of a mean dose to the kidney above 12 Gy will become extremely rare. Aortic hypoplasia and renal artery stenosis after radiotherapy with dose ranges between 18-24 Gy (fractionated) or 10-12 Gy (single fraction intra-operative) have been identified in a limited number of patients [33]. Patients developed hypertension, middle aortic syndrome, mesenteric ischemia, and critical aortic stenosis requiring bypass surgery.

In addition to a dose reduction by omission of the boost, innovative advanced radiotherapy techniques, such as image-guided intensity-modulated radiotherapy (IGRT) or pencil beam scanning proton therapy, have the potential for further reducing dose to the normal structures, especially the contra-lateral kidney, the pancreas and visceral fat, as well as- the nipple area. Therefore, it merits prospective evaluation within the context of a clinical trial [34]. Unfortunately, the close

anatomical relation of the target volume area to the musculoskeletal- and vascular structures hinders sparing and further risk reduction.

Treatment-induced neoplasms constitute a well-recognised complication after therapy for WT [35-37]. The occurrence is related to the use of radiotherapy, the radiotherapy dose, and the interaction of radiotherapy with doxorubicin [36,38,39]. After exclusion of basal cell carcinomas, Taylor et al. reported a 6.9% cumulative incidence of second primary neoplasms in the abdomen/pelvis region at 40 years post-treatment [36]. It is expected that the omission of the radiotherapy boost and doxorubicin for stage III, intermediate-risk patients, together with the use of advanced radiotherapy techniques will contribute to a risk reduction of treatment-induced neoplasms [5].

Wilms tumours **stage III, intermediate-risk** disease comprise a heterogeneous subset of patients. At one extreme, there are patients with a near complete excision of a localized tumour and a positive margin. At the other, although uncommon, there are patients with multiple unresectable deposits scattered throughout the peritoneal cavity. In addition, discordance between the histologic risk-group and the absolute blastemal volume does exist [40]. For this reason, a better knowledge of the recurrence patterns per category is a way to define optimal radiotherapy regimens with minimal risk of treatment-induced toxicity. However, the limited number of local failures observed (n= 21/583 [3.6%], alone and combined with distant metastases) in patients with stage II-III, intermediate-risk WT treated according to the SIOP-2001 protocol makes subgroup analysis of limited additional value [5].

The high loco-regional control rate after radiotherapy with or without boost irradiation does suggest that the presence of involved lymph nodes in patients with stage III, intermediate-risk WT should not be used as a distinctive criterion for

increasing the postoperative radiotherapy dose. For this subgroup of patients, an additional analysis focussed on vital status of the tumour cells found in the resected lymph nodes could not demonstrate in our series an association between the presence of vital tumour cells in the lymph node(s) after induction chemotherapy and the occurrence of an event. Whilst each of these post-hoc analyses is not powered to answer such an non-inferiority question in the traditional way, they do provide reassurance that lower radiotherapy doses provide good loco-regional control in stage III WT, even when there is lymph node involvement. In the upcoming UMBRELLA SIOP 2016 protocol, this question will continue to be kept under observation, with the possibility of incorporating other indicators of tumour sensitivity to therapy, such as somatic tumour and more accurate measurement of the total volume of residual blastema after chemotherapy. Both of these potential prognostic factors biomarkers will be evaluated in the UMBRELLA study for future incorporation into risk stratification.

CONCLUSION

The results of this descriptive study demonstrate that omission of the radiotherapy boost to the area of positive lymph nodes in patients with intermediate-risk, stage III WT with lymph node involvement after neo-adjuvant chemotherapy and surgery, results in an excellent loco-regional control rate and survival. It is anticipated that this dose reduction will contribute to a significant decreased risk of long-term toxicity in WT survivors.

FUNDING

See acknowledgements for funders.

ACKNOWLEDGMENTS

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 Leukaemia Group (CCLG) (who supported the UK section), Société Française des Cancers de l'Enfant and Association Leon Berard Enfant Cancéreux and Enfant et Santé (who supported the French section), Gesellschaft für Pädiatrische Onkologie und Hämatologie and Deutsche Krebschilfe (grant 50-2709-Gr2, who supported the German section), Grupo Cooperativo Brasileiro para o Tratamento do Tumor de Wilms and Sociedade Brasileira de Oncologia Pediátrica (who supported the Brazilian section), the Spanish Society of Pediatric Haematology and Oncology and the Spanish Association Against Cancer (who supported the Spanish section) and SIOP-NL. K P-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 centres in this study from 28 countries who enrolled and followed up patients in this study, and the patients and their families for their participation. The SIOP Renal Tumours Study Group and all authors thank the members of the independent data monitoring committee: Max Coppes (British Columbia Cancer Agency, Canada), Otilia Dalesio (Netherlands Cancer Institute, Amsterdam), and Dietmar Schmidt (Mannheim, Germany).

CONFLICT OF INTEREST STATEMENT

None declared.

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TABLES AND FIGURES

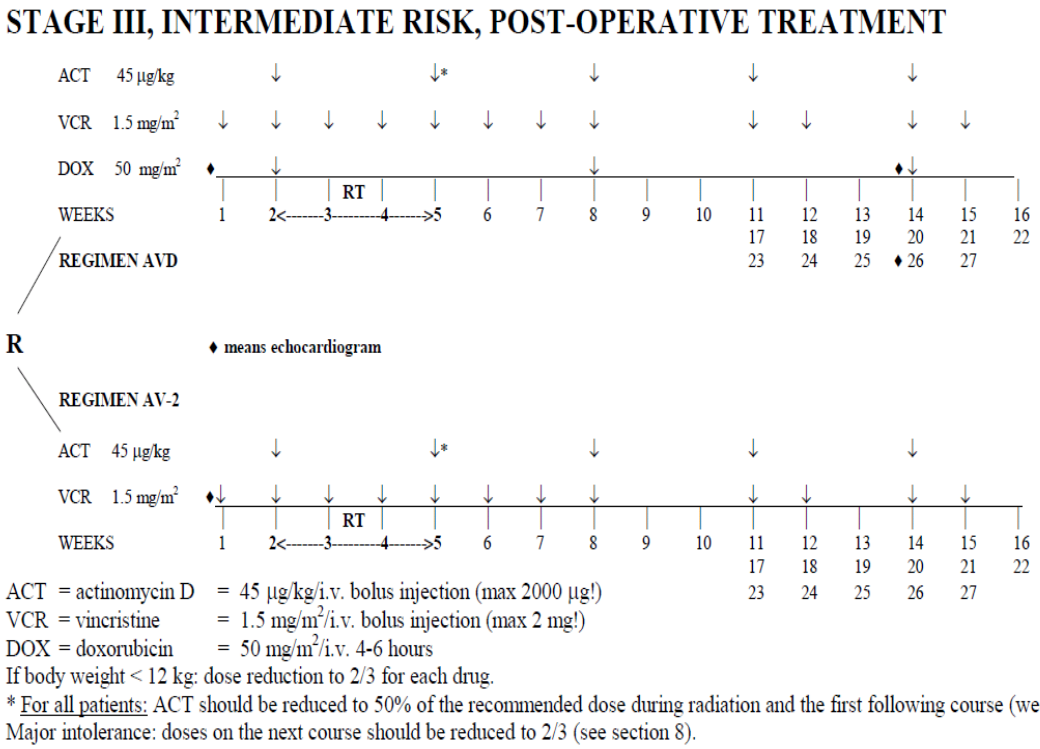
Figure 1. Event-free survival (EFS, Figure 1A) and loco-regional control (LRC, Figure 1B) for patients with stage III, intermediate risk WT with positive lymph nodes only receiving radiotherapy (RT) with/without boost dose to the involved lymph nodes.

* In one patient the site of recurrence was unknown

Figure 2. Overall survival (OS) for stage III, intermediate risk Wilms tumour with positive lymph nodes only receiving radiotherapy (RT) with/without boost dose to the involved lymph nodes.

APPENDIX

Summary of postoperative treatment for stage III, intermediate risk Wilms tumour



ACT = actinomycin D = 45 µg/kg/i.v. bolus injection (max 2000 µg!)
VCR = vincristine = 1.5 mg/m²/i.v. bolus injection (max 2 mg!)
DOX = doxorubicin = 50 mg/m²/i.v. 4-6 hours
If body weight < 12 kg: dose reduction to 2/3 for each drug.
* For all patients: ACT should be reduced to 50% of the recommended dose during radiation and the first following course (week 5).
Major intolerance: doses on the next course should be reduced to 2/3 (see section 8).