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Chapter 4

Evaluation of late adverse events in long-term Wilms' tumor survivors

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Abstract

Purpose

To evaluate the prevalence and severity of adverse events (AEs) and treatment-related risk factors in long-term Wilms' tumor (WT) survivors, with special attention to radiotherapy.

Methods and Materials

The single-center study cohort consisted of 185 WT survivors treated between 1966 and 1996, who survived at least 5 years after diagnosis. All survivors were invited to a late-effects clinic for medical assessment of AEs. AEs were graded for severity in a standardized manner. Detailed radiotherapy data enabled us to calculate the equivalent dose in 2-Gy fractions (EQD₂) to compare radiation doses in a uniform way. Risk factors were evaluated with multivariate logistic regression analysis.

Results

Medical follow-up was complete for 98% of survivors (median follow-up: 18.9 years; median attained age: 22.9 years); 123 survivors had 462 AEs, of which 392 grade 1 or 2 events. Radiotherapy to flank/abdomen increased the risk of any AE (OR, 1.08 Gy⁻¹ [CI, 1.04-1.13]). Furthermore, radiotherapy to flank/abdomen was associated with orthopedic events (OR, 1.09 Gy⁻¹ [CI, 1.05-1.13]) and second tumors (OR, 1.11 Gy⁻¹ [CI, 1.03-1.19]). Chest irradiation increased the risk of pulmonary events (OR, 1.14 Gy⁻¹ [CI, 1.06-1.21]). Both flank/abdominal and chest irradiation were associated with cardiovascular events (OR, 1.05 Gy⁻¹ [CI, 1.00-1.10], OR, 1.06 Gy⁻¹ [CI, 1.01-1.12]) and tissue hypoplasia (OR, 1.17 Gy⁻¹ [CI, 1.10-1.24], OR 1.10 [CI, 1.03-1.18]).

Conclusion

The majority of AEs, overall as well as in irradiated survivors, were mild to moderate. Nevertheless, the large amount of AEs emphasizes the importance of follow-up programs for WT survivors.

Introduction

Wilms' tumor (WT) or nephroblastoma is the most common renal neoplasm of childhood. Before 1970, WT was mainly treated by means of nephrectomy and postoperative radiotherapy, and not many patients survived their illness. After 1970, most patients in the Netherlands were treated according to the trials and studies of the International Society of Pediatric Oncology (SIOP),¹⁻⁴ including radiotherapy, chemotherapy, and surgery. Since then survival has improved impressively.⁵ At this moment, with an overall survival rate of 85%, WT is one of the most successfully treated childhood cancers. However, this survival has a downside, as it is accompanied by late treatment-related adverse events (AEs) during childhood⁶⁻⁸ and in later life.

Common treatment-related AEs in WT survivors are tissue hypoplasia and orthopedic events,^{9,10} cardiovascular events^{11,12} pulmonary events^{13,14}—in case of chest radiotherapy—and second malignancies.^{15,16} Earlier studies in childhood cancer survivors showed that radiotherapy is associated with a significantly higher risk of developing a high or severe burden of AEs, compared with treatments not involving radiotherapy.^{17,18}

The purpose of the current study was to evaluate the prevalence and severity of AEs in a cohort of long-term WT survivors treated at the Emma Children's Hospital/Academic Medical Center (EKZ/AMC), and to assess treatment-related risk factors for the occurrence and severity of AEs.

Patients and Methods

Study cohort

Between 1966 and 1996, 251 WT patients were diagnosed and treated in the EKZ/AMC in Amsterdam. Sixty-two of these patients died within 5 years after diagnosis. Death within 5 years was caused by the primary tumor or metastases in almost 89% (n = 55) of the patients. The other causes of death were sepsis (n = 2), malignant neoplasm of the frontal brain lobe (n = 1), bronchopneumonia (n = 1), acute renal failure (n = 1), cardiac complication (n = 1), and unknown in 1 patient. The local tumor was defined as Stage I-II in 20 of these patients and Stage III-V in 34 patients. For the remaining 8 patients, the tumor stage was unknown. All patients had surgery in combination with chemotherapy, whereas 56 patients additionally received radiotherapy on the primary tumor or (mainly lung) metastases.

We included 189 survivors, who survived 5 years or longer in our study cohort, with the exception of 4 survivors who were treated as WT, but diagnosed as Grawitz tumor (n = 2) and clearcell carcinoma (n = 2). The 185 survivors are part of the large cohort of childhood cancer survivors described by Geenen *et al*¹⁸ Survivors were identified using the Childhood Cancer Registry of the EKZ/AMC.

Follow-up and data collection

All survivors were invited to the Outpatient Clinic for Late Effects of Childhood Cancer (Poli­kliniek Late Effecten Kindertumoren), which was established in 1996 by the EKZ/AMC for the medical assessment of AEs in long-term survivors of childhood cancer. Of the 185 survivors, 159 visited the late-effects clinic between January 1, 1996, and January 1, 2004. Medical information of 26 survivors was obtained from other physicians. Follow-up was complete until January 1, 2004, for 181 (98%) survivors. Because of emigration, 4 survivors were lost to follow-up. Data concerning cancer diagnosis and chemotherapy were retrieved from the registry. For this study detailed radiotherapy data, such as total dose, fraction dose, fractionation schedule and field size, were obtained from radiotherapy patient records and simulation films.

Calculation of equivalent dose in 2-Gy fractions for radiotherapy

We calculated the equivalent dose in 2-Gy fractions (EQD_2) to compare the total doses of all different fractionation schedules in a uniform way. For the calculation, we used the formula: $EQD_2 = D * (d + \alpha/\beta) / (2 + \alpha/\beta)$.^{19,20} In this formula, D is the total dose, given in fractions of d Gy. The α/β parameter finds its origin in the underlying linear-quadratic model and its value varies depending on the kind of tissue. For our calculations, we used an α/β ratio of 3 Gy for late responding tissues.²⁰ The EQD_2 is expressed in Gy.

We calculated the EQD_2 for two radiotherapy treatment locations: flank/abdomen and chest, which resulted in the $EQD_{2_flank/abdomen}$ and EQD_{2_chest} . All calculated EQD_2 s correspond to the maximum applied dose for each treatment location.

Definition of AEs

AEs were graded according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv3.0)²¹ as described by Geenen *et al*.¹⁸ The CTCAE is a descriptive terminology which can be used for reporting both acute and chronic AEs and presents Grades 1 through 5. Grades 1 and 2 are mild and moderate AEs respectively, Grade 3 is a severe AE, Grade 4 is a life-threatening or disabling AE, and Grade 5 is an AE-related death.

Statistical analysis

The outcome of interest was the prevalence and severity of AEs in WT survivors who survived at least 5 years. Multivariate logistic regression analysis was used to evaluate treatment-related risk factors for the occurrence and severity of AEs. Risk factors were reported as odds ratios (ORs). All analyses were adjusted for gender, age at diagnosis and follow-up time.

From the registry, we retrieved the specification of the chemotherapeutic agents. For the analyses concerning prevalence and severity of AEs, we created the following variables: anthracyclines (yes/no), alkylating agents (yes/no) and other agents (yes/no). To evaluate the treatment-related risk factors for selected AEs, we combined different types of chemotherapy, because in some categories, the amount of survivors with selected AEs was too

small to analyze. For radiotherapy the EQD_{2_flank/abdomen} and EQD_{2_chest} were used as continuous variables in all models.

Four survivors with unknown AEs and 3 survivors with lack of information on radiotherapy dose were excluded from the analyses. We used SPSS, version 16.0.1 (Statistical Package for the Social Sciences) for Windows for our analyses.

Results

Study cohort

Table 1 shows the characteristics of the WT survivors who survived at least 5 years. Most of the survivors (77%) were diagnosed at 4 years of age or younger; median age at diagnosis was 3.7 years (range, 0.3-16.5 years). The median age at the end of follow-up was 22.9 years (range, 6.8-42.0 years), with almost 68% of survivors age 18 years or older. The median follow-up time was 18.9 years (range, 5.0-36.7 years). During follow-up time, 8 survivors died, 5 as a consequence of the primary tumor, and 3 from AEs.

Treatment was based on SIOP protocols in 83% (154/185) of the cases. We redefined the WT stages according to the ongoing SIOP 2001 study. After redefining the stages, 65% of the tumors were classified as Stage I or II.

Initial treatment consisted of surgery (i.e., complete or partial nephrectomy) in all survivors, combined with chemotherapy in 182 survivors. Anthracyclines and alkylating agents with or without other agents were used in 27% of these survivors (49/182). The majority (73%) was treated with other agents only, such as vinblastine, vincristine and dactinomycin. Additionally, initial radiotherapy to flank or abdomen was given to 80 survivors, and 1 survivor with a Stage IV tumor received initial radiotherapy to the chest without being radiated on flank or abdomen. Three survivors had surgery only. In total, 28 survivors had at least one recurrence, of whom 12 received radiotherapy to the chest.

Radiotherapy

Before the introduction of chemotherapy, radiotherapy was a substantial part of the treatment of WT. From the 1970s on, international trials have led to a diminished role of radiotherapy. In our cohort, 61% (52/85) of survivors treated with radiotherapy were diagnosed before 1980. Radiotherapy data were available for all 85 survivors who had been irradiated (Table 2). Children were treated with opposed beam irradiation, mostly in supine position only, and in the early years the anteroposterior and posteroanterior beams used to be delivered every other day. Consequently, applied fraction and total doses were almost twice as higher as in later years. It was also common to use a kind of adaptation dose, with the intention to avoid acute complications. This means that the treatment started with low doses, such as one third of the intended fraction dose, increasing every subsequent fraction until the ultimately prescribed fraction dose was reached.

In 3 of the survivors who had abdominal radiation (n = 17), the contralateral kidney was

Table 1. Survivor characteristics of the EKZ/AMC Wilms' tumor survivors cohort

	Number of survivors		
	RT, N = 85 (%)	no RT, N = 100 (%)	Total, N = 185 (%)
Gender			
Male	44 (48.2)	56 (56.0)	97 (52.4)
Female	41 (51.8)	44 (44.0)	88 (47.6)
Age at diagnosis (y)			
0.0-0.4	1 (1.2)	5 (5.0)	6 (3.2)
0.5-2	30 (35.3)	46 (46.0)	76 (41.1)
3-4	30 (35.3)	30 (30.0)	60 (32.4)
5-7	18 (21.2)	14 (14.0)	32 (17.3)
8-18	6 (7.1)	5 (5.0)	11 (5.9)
Year of diagnosis			
1968-1974	24 (28.2)	4 (4.0)	28 (15.1)
1975-1981	28 (32.9)	20 (20.0)	48 (25.9)
1982-1988	23 (27.1)	41 (41.0)	64 (34.6)
1989-1995	10 (11.8)	35 (35.0)	45 (24.3)
Stage of disease			
I	18 (21.2)	74 (74.0)	92 (49.7)
II	14 (16.5)	14 (14.0)	28 (15.1)
III	38 (44.7)	3 (3.0)	41 (22.2)
IV	13 (15.3)	5 (5.0)	18 (9.7)
V	2 (2.4)	3 (3.0)	5 (2.7)
Unknown	0	1 (1.0)	1 (0.5)
Overall treatment			
Surgery only	0	3 (3.0)	3 (1.6)
Surgery with CT only	0	97 (97.0)	97 (52.4)
Surgery with CT and RT	85 (100.0)	0	85 (45.9)
Type of chemotherapy			
Anthracyclines ± other CT	23 (27.1)	12 (12.0)	35 (18.9)
Alkylating agents ± other CT	3 (3.5)	1 (1.0)	4 (2.2)
Anthracyclines and alkylating agents ± other CT	9 (10.6)	1 (1.0)	10 (5.4)
Other CT only	50 (58.8)	83 (83.0)	133 (71.9)
No CT	0	3 (3.0)	3 (1.6)
Recurrence			
Yes	21 (24.7)	7 (7.0)	28 (15.1)
No	64 (75.3)	93 (93.0)	157 (84.9)
Survival after diagnosis (y)			
5-9	8 (9.4)	23 (23.0)	31 (16.8)
10-14	9 (10.6)	20 (20.0)	29 (15.7)
15-19	16 (18.8)	26 (26.0)	42 (22.7)
20-24	14 (16.5)	20 (20.0)	34 (18.4)
≥ 25	38 (44.7)	11 (11.0)	49 (26.5)
Age at end of follow-up (y)			
5-14	8 (9.4)	28 (28.0)	36 (19.5)
15-19	11 (12.9)	23 (23.0)	34 (18.4)
20-24	14 (16.5)	27 (27.0)	41 (22.2)
25-29	22 (25.9)	17 (17.0)	39 (21.1)
30-34	19 (22.4)	3 (3.0)	22 (11.9)
≥ 35	11 (12.9)	2 (2.0)	13 (7.0)
Vital status at end of follow-up			
Alive	77 (90.6)	100 (100)	177 (95.7)
Dead	8 (9.4)	0	8 (4.3)

EKZ/AMC Emma Children's Hospital/Academic Medical Center, RT radiotherapy, SIOP International Society of Pediatric Oncology, CT chemotherapy, ± with or without

Table 2. Radiotherapy treatment characteristics of 85 EKZ/AMC Wilms' tumor survivors

Characteristic	Number of survivors (%)
RT location categories (N = 85)	
Flank only	53 (62.4)
Abdomen only	12 (14.1)
Flank and abdomen	4 (4.7)
Flank/abdomen and chest	9 (10.6)
Chest only	5 (5.9)
Unknown	2 (2.4)
Initial RT (N = 81)	
Right flank	25 (30.9)
Left flank	36 (44.4)
Total abdomen and right or left flank	4 (4.9)
Total abdomen only	10 (12.3)
Cranial part of abdomen only	4 (4.9)
Chest only	1 (1.2)
Unknown localization	1 (1.2)
Treatment position	
AP/PA supine only, every other day	51 (63.0)
AP/PA supine and prone, every other day	6 (7.4)
AP/PA supine only, daily	17 (21.0)
AP supine only, daily	3 (3.7)
Unknown	4 (4.9)
Treatment energy	
60-Cobalt	8 (9.9)
4-8 MV	69 (85.2)
Unknown	4 (4.9)
Adaptation dose	
Yes	64 (79.0)
No	14 (17.3)
Unknown	3 (3.7)
Recurrence	
Yes	17 (21.0)
No	64 (79.0)
Recurrence RT (N = 13)	
Right lung	4 (30.8)
Left lung	0
Total chest	9 (69.2)
Treatment position	
AP/PA supine, every other day	7 (53.8)
AP/PA supine, daily	1 (7.7)
Unknown	5 (38.5)
Treatment energy	
4-8 MV	13 (100)
Adaptation dose	
Yes	4 (30.8)
No	8 (61.5)
Unknown	1 (7.7)

EKZ/AMC Emma Children's Hospital/Academic Medical Center, RT radiotherapy, N number, AP anteroposterior, PA posteroanterior, AP/PA opposing beams, MV MegaVolt

shielded by a transmission block. In those cases, the dose absorbed by the contralateral kidney was 10–12 Gy. Most irradiated survivors were treated with 8 MV photon energy, whereas occasionally 60-Cobalt or 4–5 MV photon energy was used.

The actual irradiation dose to flank or abdomen varied from 13.0 to 41.1 Gy, given in 9–25 fractions and an overall treatment time from 11 to 39 days. The actual lung dose, varying from 18.0 to 45.0 Gy spread over 12–25 fractions and applied in 16 to 38 days, was higher than usually prescribed. Thirteen of the 14 cases concerned children with lung recurrence.

Calculation of the EQD₂ resulted in the EQD_{2,flank/abdomen} for 77 survivors (range, 11.6–39.0 Gy; median, 27.7 Gy) and the EQD_{2,chest} for 13 survivors (range, 16.2–43.7 Gy; median, 27.0 Gy).

AEs

Table 3 presents the number of survivors with AEs in the WT survivor cohort. Complete information concerning AEs was obtained for 181 of the 185 survivors. Almost 68% of survivors with medical follow-up data (123/181) had one event or more, and 21% (38/181) of survivors had at least five events. At least 1 Grade 3 or 4 event was registered in 24% of survivors (43/181). Survivors treated with radiotherapy seemed to be at highest risk for developing an AE with 58% (49/85) of those survivors having a Grade 1 or 2 AE, and 30% (26/85) showing an AE ≥Grade 3. The mean number of AEs per irradiated survivor with known AEs was 4.0

Table 3. Number of survivors with adverse events in the EKZ/AMC Wilms' tumor survivors cohort

Events	Number of survivors		
	RT, N = 85 (%)	no RT, N = 100 (%)	Total, N = 185 (%)
Adverse events at end of follow-up			
Yes			
Female	41 (48.2)	23 (23.0)	64 (34.6)
Male	34 (40.0)	25 (25.0)	59 (31.9)
No	8 (9.4)	50 (50.0)	58 (31.4)
Unknown	2 (2.4)	2 (2.0)	4 (2.2)
Number of adverse events per survivor			
0	8 (9.4)	50 (50.0)	58 (31.4)
1	15 (17.6)	20 (20.0)	35 (18.9)
2	11 (12.9)	8 (8.0)	19 (10.2)
3	7 (8.2)	6 (6.0)	13 (7.0)
4	10 (11.8)	8 (8.0)	18 (9.7)
5	8 (9.4)	2 (2.0)	10 (5.4)
≥ 6	24 (28.2)	4 (4.0)	28 (15.1)
Unknown	2 (2.0)	2 (2.0)	4 (2.2)
Maximum grade of adverse events per survivor			
0 (no adverse event)	8 (9.4)	50 (50.0)	58 (31.4)
1 (mild)	5 (5.9)	6 (6.0)	11 (5.8)
2 (moderate)	44 (51.8)	23 (23.0)	67 (36.2)
3 (severe)	18 (21.2)	13 (13.0)	31 (16.8)
4 (life-threatening or disabling)	5 (5.9)	6 (6.0)	11 (5.8)
5 (death)	3 (3.5)	0	3 (1.6)
Unknown	2 (2.4)	2 (2.0)	4 (2.2)

EKZ/AMC Emma Children's Hospital/Academic Medical Center, RT radiotherapy, N number

(336/83), compared with 1.3 (126/98) per nonirradiated survivor. Figure 1 gives an overview of all events in the 123 WT survivors with AEs. Eighty-five percent of all events (392/462) were Grade 1 or 2 AEs. The most frequently scored AEs were tissue hypoplasia, orthopedic, nephrologic and psychosocial events. Especially in survivors treated with radiotherapy, tissue hypoplasia and orthopedic events were observed. Fertility problems and pulmonary and cardiovascular events also occurred more in survivors treated with radiotherapy. Diabetes mellitus only occurred in survivors who had radiotherapy. Table 4 shows the chemotherapy and radiotherapy treatment specification for a number of selected AEs.

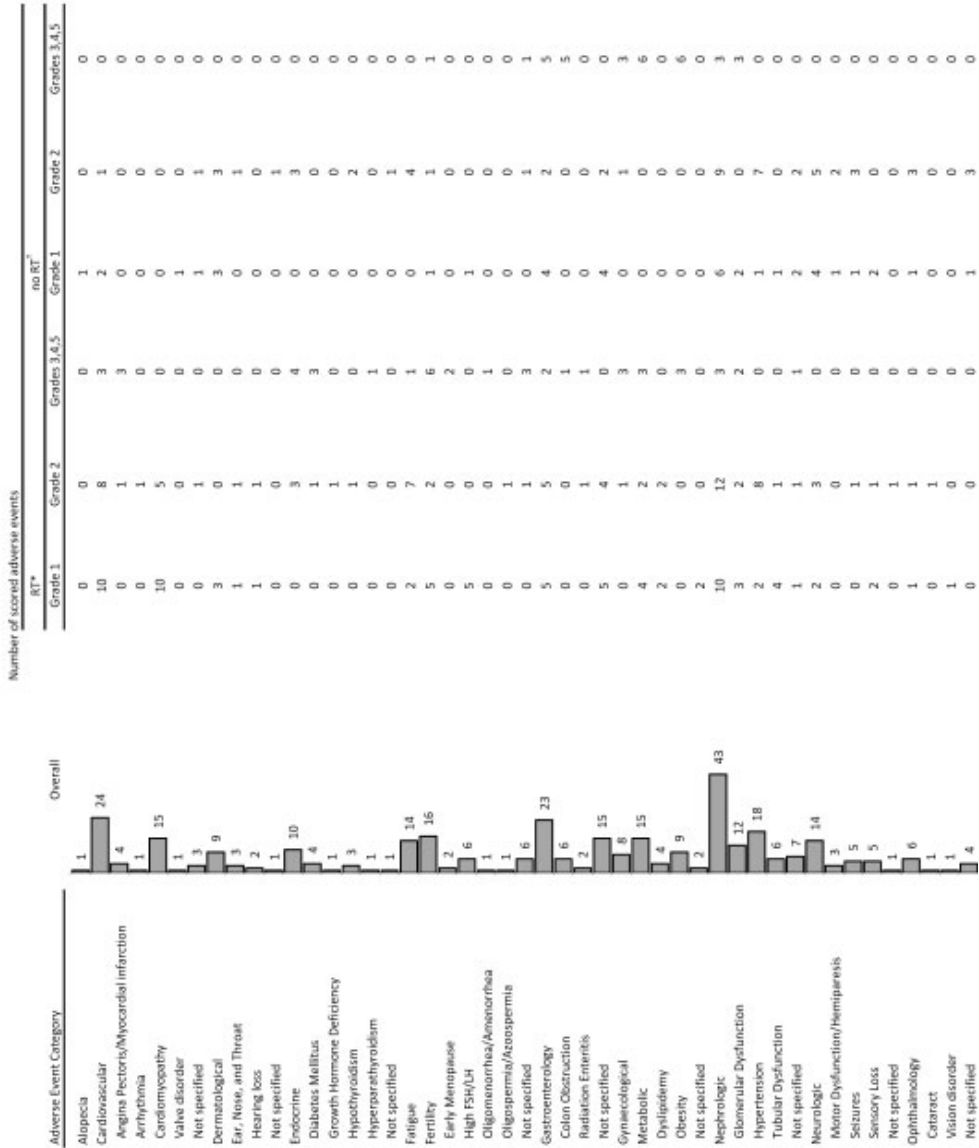
During follow-up, 3 survivors died as a consequence of complications that occurred within the former radiation field. One of them developed radiation enteritis after an actual dose of 30.0 Gy (EQD₂, 28.1 Gy) on the left flank. Another death was caused by a colon obstruction that occurred after an actual dose of 35.5 Gy on the left flank, with a boost dose up to 40.0 Gy on the kidney hilus (maximum EQD₂, 38.3 Gy). Another survivor developed a malignant fibrohistocytoma after an actual dose of 30.5 Gy (EQD₂, 27.1 Gy) on the total abdomen. No AE-related deaths were observed in nonirradiated survivors.

With regard to second tumors, we observed 14 second tumors (10 malignant and 4 benign) in 13 survivors, of whom 11 were female. One survivor, who had surgery only, developed a malignant melanoma. Eight tumors in 7 survivors were located within the former radiation field, or on its border. One of these survivors had multiple basal cell carcinomas, not only within, but also far outside the former irradiation field. Her mother was also had multiple basal cell carcinomas.

Table 4. Overview of treatment for a number of selected adverse events

Selected adverse event	Number of survivors	RT location (n)	EQD ₂ range (median); Gy	Anthra ± other CT	Alkyl ± other CT	Anthra and alkyl ± other CT	Other CT only	No CT
Cardiovascular	23	Flank/abdomen (17) Chest (6)	18.5 - 39.0 (31.4) 18.7 - 27.5 (21.6)	6	1	3	13	0
Diabetes mellitus	4	Flank/abdomen (4)	18.1 - 30.1 (25.9)	1	0	0	3	0
Fertility	13	Flank/abdomen (8) Chest (2)	11.6 - 32.5 (27.5) 23.2 - 31.5 (27.3)	2	1	0	10	0
Nephrologic	30	Flank/abdomen (18) Chest (1)	11.6 - 39.0 (29.0) 20.1	4	1	5	19	1
Orthopedic	51	Flank/abdomen (39) Chest (3)	13.0 - 39.0 (28.8) 20.1 - 27.5 (23.1)	11	1	3	36	0
Pulmonary	15	Flank/abdomen (8) Chest (8)	18.5 - 34.9 (27.0) 16.2 - 31.5 (24.3)	3	1	2	9	0
Second tumor	13	Flank/abdomen (12) Chest (1)	18.6 - 33.4 (28.1) 27.4	1	0	1	10	1
Tissue hypoplasia	47	Flank/abdomen (41) Chest (8)	13.0 - 39.0 (29.1) 16.2 - 27.5 (21.6)	9	1	4	33	0

RT radiotherapy, EQD₂ equivalent dose in 2-Gy fractions, CT chemotherapy, anthra anthracyclines, alkyl alkylating agents, ± with or without



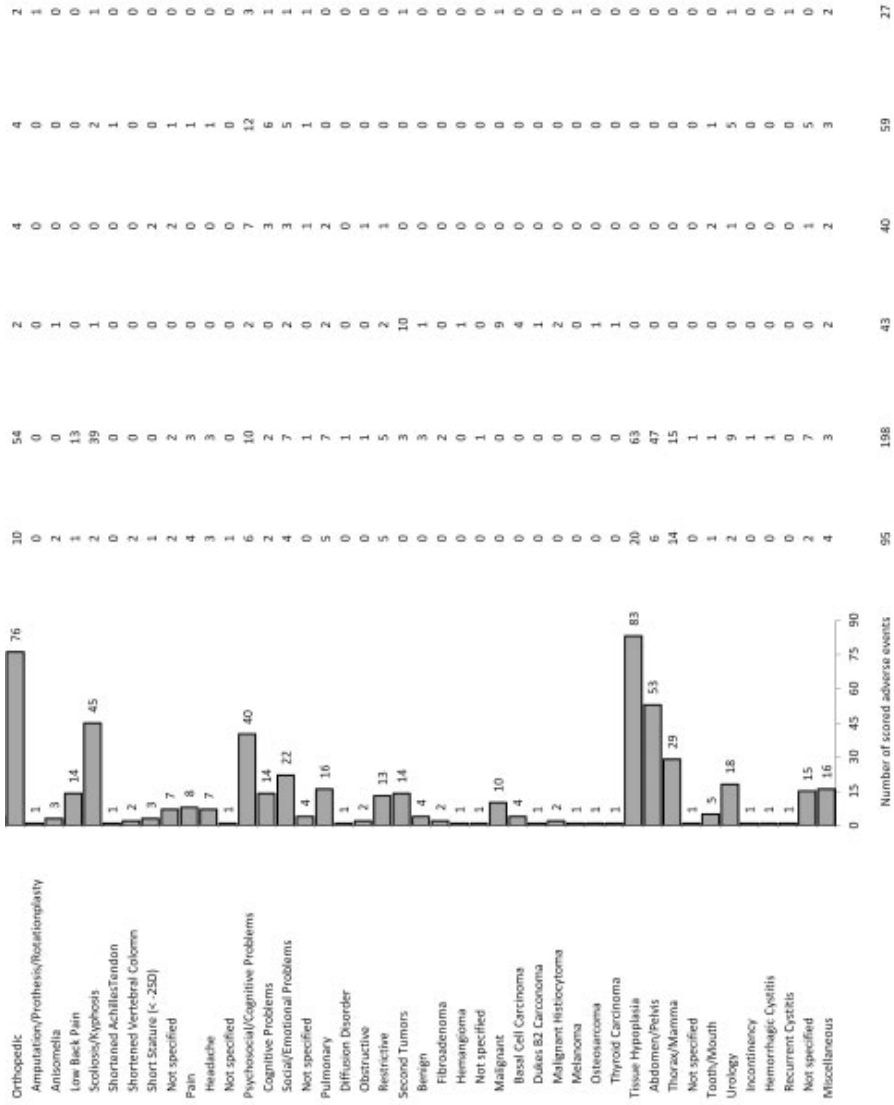


Figure 1. Overview of all adverse events in 123 Wilms' tumor survivors.

*RT: Survivors treated with surgery, chemotherapy and radiotherapy.

†no RT: Survivors treated with surgery and chemotherapy, including 3 survivors treated with surgery only.

Treatment-related risk factors for any AE and severity of AEs

In the evaluation of treatment-related risk factors, the multivariate logistic regression analysis showed, that the risk of developing an AE of any grade increased significantly with radiotherapy to flank and/or abdomen (OR, 1.08 Gy⁻¹ [CI, 1.04–1.13]) (Table 5).

The risks of developing Grade 1–2 AEs compared with no AEs, and Grade 3–5 AEs compared with no AEs were similar (OR, 1.10 Gy⁻¹ [CI, 1.04–1.16] and OR, 1.09 Gy⁻¹ [CI, 1.03–1.15], respectively).

Table 5. Treatment-related risk factors of adverse events in the EKZ/AMC Wilms' tumor survivors' cohort

Risk factor	Adverse event, OR (95% CI)		
	Grade 1-5 vs. no AE	Grade 1-2 vs. no AE	Grade 3-5 vs. no AE
Gender, female vs. male	1.50 (0.70-3.19)	0.91 (0.38-2.18)	2.98 (1.09-8.13)*
Age at diagnosis	1.01 (0.87-1.18)	1.09 (0.91-1.30)	0.90 (0.71-1.14)
Radiotherapy			
EQD ₂ flank/abdomen	1.08 (1.04-1.13)*	1.10 (1.04-1.16)*	1.09 (1.03-1.15)*
EQD ₂ chest	1.00 (0.94-1.06)	1.01 (0.94-1.08)	1.00 (0.92-1.08)
Chemotherapy			
Anthra (y/n)	2.32 (0.79-6.81)	2.43 (0.72-8.22)	2.37 (0.59-9.49)
Alkyl (y/n)	0.40 (0.09-1.82)	0.18 (0.02-1.40)	0.60 (0.10-3.77)
Other (y/n)	0.34 (0.02-4.79)	0.36 (0.02-7.42)	0.47 (0.01-23.02)

EKZ/AMC Emma Children's Hospital/Academic Medical Center, OR odds ratio, CI Confidence Interval, anthra anthracyclines, alkyl alkylating agents, EQD₂ equivalent dose in 2-Gy fractions

All ORs were adjusted for gender, age at diagnosis, follow-up time, chemotherapy, and radiotherapy, where appropriate. Logistic regression excluded 4 survivors with lack of information on adverse events, and 3 survivors with lack on information on EQD₂.

* Significant ORs

Treatment-related risk factors for selected AEs

Table 6 shows the results of the multivariate logistic regression analyses for selected AEs in the WT survivor cohort. Radiotherapy to flank or abdomen and chest increased the risk of cardiovascular events (OR, 1.05 Gy⁻¹ [CI, 1.00–1.10], OR, 1.06 Gy⁻¹ [CI, 1.01–1.12], respectively). Radiotherapy to flank or abdomen also increased the risk of orthopedic events, second tumors, and tissue hypoplasia (OR, 1.09 Gy⁻¹ [CI, 1.05–1.13], OR, 1.11 Gy⁻¹ [CI, 1.03–1.19], OR, 1.17 Gy⁻¹ [CI, 1.10–1.24], respectively). Furthermore, chest radiotherapy was associated with a higher risk of pulmonary events and tissue hypoplasia (OR, 1.14 Gy⁻¹ [CI, 1.06–1.21] and OR, 1.10 Gy⁻¹ [CI, 1.03–1.18]).

With regard to chemotherapy, our analyses showed that the use of anthracyclines or alkylating agents increased the risk of cardiovascular events and tissue hypoplasia (OR, 9.10 [CI, 1.68–49.22], OR, 6.39 [CI, 1.08–37.69], respectively). Detailed analyses demonstrated that survivors treated with anthracyclines had a higher risk of cardiovascular events (OR, 10.13 [CI, 1.81–56.82]) and of tissue hypoplasia (OR, 7.41 [CI, 1.22–44.93]), compared with survivors who had not been treated with anthracyclines. Treatment with alkylating agents increased the risk of developing nephrologic events (OR, 12.74 [CI, 3.06–53.10]).

Compared with male survivors, female survivors had a higher risk of developing second tumors and tissue hypoplasia (OR, 8.07 [CI, 1.51–43.16], and OR, 3.64 [CI, 1.13–11.72]).

Discussion

Our study showed that the prevalence of AEs in long-term WT survivors is high, especially when they have been treated with radiotherapy. Radiotherapy to flank/abdomen increased the risk of having any AE in general. The majority of AEs in both irradiated and nonirradiated survivors were Grade 1-2 events. The risk of developing Grade 1-2 events compared with no events was similar to the risk of developing Grade 3-5 events compared with no events.

Numerous studies have previously described late effects after treatment for WT. However, these studies mainly focused on a specific part of the treatment, like chemotherapy¹² or radiotherapy,^{7,22,23} or on particular late effects such as second neoplasms, heart failure or musculoskeletal deformities.^{11,15,24} We evaluated the prevalence and severity of AEs in a complete cohort of WT survivors in relation to detailed radiotherapy data and type of chemotherapy.

Strengths of our study are the completeness of the cohort identified by the EKZ/AMC Childhood Cancer Registry, the almost complete follow-up (98%), and the use of the CTCAEv.3.0 to grade all AEs. In addition, we succeeded in obtaining detailed radiotherapy data of 96% of survivors treated with radiotherapy (82/85), and we calculated the EQD₂ for two radiotherapy treatment locations. We chose to use the EQD₂ to compare all different fractionation schedules in a uniform way. The EQD₂ is comparable to the biological effective dose (BED), but the EQD₂ is a closer estimation of the physical dose, because it represents the biological equivalent dose in 2-Gy fractions.

The results of this study showed that 68% of the WT survivors had minimal one AE, and 21% of the WT survivors had at least 5 AEs. These percentages are similar to the overall percentages reported in our earlier study on all childhood cancer survivors in the EKZ/AMC.¹⁸ However, the percentage of WT survivors having a severe or life-threatening or disabling AE was lower (24% vs. 40%). In our cohort, we see also in absolute numbers more mild and moderate events (392) and less serious events (70). This confirms the results of a previous, small study on late effects in WT survivors.⁷

Almost 90% of survivors treated with radiotherapy developed an AE, compared with 50% of survivors who had not been treated with radiotherapy. The number of AEs per survivor was higher among irradiated survivors compared with nonirradiated survivors. However, in interpreting these results, we have to consider that the median attained age of irradiated survivors at end of follow-up is higher than that of nonirradiated survivors (27.4 vs. 19.8 years), and the median follow-up time of irradiated survivors is higher than that of nonirradiated survivors (22.2 vs. 16.2 years). All 3 survivors, who died as a consequence of an AE, had been treated with radiotherapy.

For WT survivors a higher risk of musculoskeletal events, heart failure, and second tumors^{15,16} after radiotherapy has been reported earlier. In this study, we confirmed the relationship between those outcomes and radiotherapy. Almost half of the AEs in irradiated survivors consisted of orthopedic events and tissue hypoplasia (22.6% and 24.7%, respec-

tively). However, our multivariate analysis of selected AEs demonstrated that age at diagnosis, radiotherapy, and treatment with anthracyclines were independent risk factors for tissue hypoplasia. The latter might be explained by the extravasation caused by the application of anthracyclines. Anthracyclines are also known as a risk factor for cardiovascular events,¹¹ which is confirmed by our results; besides radiotherapy, treatment with anthracyclines was an important risk factor. Thirteen of the 14 second tumors were diagnosed in survivors treated with radiotherapy, and 8 tumors occurred in the former radiation field. Furthermore, our results showed that survivors who received chest irradiation had a higher risk of developing pulmonary events, which is in agreement with earlier findings.^{13,14} But our analyses did not show radiotherapy to be a significant risk factor for the development of fertility problems, even though 13 of the 16 fertility problems occurred in irradiated survivors.

It has been reported that female childhood cancer survivors have a higher risk of poor long-term outcomes as compared with male survivors.²⁵ In our cohort, 64 female survivors had 258 AEs, vs. 59 males with 204 AEs. Females had a higher risk of developing a Grade 3-5 event. They also had a higher risk on tissue hypoplasia or a second tumor.

Remarkable is that 4 survivors treated with radiotherapy developed diabetes mellitus, type I as well as type II. All those survivors had received flank irradiation which included the pancreas region. Diabetes mellitus in irradiated childhood cancer survivors has been documented before.²⁶⁻²⁸ Cicognani *et al*²⁸ found an impaired insulin response in (mainly male) WT survivors who received abdominal radiotherapy. They hypothesized that this effect might have occurred as a consequence of radiotherapy. Neville *et al*²⁷ found an association between diabetes mellitus and total body irradiation.

Our multivariate analyses to evaluate the treatment-related risk factors confirm that radiotherapy on flank/abdomen was the most important risk factor to develop an AE. The odds ratios (ORs) obtained from the logistic regression analyses cannot be interpreted as relative risks, because the prevalence of most AEs in our study cohort is higher than 10%. In interpreting the results of the analyses, we must bear in mind that the ORs overestimate the relative risks associated with specific treatments.

In summary, our study demonstrated that the prevalence of AEs in long-term WT survivors is high, especially after radiotherapy and treatment with anthracyclines. But radiotherapy and anthracyclines have been used only in higher risk patients to improve their cure rates. Considering that the majority of AEs were mild or moderate, continuation of this treatment would be justified. Our results emphasize that follow-up programs for these survivors are essential. Current treatment protocols, in which radiotherapy is omitted where possible, or smaller volumes and lower doses are applied, have already led to lesser and milder events. Future protocols should be based on weighing the benefits of treatment and the risk of developing late side effects.

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