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ORIGINAL ARTICLE

De-escalated Radiotherapy for Advanced Stage Wilms' Tumor

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OBJECTIVE

Survival rates have dramatically improved in Wilms' tumor (WT) with multimodal treatment. Herein, we aimed to compare the efficacy of 9–10.8 Gy flank irradiation or whole abdominal irradiation (WAI) in patients with WT treated in a single tertiary treatment center.

METHODS

This study includes 42 patients with a unilateral or bilateral WT with a local Stage III disease who received a low-dose (10.8 Gy) or lower-dose (9 Gy) flank radiotherapy (RT) or whole abdominal irradiation between 1998 and 2018. Patients had undergone either upfront surgery followed by adjuvant chemotherapy (CXT) or neoadjuvant CXT followed by surgery. Patients with lung metastasis without a complete response to CXT also received whole lung irradiation (WLI) of 9–12 Gy.

RESULTS

The disease was staged as III in 22, IV in 12, and V in nine patients, respectively. After a median follow-up of 75 months, the 2-and 5-year overall survival, locoregional relapse-free survival, and distant metastasis-free survival rate was 92% and 79%, 87% and 76%, and 75% and 69%, respectively. None of these survival rates were significantly different among 9 Gy and 10.8 Gy doses. Among patients receiving WLI, the lung relapse rate was also similar between <12 Gy and 12 Gy of irradiation. Late toxicity was observed in 4 (10%) patients as scoliosis, cardiac dysfunction, renal injury with hypertension, and short stature in each.

CONCLUSION

De-escalated RT of 9 Gy to the flank or abdomen does not compromise oncologic outcomes in patients with a local Stage III WT.

Keywords: De-escalated treatment; radiotherapy; Wilms' tumor.

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INTRODUCTION

Wilms' tumor (WT) is the most common renal tumor in children.[1] The 5-year overall survival (OS) and event-free survival (EFS) rates have reached >90% with locoregional control (LRC) rates of up to 94% with multimodal treatment.[2–6] However, aggressive treatments entail major acute and long-term toxicity.[7] Therefore, less intensive treatment options have gained more importance.

The first national multi-centric WT program was conducted by the Turkish Pediatric Oncology Group (TPOG) in 1997.[8] According to this protocol, all patients are initially evaluated for surgery. If the patient is not suitable for surgery, neoadjuvant chemotherapy (CXT) is applied. The combination of surgery and adjuvant CTX is the treatment of choice in the absence of anaplasia in Stage I and II disease. In Stage III disease and in case of anaplasia, radiotherapy (RT) is an indispensable part of treatment. The dose of locoregional RT in Stage II and III disease is 9 Gy or 10.8 Gy depending on which day of the week the treatment starts. In the current retrospective study, we aimed to compare the efficacy of 9 Gy flank RT to 10.8 Gy with regard to LRC and survival outcomes in a single tertiary treatment center.

MATERIALS AND METHODS

Patients with a local Stage III WT that received a low-dose (10.8 Gy) or lower-dose (9 Gy) flank RT or whole abdominal irradiation (WAI) between 1998 and 2018 were retrospectively evaluated. According to TPOG, Stage III disease includes: (1). Biopsy prior to surgery, (2). tumor implants on peritoneal surface, or spillage during surgery, (3). regional lymph node (LN) involvement, (4). incomplete resection or positive surgical margins, and (5). separately excised tumor (e.g., tumor thrombus within the renal vein or adrenal gland or extension into the vena cava).[8] Exclusion criteria included clear cell sarcoma or rhabdoid tumor of the kidney, Stage IV or V patients with a local Stage I or II, no RT at first diagnosis, >10.8 Gy RT to the flank or abdomen, no CXT, no surgery, or inadequate or missing data. This study was approved by the local Institutional Review Board (approval date: 03.11.2020; No: 16969557-1558).

Treatment of all patients were decided by a multidisciplinary tumor board. Upfront surgery followed by adjuvant CXT was performed in patients eligible for surgery. If the tumor was not amenable for total resection or in case of a thrombus, neoadjuvant CXT was administered. CXT regimens consisted of vincristine (1.5 mg/m^2 [2 mg maximum] once weekly for 4 weeks) and actinomycin-D (15 μg/kg/day for 5 days in the 1st week) (VA) every 6 weeks, or vincristine (same dose once weekly for the first 10 weeks, then every 3 weeks), actinomycin-D (same dose), and doxorubicin (20 mg/m^2/day for 3 days) (VAD) +/− etoposide (E) (100 mg/m^2/day for 3 days) every 6 weeks for 12 and 18 months for Stage III and IV disease, respectively.

All patients were treated with a 9–10.8 Gy in 1.8-Gy fractions flank RT or 9–0.8 Gy in 1.5-Gy fractions WAI. If RT started on Monday, 9 Gy was applied, if started on another day of the week, 10.8 Gy was applied. Patients were treated with 2-dimensional (2D)-external beam RT (EBRT) before 2009 and 3-dimensional conformal RT (3D CRT) or volumetric modulated arc therapy (VMAT) after 2009. The clinical target volume (CTV) was the tumor at diagnostic imaging plus a 1-cm margin including the whole operative bed. Whole vertebral bodies were included in the RT portals at the levels concerned. Involved LN sites were irradiated in patients with gross LNs at diagnosis or metastatic LNs found in the pathology specimen. In case of a tumor thrombosis in the renal vein or inferior vena cava, the thrombus bed was also included. The planning target volume (PTV) was formed with a 0.7–1 cm margin to the CTV for 3D CRT and VMAT plans which were optimized according to the requirement that ≥95% of the PTV and ≥99% of the CTV received 95% of the prescribed dose. Patients with pre-operative tumor rupture, diffuse tumor spillage during surgery or peritoneal seeding received WAI. In case of compromised surgical margins, flank RT was also added. WAI included the whole abdominal cavity from the dome of the diaphragms superiorly to the inferior aspect of the obturator foramina including the lateral peritoneal reflections. All efforts were made to decrease the dose to the contralateral kidney.[9]

Patients without a complete response in the lungs after the first course of adjuvant CXT underwent 9–12 Gy whole lung irradiation (WLI) in 1.5-Gy fractions. The RT field included both lungs from the apices superiorly to the level of the posterior costophrenic angles inferiorly, the lateral borders being bilateral thoracic walls. Patients with residual macroscopic nodule(s) following WLI also received a boost dose to the nodule(s).

All patients were evaluated weekly during the course of RT and followed every 3 months for the first 2 years, every 6 months until the 5th year, and annually thereafter following RT. The incidence of acute and late toxicity was evaluated based on Common Terminology Criteria for Adverse Events version 4.0.[10]

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Table 1 Surgical and histopathological characteristics of all patients

Characteristic	Number of tumors	%
Anaplasia (focal or diffuse)		
No	40	93
Yes	3	7
Capsular invasion		
Yes	18	42
No	25	58
Capsular rupture		
Yes	22	51
No	21	49
Tumor spillage during surgery		
Yes	10	23
No	33	77
Surgical margin status		
Positive	21	49
Negative	22	51
Renal vein involvement		
Yes	16	37
No	27	63
Peritoneal invasion		
Yes	11	26
No	32	74
Regional lymph node involvement		
Yes	21	49
No	22	51
Tumor thrombus in the vena cava		
Yes	10	23
No	33	77
Number of risk factors		
1	6	14
2	16	37
3	12	28
4	4	9
5	4	9
6	1	3

Table 2 Details of radiotherapy in all patients

Characteristic	Number of tumors	%
Fraction dose of flank RT (Gy)		
1.5	5	14
1.8	31	86
Total dose of flank RT (Gy)		
9	22	61
10.8	14	39
Modality of flank RT		
2D	20	56
3D	16	44
Total dose of WAI (Gy)		
9	6	46
10.5	6	46
10.8	1	8
Modality of WAI		
2D	8	62
3D	5	38
Total dose of WLI (Gy)		
9	4	29
10.5	1	7
12	9	64
Modality of WLI		
2D	6	43
3D	7	50
VMAT	1	7

RT: Radiotherapy; WAI: Whole abdominal irradiation; WLI: Whole lung irradiation; 2D: 2-dimensional; 3D: 3-dimensional; VMAT: Volumetric-modulated arc therapy; Gy: Gray

Statistical analyses were performed using Statistical Package for the Social Sciences version 23.0 (SPSS Inc., Chicago, IL, USA). The primary end points were LRC and patterns of failure. Secondary end points included OS, EFS, locoregional recurrence-free survival (LRRFS), distant metastasis-free survival (DMFS), and treatment toxicity. LRC was defined as no relapse in the renal fossa, or relapsed or de novo LN(s) in the renal and the para-aortic (PA) region, and DM as the relapse in a distant localization, diffuse peritoneal disease, or extra-abdominal LN(s). OS was defined as the time from diagnosis to the last follow-up or death from any cause; EFS as the time from diagnosis to the date of LRR or DM, whichever comes first, or death from any cause; LRRFS as the time from diagnosis to the date of LRR or death from any cause; and DMFS as the time from diagnosis to the date of DM or death from any cause, respectively. Survival analyses were carried out using the Kaplan–Meier method and compared using the log-rank test. The risk factors (RF) (e.g., ones making a local Stage III disease according to the TPOG plus neoadjuvant CXT) were also analyzed. Multivariate analysis was performed using the Cox proportional hazards model. $P<0.05$ was considered statistically significant.

RESULTS

Among 42 children included, 8 (19%) had bilateral WT but only one underwent RT to both sides. The number of irradiated WT was 43 and outcome analyses were made based on the number of tumors. Twenty-two (52%) patients were female, and 20 (48%) were male. Median age was 3.8 years (range: 0.3–13.2 years). One patient had a

Table 3 Results of univariate analysis

Prognostic factor	OS			EFS			LRRFS			DMFS		
	2-y (%)	5-y (%)	p	2-y (%)	5-y (%)	p	2-y (%)	5-y (%)	p	2-y (%)	5-y (%)	p
Gender												
Female	100	89	0.075	85	85	**0.029**	100	89	**0.029**	85	85	**0.03**
Male	84	67		64	53		73	61		65	53	
Neoadjuvant CXT												
No	100	100	**0.048**	91	91	0.061	91	91	0.219	91	91	0.059
Yes	89	69		68	60		86	70		68	60	
Time to surgery*												
<63 days	100	94	**0.018**	84	84	**0.038**	95	88	0.072	84	84	**0.035**
≥63 days	84	63		65	54		80	64		65	54	
Peritoneal invasion												
No	97	86	**0.037**	87	79	**0.002**	93	86	**0.006**	87	79	**0.002**
Yes	78	56		36	36		68	45		36	36	
Capsular invasion												
No	100	85		91	80	**0.026**	96	85	0.101	91	80	**0.028**
Yes	82	71	0.244	53	53		76	63		53	53	
Stage												
III	96	88	**0.017**	85	85	**0.002**	96	88	**0.004**	85	85	**0.002**
IV	83	56		51	31		67	48		52	31	
Tumor size												
<14 cm	95	89		90	78	0.09	95	89	0.053	85	79	0.123
≥14 cm	89	67	0.120	56	56		78	61		61	56	
No. of RF**												
≤2	100	84		90	84	**0.02**	100	83	0.190	85	85	**0.029**
>2	84	73	0.330	59	53		74	68		65	53	
Flank/WAI dose												
≤10.5 Gy	95	79	0.935	75	64	0.717	84	73	0.705	75	64	0.710
>10.5 Gy	90	78		75	75		90	78		75	75	

*: From the time of diagnosis; **: Number of factors required for Stage III disease. OS: Overall survival; EFS: Event-free survival; LRRFS: Locoregional recurrence-free survival; DMFS: Distant metastasis-free survival; CXT: Chemotherapy; No: number; RF: Risk factor; WAI: Whole abdominal irradiation; Gy: Gray

family history of WT, and three had additional anomalies (2: hemihypertrophy and 1: horseshoe kidney). Median tumor size was 14 cm (range: 4–22 cm). Thirteen (30%) patients had DM at the time of diagnosis.

A biopsy was performed in 12 (28%) patients. Twenty-nine (69%) patients underwent neoadjuvant CXT (VA: 8, VAD: 9, VAD-E: 2). The response to neoadjuvant CXT was partial in 26 (87%), stable in one (3%), and progression in three (10%) tumors. Median time to surgery was 63 days (range: 4–407 days). Total nephrectomy was performed for 38 tumors whereas four patients underwent partial nephrectomy. The disease was Stage III in 22 (52%), IV in 12 (29%), and V in 8 (19%) patients, respectively. Detailed surgical and histopathological findings are shown in Table 1.

Median time from surgery to RT start was 20 days (range: 3–152 days). RT was started in the first 14 days in 12 (28%), and later than day 14 in 31 (72%) patients, respectively. The reason for late RT is the late referral of patients from other clinics. However, all patients that applied late to our department had received CXT until RT start. Flank RT alone was applied for 30 (70%) tumors and WAI for seven (16%), respectively. Six (14%) tumors with residual disease after surgery were treated with WAI followed by a flank RT boost. Fourteen (33%) patients received WLI, and a boost dose (7.2–9 Gy) to residual nodules was applied in two patients. RT details are given in Table 2. All patient, tumor, and treatment characteristics were similar between patients that received <10.5 Gy and ≥10.5 Gy. Median duration between surgery and adjuvant CXT was 18 days (range: 1–104 days). The regimen was VAD in 29 (69%), VAD-E in eight (19%), and VA in five (12%) patients, respectively.

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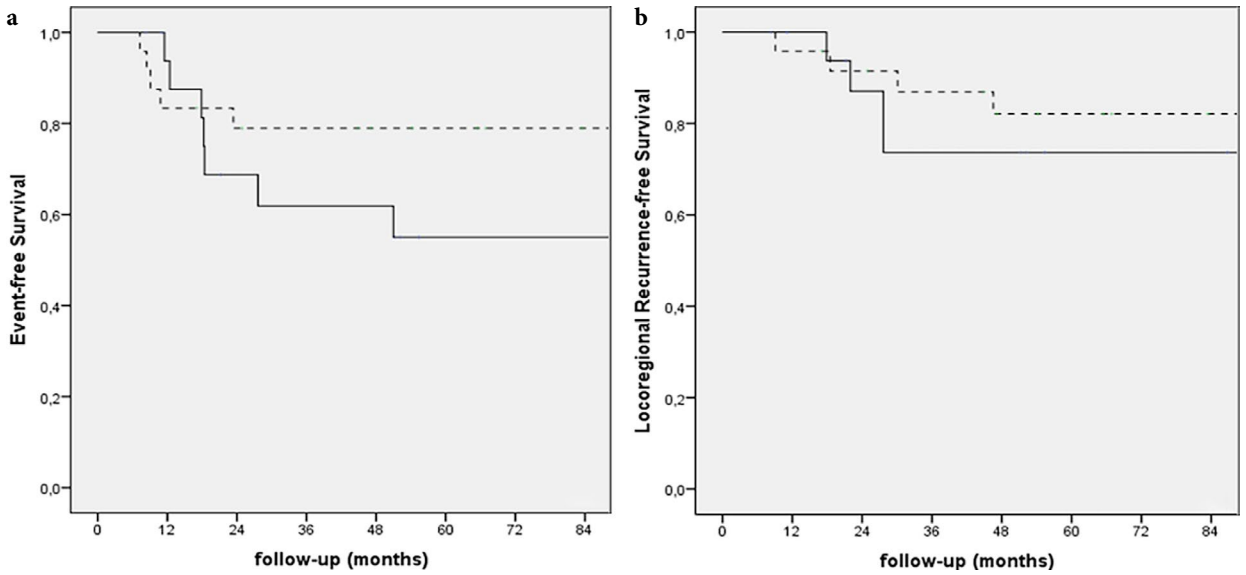

Fig. 1. (a) EFS rate for flank RT dose of <10.5 Gy (straight line) vs. ≥10.5 Gy (dashed line), (b) LRRFS rate for flank RT dose of <10.5 Gy (straight line) vs. ≥10.5 Gy (dashed line).
EFS: Event-free survival; RT: Radiotherapy; LRRFS: Locoregional recurrence-free survival; Gy: Gray.

Median follow-up was 75 months (range: 8–278 months). The 2- and 5-year OS rate was 92% and 79%, respectively. The 2-and 5-year EFS rate was 75% and 69%, respectively. Four patients developed LRR. The 2-and 5-year LRRFS rate was 87% and 76%, respectively. Most relapses (92%) occurred within 2 years of diagnosis. In relapsed patients, median OS was 16.3 months with a 2-and 5-year OS rate of 33% and 33% after recurrence, and 75% and 33% after diagnosis, respectively. Total relapse rate was significantly higher in Stage IV patients (62%) compared to Stage III patients (14%) (p=0.002). Factors associated with a higher rate of LRR were renal vein invasion and a higher number of RF (p=0.049 and p=0.005, respectively). The 2- and 5-year LRC rate was similar between <10.5 Gy and ≥10.5 Gy (88% and 88% vs. 96% and 96%; p=0.4). Duration between surgery and RT had no impact on the LRC rate (p=0.55).

Eleven (26%) patients developed DM during the follow-up (64% in the lung). The 2-and 5-year DMFS rate was 75% and 69%, respectively. Factors associated with a higher rate of DM were capsular invasion and peritoneal invasion (p=0.02, and p=0.013, respectively). The lung relapse rate did not differ between <12 Gy and ≥12 Gy WLI (p=0.9), and neither did the survival rates (p=0.5 for OS, p=0.4 for EFS, p=0.3 for LRRFS, and p=0.4 for DMFS, respectively).

In univariate analysis, peritoneal invasion and higher stage significantly decreased all survival rates. Male gender also decreased the EFS, LRRFS and DMFS rates. Other prognostic factors are shown in Table 3. There was no statistically significant difference with regard to the flank RT dose, and comparison of EFS and LRRFS rates is shown in Figure 1a and b. In multivariate analysis, male gender and peritoneal invasion were significant negative prognostic factors for all survival outcomes, and a higher stage was for OS and LRRFS (Table 4). All characteristics were similar between males and females except for spillage during surgery which was significantly higher in male patients (40% vs. 9%, p=0.019).

No severe acute toxicity was observed during RT. Late toxicity was observed in four (10%) patients. One patient developed scoliosis after 9 Gy WAI followed by 9 Gy flank RT via 2D EBRT at 4 years old, and developed scoliosis 10 years after RT was completed. She has also been observed for suspicious diabetes and is now alive with lung metastases. One patient diagnosed at age 1 developed systolic cardiac dysfunction 13 years following adjuvant CXT and 10.5 Gy WAI and is still alive with no evidence of disease. One patient developed renal failure and hypertension 2 years after adjuvant CXT was completed. She was diagnosed at age 3 and underwent neoadjuvant CXT, total nephrectomy, and 10.8 Gy flank RT. She is alive with no evidence of disease but under anti-hypertensive drugs. Finally, one patient is observed with a short stature who was diagnosed at age 3, received 10.8 Gy flank RT, and is alive with no evidence of disease. No patients devel-

Table 4 Results of multivariate analysis

Survival type	Prognostic factor	RR	95% CI	p
OS	Gender			
	Female	1	1.24-49	0.029
	Male	7.8		
	Peritoneal invasion			
	No	1	1.58-9.27	0.016
	Yes	12		
	Stage			
	III	1	1.01-39.8	0.049
	IV	6.3		
EFS	Gender			
	Female	1	1.9-112.14	0.01
	Male	14.6		
	Peritoneal invasion			
	No	1	1.05-643.6	0.047
	Yes	26		
LRRFS	Gender			
	Female	1	1.6-75.6	0.014
	Male	11		
	Peritoneal invasion			
	No	1	1.29-36.29	0.024
	Yes	6.8		
	Stage			
	III	1	1.67-68.27	0.012
	IV	10.7		
DMFS	Gender			
	Female	1	2.16-244.96	0.009
	Male	23		
	Peritoneal invasion			
	No	1	1.66-266.2	0.019
	Yes	21		

RR: Relative risk; CI: Confidence interval; OS: Overall survival; EFS: Event-free survival; LRRFS: Locoregional recurrence-free survival; DMFS: Distant metastasis-free survival

oped a secondary malignancy. One patient succumbed to complications of a salvage stem cell transplantation for relapsed disease.

DISCUSSION

Optimal treatment for WT includes surgery and CXT with RT in patients with anaplasia or advanced stage disease. In the first National Wilms Tumor Study (NWTS), patients of all stages underwent flank/abdomen RT started within 48 h after surgery.[9] RT was administered to the flank in Stages I and II, and as WAI in Stages III and IV with doses varying between 18 Gy and 40 Gy based on patient age. The results showed that RT was not necessary in Stage I disease. During NWTS-2, WLI dose was reduced to 12 Gy because of the 10% pneumopathy rate with 14 Gy when combined with CXT.[11] In the NWTS-3, the authors compared 20 Gy to no RT in Stage II disease, and 10 Gy to 20 Gy in Stage III disease.[2] RT was found redundant in Stage II disease without anaplasia, and 10 Gy flank/abdomen RT is sufficient in Stage III disease.

We follow the recommendations of TPOG WT protocol in which the main difference of RT from NWTS is the reduced dose to the flank/abdomen. With 9 Gy de-escalated RT, we found the 2-and 5-year OS rate 92% and 79% for all, 96% and 88% for Stage III, and 83% and 56% for Stage IV patients; and the 2-and 5-year EFS was 78% and 69% for all, 85% and 85% for Stage III, and 51% and 31% for Stage IV patients, respectively. In the NWTS-2 with 18–40 Gy RT, the 2-year OS and relapse-free survival (RFS) rate was 84% and 70% for Stage III, and 54% and 49% for Stage IV disease, respectively.[11] In the NWTS-3 with a lower RT dose, the 2-year OS and RFS rate was 92% and 85% for all patients, and the 4-year OS and RFS rate was 73% and 68% in Stage III and IV disease, respectively.[2] In the NWTS-4, the 2-year RFS was >91% for all patients.[3] In the Children's Oncology Group (COG) AREN0532 study, Fernandez et al.[12] reported the 4-year OS and EFS rates 97% and 88% in Stage III disease which is very similar to our results. The Japanese study which applied the same protocol as in the NWTS-5 also demonstrated the 5-year OS and RFS rates 95% and 91% in Stage III disease.[13]

Although TPOG recommends upfront surgery, the majority of our patients had undergone neoadjuvant CXT due to unresectable tumors at diagnosis. Neoadjuvant CXT is recommended by recent The International Society of Pediatric Oncology (SIOP) guidelines which primarily aims to reduce the need for RT due to abdominal spillage during surgery. Flank doses varied between 15 Gy and 30 Gy based on disease stage and risk groups with an additional boost dose to positive LNs in the older SIOP trials.[14] The 5-year EFS rate was 82% in patients with Stage III disease treated according to the SIOP 9301/GPOH trial.[14] In the SIOP 9 trial, the 2-year OS and RFS was reported 85% and 71%, respectively, in patients with Stage II, III, and LN+ disease.[15] Although the flank doses were decreased in the modern SIOP studies, they are still higher than the NWST studies, ranging from 14.4-25.2 Gy.[16] With the very low dose of 9 Gy, our results are similar to SIOP's studies.

The primary aim of this study was to compare the oncologic outcomes with regard to the flank RT dose. The rationale for our de-escalated RT dose comes from

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the radiobiologic phenomenon of tumor repopulation between RT fractions. We found no significant difference in terms of LRC with 9 Gy when compared to 10.8 Gy. The recurrence rate was 29% which was significantly higher in Stage IV disease compared to Stage III. This rate is similar to the NWTS-3 results with a relapse rate of 14–23% for Stage III favorable histology (FH), 21–28% for Stage IV FH, 32–34% for Stage I–III unfavorable histology (UH), and 42–47% for Stage IV UH, respectively.[2] The relapse rate was 7% in Stage III disease in the Japanese study.[13] A possible reason for this can be the higher rate of patients with LN metastasis in our study (56% vs. 25%).

In the NWTS-3, 10 Gy and 20 Gy WAI were equally effective in patients with diffuse tumor spillage.[2] We also did not find a significant difference in oncological outcomes between 9 Gy and 10.8 Gy WAI. Besides, <12 Gy WLI yielded similar results to 12 Gy in our study. The main pattern of failure was DM, in accordance with the previous data.[2,12] Furthermore, 92% of all recurrences occurred in the first 2 years similar to the NWTS-1 and AREN0532.[12,17] In patients with recurrence, the 2- and 5-year OS rate was 33% and 33% after recurrence and 75% and 33% after the first diagnosis, respectively, in our study. Green et al.[18] reported the 4-year OS rate 80% after diagnosis in relapsed patients of all stages. The 2-year OS rate was 43% after relapse in the NWST-4.[3] The 5-year OS rate after relapse was 54% in the UKW3 study.[19] In the TPOG trial, Akyuz et al.[8] reported the 4-year OS rate of 81% after recurrence for all stages, and the main recurrence pattern intra-abdominal. In the present study, we only included local Stage III patients all treated with adjuvant RT, the majority had LN metastasis, and the main pattern of recurrence was DM. No study has yet reported the OS rate after recurrence in Stage III or IV disease solely, and our rates seem satisfactory.

The rate of DM in our study was found 26%, mostly being in the lungs. This rate might seem high for patients treated with a curative intend. However, all patients in our series are already high-risk and the vast majority of them could start RT later than 14 days due to late referral to our center. Therefore, the 26% of DM rate is not higher than the outcomes reported in the literature.

The AREN0532 study including Stage III disease with FH revealed male gender as an independent negative factor for OS and EFS.[12] Male gender is also an independent negative prognostic factor for all survival outcomes in our study. When compared to the females, male patients had significantly higher rates of diffuse peritoneal tumor spillage. The unfavorable prognosis may be due to this finding or having male gender per se.

The Childhood Cancer Survivor Study reported increased congestive heart failure, renal failure, and hypertension rates in children treated for WT compared to their siblings with hazard ratios of 23.6, 50.7, and 8.2, respectively.[20] Cardiac RT was associated with a high risk of heart failure while doxorubicin did not increase the risk alone. However, RT alone was not a risk factor for renal failure or hypertension. In our study, one patient developed systolic cardiac dysfunction 13 years after adjuvant VAD. Another patient developed renal failure and hypertension after neoadjuvant VAD, total nephrectomy, and 10.8 Gy flank RT followed by adjuvant VA.

Deterioration of the linear growth caused by vertebral irradiation which is unavoidably included in the RT field is dose-dependent.[21] Considering that the steepest part of the dose-response curve for growth disorder is between 15 and 21 Gy, the importance of reducing the RT dose to the level of 10 Gy can be understood more clearly. We observed a short stature in one patient who received 9 Gy flank RT, and scoliosis in one patient who received 9 Gy WAI followed by 9 Gy flank RT despite the whole vertebral bodies in the concerning levels were included in the RT portals in both patients. Another side effect of RT is the development of diabetes. De Vathaire et al.[22] reported a cumulative increase in the incidence of diabetes in patients that received ≥10 Gy RT to the pancreatic tail. The patient with scoliosis in our study is also under observation for suspected diabetes.

Limitations of the Study

The present study has some limitations. It is retrospective in nature and the number of patients is limited as we aimed to report our results in a homogenous group. Although the plot lines of survival analyses were broad from each other, we could not find a statistical significance for prognostic factors reported in the literature. Importantly, we showed that 9 Gy local RT does not compromise LRC or survival outcomes in patients with a local Stage III WT. Besides, <12 Gy WLI seems adequate in patients with lung metastasis.

CONCLUSION

Deintensifying the treatment scheme results in a low rate of toxicity with satisfactory oncologic outcomes which supports the importance of assessing further RT dose reduction and validation on a larger, multi-institutional, and prospective trial.

Peer-review: Externally peer-reviewed.

Conflict of Interest: All authors declared no conflict of interest.

Ethics Committee Approval: The study was approved by the Hacettepe University Non-İnterventional Clinical Trials Ethics Committee (no: 16969557-1558, date: 03/11/2020).

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