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Original Article

Locoregional control using highly conformal flank target volumes and volumetric-modulated arc therapy in pediatric renal tumors: Results from the Dutch national cohort

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ABSTRACT

Background and purpose: In pediatric renal tumors, conventional two opposing photon beams have been used to cover the postoperative flank target volume for decades. This single center study describes the locoregional outcome using highly conformal flank target volumes adjusted for postoperative changes and intra-fraction motion combined with Volumetric-Modulated Arc Therapy (VMAT).

Materials and methods: Between 01-2015 and 12-2019, 36/161 newly diagnosed patients with renal tumors underwent flank only irradiation (n = 30) or flank + whole lung irradiation (n = 6) using highly conformal target volumes in line with the SIOP-RTSG consensus statement. VMAT consisted of full-arc 10MV photon beams optimized for constraints of the organs at risk. In case of locoregional relapses, image co-registration and dose reconstruction was performed. Each relapse was classified as either *'in-field'* ($V95\%_{relapse}$: ≥99.0%), *'marginal'* ($V95\%_{relapse}$: 20.0–98.9%) or *'outfield'* ($V95\%_{relapse}$: 0–19.9%).

Results: At a median follow-up from diagnosis of 3.1 years (range:0.4–5.7), the estimated 2-year Locoregional Control Rate, Disease-Free Interval and Overall Survival were 94%, 91% and 94%, respectively. Locoregional relapse was observed in two patients. One patient had a combined tumor bed and regional recurrence, classified as *infield* ($V95\%_{relapse}$: 100%) and *outfield* ($V95\%_{relapse}$: 1.2%). The second patient had a regional relapse in the inferior vena cava classified as *marginal recurrence* ($V95\%_{relapse}$: 93%). Relapses would not have been adequately covered by conventional beams.

Conclusions: This single center analysis provides encouraging evidence that excellent locoregional control can be obtained by using highly conformal flank target volumes with VMAT in pediatric renal tumors. The safety of this approach will be validated in a prospective multicenter study.

Renal tumors account for 5–6% of all pediatric malignancies [1]. Of these tumors, around 90% are considered nephroblastoma's or Wilms tumors (WT), while non-WT such as Malignant Rhabdoid Tumors of the Kidney (MRTK), Clear Cell Sarcoma of the Kidney (CCSK), Renal Cell Carcinoma (RCC) and Congenital Mesoblastic Nephroma (CMN) are less common [2]. Annually, 30–35 children in The Netherlands are diagnosed with a renal tumor and treated according to the guidelines of the International Society for Pediatric Oncology - Renal Tumor Study Group (SIOP-RTSG) [3]. Approximately 20–25% of these children require postoperative Radiotherapy (RT) of the flank during first line treatment, which can increase the risk of musculoskeletal defects, components of the metabolic syndrome, functional asplenia, cardiovascular disease or secondary tumors in later life [4–15].

Abbreviations: WT, Wilms Tumor; MRTK, Malignant Rhabdoid Tumor of the Kidney; CCSK, Clear Cell Sarcoma of the Kidney; RCC, Renal Cell Carcinoma; CMN, Congenital Mesoblastic Nephroma; SIOP-RTSG, International Society of Pediatric Oncology – Renal Tumor Study Group; RT, Radiotherapy; AP/PA, Anterior-Posterior/Posterior-Anterior; VMAT, Volumetric-Modulated Arc Therapy; IR/HR, Intermediate-/High-risk; GTV, Gross Tumor Volume; CTV, Clinical Target Volume; ITV, Internal Target Volume; PTV, Planning Target Volume; $V95\%_{relapse}$, Volume of the relapse receiving 95% of the initially prescribed dose; PD, Prescribed Dose; EU-RHAB, European Rhabdoid Registry; CBCT, Cone Beam Computed Tomography; LN, Lymph Nodes; Gy, Gray; FU, Follow-Up; IVC, Inferior Vena Cava; BEV, Beam's Eye View; LCR, Locoregional Control Rate; DFI, Disease-Free interval; OS, Overall Survival; SIB, Simultaneously Integrated Boost; AIEOP, Associazione Italiana di Ematologia e Oncologia Pediatrica; NWTS, National Wilms Tumor Study.

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For decades, the use of two opposing Anterior–Posterior/Posterior–Anterior (AP/PA) photon beams has been considered standard of care for flank RT, using the tumor volume before surgery as the target volume [16]. In the past years, the SIOP-RTSG has developed a new flank target volume definition that adjusts for the postoperative changes and intra-fraction motion [17]. Combined with modern RT techniques, this new target volume allows highly conformal dose distributions that reduce the risk of late toxicity to the surrounding healthy tissue [18-20]. However, in these children, a potential underestimation of the area at risk may increase the number of locoregional recurrences compared to those treated with conventional flank RT.

Since November 2014, pediatric renal cancer care in The Netherlands has been centralized and all patients eligible for flank irradiation received Volumetric-Modulated Arc Therapy (VMAT) on highly conformal flank target volumes [17]. The aim of the current report was to describe the locoregional control and outcome after highly conformal flank irradiation and to evaluate whether recurrences might have been avoided by conventional RT by performing an in-depth dose reconstruction.

Materials and methods

Patient selection

From January 2015 to December 2019, 161 children with a newly diagnosed renal tumor presented at the Princess Máxima Center for Pediatric Oncology. From this complete cohort, children with a local stage II WT with diffuse anaplastic histology, local stage III WT with Intermediate-/High-risk (IR/HR) histology, local stage I–III MRTK or local stage II–III CCSK, were irradiated by VMAT on highly conformal flank volumes with dose prescriptions according to the SIOP-RTSG-2001 (EudraCT number 2007-004591-39), the SIOP-RTSG-UMBRELLA-2016 (EudraCT number 2016 004180 39) or the European Rhabdoid Registry guideline (EU-RHAB version 2.0, 2010), and included in the current descriptive analysis (institutional review board approval number: PMCLAB2020.134) (Supplementary Table 1). Patients who underwent partial nephrectomy were excluded.

Highly conformal flank irradiation

After chemotherapy and before surgery, T1 and T2-weighted MRI scans (Achieva 1.5T, Philips Medical Systems, Best, The Netherlands, slice thickness of 1.5 mm) with and without gadolinium contrast were obtained. These MRI scans were rigidly co-registered to a postoperative planning CT-scan (Brilliance, Philips Medical Systems, Best, The Netherlands, slice thickness of 2–3 mm) with the patient in supine position in a vacuum mattress (Bluebag, Elekta, Stockholm, Sweden) and the arms wide along the body. To quantify intra-fraction motion of the tumor bed, each complete respiratory cycle during spontaneous breathing was captured with a 4D-CT scan. As standard of care at our institution, four surgical clips were placed in each patient to indicate the borders of the operative field. For target volume delineation, the lateral clip was used to determine the lateral tumor extension, while the superior clip was used to capture the intra-fraction motion of the tumor bed, as described in a previous report [21]. Gross Tumor Volumes (GTV) and Clinical Target Volumes (CTV) were corrected for the postoperative changes in anatomy, in line with the SIOP-RSTG consensus statement on highly conformal flank target volume delineation [17]. An Internal Target Volume (ITV) margin, defined as the maximum intra-fraction motion registered by the 4D-CT-scan, was used to expand the CTV. The Planning Target Volume (PTV) consisted of a 5 mm isotropic expansion of the ITV.

The Prescribed Doses (PD) for highly conformal flank irradiation were based on the SIOP-2001/UMBRELLA 2016 protocol (WT/CCSK), and the EU-RHAB guideline (MRTK). A boost dose was only indicated in case of macroscopic residual disease, and not administered in case of positive microscopic Lymph Nodes (LN) [22].

VMAT consisted of a full-arc 10 MV photon beam. Target volume coverage was considered adequate if 95% of the PD was given to at least 99% of the CTV (CTV V95%: ≥99%) and 95% of the PTV (PTV V95%: ≥95%), respectively. Dose constraints of the organs at risk, as defined in the SIOP-2001/UMBRELLA 2016 protocol (kidney, liver, lung) and additional papers (pancreas, spleen, heart), were taken into account during plan optimization [8,10,12–14]. To minimize the risk of asymmetric growth, left to right and ventral to dorsal dose gradients above 3 Gy and 5 Gy on the primary ossification centers of the vertebrae adjacent to the PTV were avoided for patients aged 0–2 years and >2 years, respectively [23]. To correct for setup uncertainties between fractions, daily pre-treatment Cone Beam (CB) CT-scans were acquired using the Elekta XVI 4.5.1 on-board CBCT imaging system (Elekta, Stockholm, Sweden).

Follow-up and analysis of outcome

According to the SIOP-2001/SIOP-RTSG-UMBRELLA-2016 protocol, Follow-Up (FU) of patients included routine physical examination, chest X-ray and abdominal ultrasound. When tumor recurrence was suspected, cross-sectional imaging of the abdomen and chest was performed including a biopsy of one of the lesions. Tumor recurrence at the primary tumor bed (nephrectomy site) was classified as a local relapse, while tumor recurrence in the periaortic LN or in an area with tumor extension *per continuitatem* (e.g. in the Inferior Vena Cava, IVC) was classified as a regional relapse. Disease recurrence in a LN outside the abdomen, lungs, liver, brain, or bone/bone marrow was considered distant/metastatic relapse. Recurrences caused by tumor spillage or iatrogenic displacement of the tumor were classified as an abdominal relapse.

For patients with a locoregional or abdominal relapse, imaging at the time of recurrence was co-registered with the dose distribution at first line RT to calculate the dose received by each site of relapse. Based on this dose reconstruction, a recurrence was categorized as *'infield'* in case of adequate dose coverage (i.e. V95% $_{relapse}$: ≥99.0%), as '*marginal*' in case of partial coverage (i.e. V95% $_{relapse}$: 20.0–98.9%) or as '*outfield*' (i.e. V95% $_{relapse}$: 0–19.9%) [24]. Additionally, flank RT plans using conventional target volumes and AP/PA photon beams were generated following the approach of the SIOP-RTSG-UMBRELLA-2016 protocol [3]. Subsequently, the Beam's Eye View (BEV) projection and dose reconstruction were used to determine whether *marginal* and *outfield* recurrences could have been adequately covered by a conventional RT approach.

Statistical analysis

Locoregional Control Rate (LCR) was defined as freedom from first local or regional recurrence. Disease-Free interval (DFI) was defined as the time to any recurrence (locoregional, abdominal and distant), and Overall Survival (OS) as the time to death of any cause. All intervals were calculated from the date of diagnosis and censored at event or last follow-up. The Kaplan-Meier method was used to estimate the 2-year LCR, DFI and OS with the 95% confidence interval according to Greenwood. Analysis were performed using R package version 4.02.

Results

A total of 36/161 patients received highly conformal flank irradiation (flank RT only: n = 30; flank and whole lung RT combined: n = 6). Table 1 depicts the patient, tumor and radiotherapy characteristics.

For the whole group of 36 patients, the estimated 2-year LCR, DFI and OS were 94% (95% CI: [0.86, 1.00]), 91% (95% CI: [0.81, 1.00]), and 94% (95% CI: [0.86, 1.00]), respectively, at a median FU from diagnosis of 3.1 years (range: 0.4–5.7) (Fig. 1). Three patients developed disease recurrence: one combined locoregional and distant relapse at 1.0 years from diagnosis, one regional and abdominal relapse at 0.5 years from diagnosis, and one distant relapse at 0.8 years from diagnosis.

The first relapsed patient, at primary diagnosis irradiated for a localized left-sided intermediate-risk stage III WT because of a positive resection margin, developed tumor recurrence at the ipsilateral adrenal gland region (site #1), along the contralateral paravertebral space at the level of thoracic vertebra 12 (site #2), as well as two nodules in the right lung (Fig. 2A and B). The locoregional relapses at the adrenal gland region and paravertebral space were classified as *infield* (D_{mean}: 14.4 Gy; V95% $_{relapse}$: 100%) and *outfield* (D_{mean}: 10.3 Gy; V95% $_{relapse}$: 1.2%), respectively (Fig. 2C–F). The BEV and dose reconstruction showed that the paravertebral tumor volume at the time of relapse would not have been adequately covered by conventional flank RT (site #2, V95% $_{relapse}$: 81%) (Fig. 2G). With second-line therapy, consisting of 4-drugs chemotherapy (SIOP-RTSG UMBRELLA 2016 protocol, AA-regimen) and whole lung irradiation (12.0 Gy in 8 daily fractions of 1.5 Gy) with a Simultaneously Integrated Boost (SIB) at all four relapsed sites (22.0 Gy in 2.75 Gy fractions), complete remission was achieved. Patient is alive and disease free at 4.2 years after the second course of radiotherapy.

In the second patient radiotherapy was indicated during first-line treatment because of a localized left-sided intermediate-risk stage III WT with a viable tumor thrombus in the IVC and right atrium of the heart after preoperative chemotherapy. At the end of first-line treatment evaluation, MRI scan revealed recurrent disease in the IVC (site #1) and the contralateral retroperitoneal space lateral to the healthy kidney (site #2) (Fig. 3A and B). The respective relapses were classified as *marginal* (D_{mean}: 14.0 Gy; V95% $_{relapse}$: 93%) and *outfield* (D_{mean}: 2.4 Gy; V95% $_{relapse}$: 0%) (Fig. 3C–E). BEV and dose reconstruction showed that both relapse sites would not have been adequately covered by conventional flank RT beams (site #1, V95% $_{relapse}$: 97%; site #2, V95% $_{relapse}$: 0%) (Fig. 3G). Second-line therapy consisted of 5-drug chemotherapy (SIOP-RTSG UMBRELLA 2016 protocol BB-regimen), autologous stem cell transplantation, followed by resection of the relapsed sites which showed viable tumor cells in the IVC. Re-irradiation including the whole abdominal volume (15.0 Gy in 1.5 Gy fractions) with integrated boost to the IVC and right-atrium (20.0 Gy in 2.0 Gy fractions) was administered. Five months after re-irradiation, the patient is alive and in complete remission.

The third patient, diagnosed with MRTK and presenting with a distant relapse only, died of disease progression at 1.2 years from diagnosis, despite second-line therapy. One patient without disease recurrence died during first-line treatment as a result of a synchronous embryonal rhabdomyosarcoma, either arising in the brain or brain metastasis with unknown primary (Supplementary Table 2).

Table 1
Patient, tumour and treatment characteristics (n = 36).

	Number	Percentage
Patient characteristics		
Gender		
Male	18	50
Female	18	50
Age at diagnosis (years)		
Median (min–max)	3.1 (0.3–14.0)	
Follow-up (years)		
Median (min–max)	3.1 (0.4–5.7)	
Tumour characteristics		
Stage		
II	5	14
III	15	42
IV	14	39
V	2	6
Local stage		
II	5	14
III	31	86
Histology		
WT–IR	27	75
WT–HR	5	14
MRTK	3	8
CCSK	1	3
Side		
Left	15	42
Right	21	58
Reason for stage III		
Lymph node involvement	18	50
Resection margin	20	56
Inferior vena cava thrombus	6	19
Upstaging after multidisciplinary evaluation	2	1
Radiotherapy		
Radiotherapy field		
Flank only	30	83
Flank + lung RT		
Synchronous	5	14
Metachronous	1	3
Time from surgery to onset of flank RT (weeks)		
Flank only		
Median (min–max)	3.9 (2.6–16.7)	
Flank + lung RT		
Median (min–max)	13.1 (4.7–17.7)	
Flank radiation dose		
10.8 Gy	4	11
14.4 Gy	28	78
25.2 Gy	4	11
Abdominal boost required	4	11

Note: Percentages do not always add up to 100 due to rounding.
Abbreviations: WT, Wilms Tumour; IR/HR, Intermediate-/High-risk; CCSK, Clear Cell Sarcoma of the Kidney; MRTK, Malignant Rhabdoid Tumour of the Kidney RT, radiotherapy; Gy, Gray.

Discussion

To our knowledge, this is the first cohort of pediatric patients with a renal tumor that describes the locoregional outcome of highly conformal flank irradiation using new target volumes adjusted for postoperative organ shifts and optimized by the use of surgical clips and 4D-CT scans [17,21]. After a median follow-up of 3.1 years, two patients developed a locoregional relapse resulting in a 2-year LCR of 94%, which is in line with the reported number of locoregional events observed in patients with stage III WT treated by the use of a conventional technique within the SIOP-2001 and AREN0532 studies [4,25]. Moreover, dose reconstruction in both patients with a locoregional recurrence demonstrated that the sites of relapse would not have been adequately covered by the use of conventional target volumes combined with AP/PA photon beams. As such, these failures appear to be caused by other factors than highly conformal flank irradiation.

For all types of pediatric renal tumors, the most frequent site of relapse are the lungs (~50–60%), while abdominal relapses at the primary tumor bed, in the regional lymph nodes or intra-abdominal are less common [26,27]. In a report by the Associ-

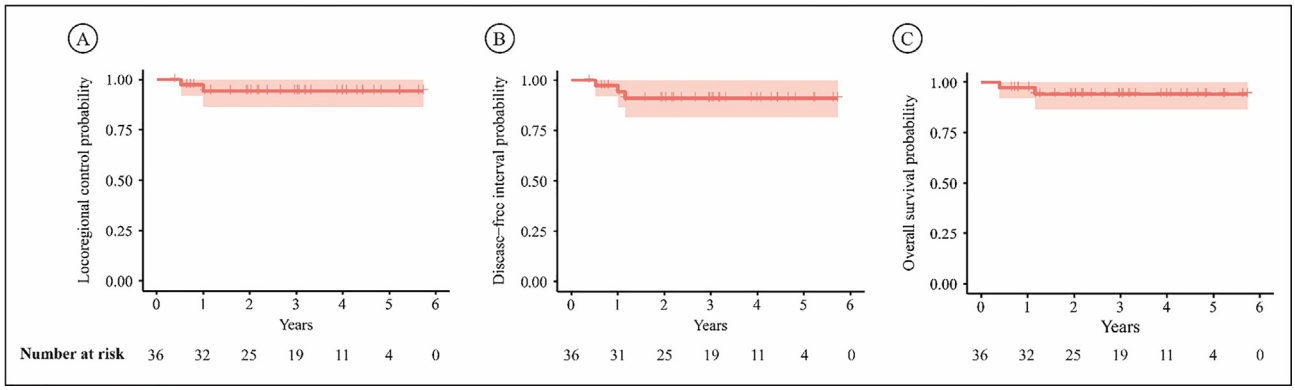

Fig. 1. The estimated locoregional control (A), disease-free interval (B) and overall survival (C) from time of diagnosis in 36 pediatric patients with renal tumors treated by VMAT on highly conformal flank volumes.

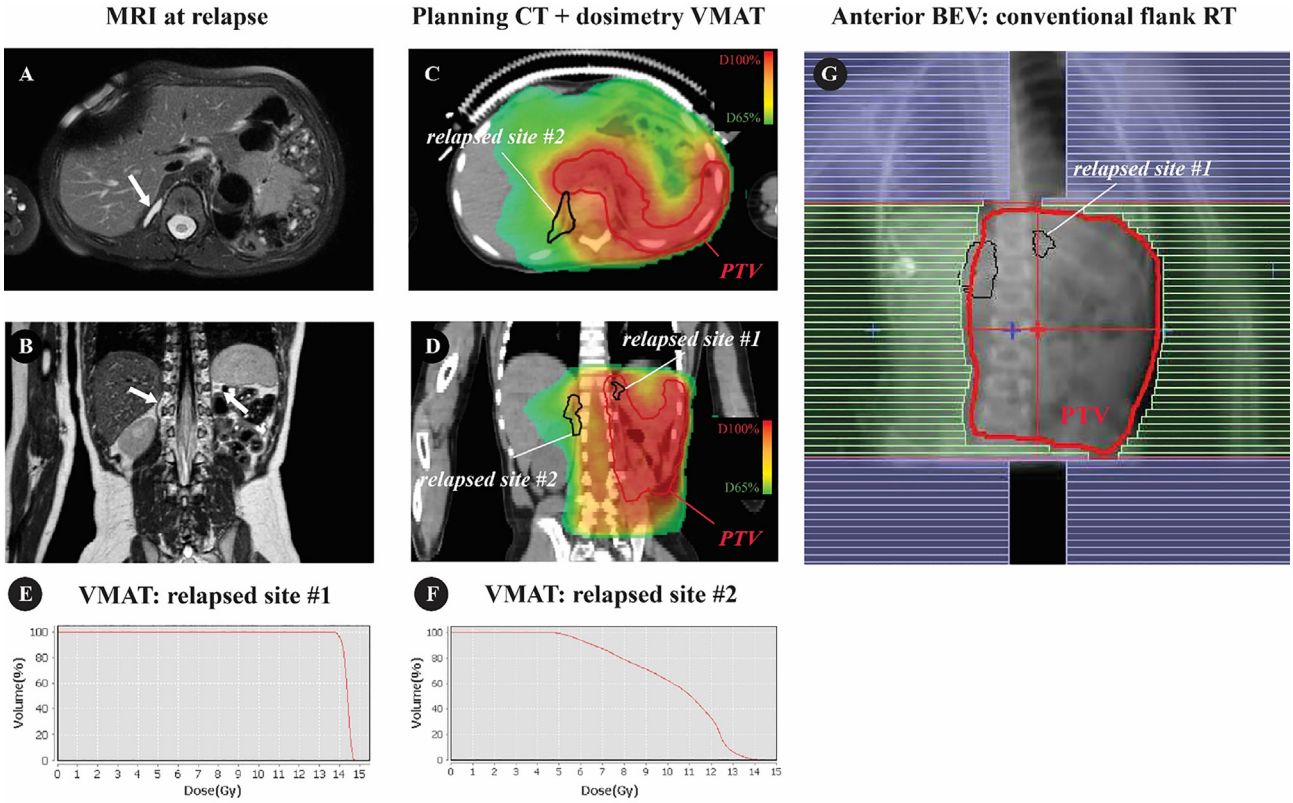

Fig. 2. Dose reconstruction of the locoregional relapses for the first patient, who was irradiated for an intermediate risk stage III WT due to a positive resection margin. The relapses at the ipsilateral adrenal gland (site #1) and contralateral paravertebral space (site #2), visible on an axial (A) and coronal (B) MRI-scan, are reconstructed on the planning CT-scan with highly conformal dose distributions (C and D), while dose coverage is depicted in dose volume histograms (E and F). Both relapsed sites are projected on a Beam's Eye View (anterior to posterior beam) with the conventional Planning Target Volume indicated in red (G). Abbreviations: VMAT, Volumetric-Modulated Arc Therapy; RT, radiotherapy; Gy, Gray. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article).

azione Italiana di Ematologia e Oncologia Pediatrica (AIEOP), 6 out of 99 patients (6%) with a non-anaplastic stage III WT developed a locoregional recurrence after flank irradiation, which were found in the tumor bed (n = 1), tumor bed and LN area combined (n = 2), LN area only (n = 1), IVC (n = 1) and in the pelvis (n = 1) [28]. In the fourth National Wilms Tumor Study (NWTS-4), locoregional recurrence occurred in 100 of the 2484 included patients (4%) with a renal tumor [29]. In these patients, the specified sites of relapses were the original tumor bed (n = 46), pelvis (n = 11), LN area (n = 6), peritoneum (n = 5) or diaphragm (n = 3) [29]. In a single-center cohort of 280 patients with a WT (all stages/histologies) consecutively treated at the St. Jude Children's Hospital, 7 patients (2.5%) developed an abdominal recurrence in the peritoneum (n = 4), nephrectomy site (n = 2) and regional LN (n = 1) [30]. Moreover, operative or traumatic tumor spillage during first-line therapy had occurred in all patients with peritoneal recurrences [30]. Only one SIOP-mandated study compared the site of locoregional relapse with the extent of the radiation field [31]. In 135 patients with IR or HR WT treated with conventional flank irradiation, 8 of the 12 patients with locoregional failure had relapses within the treatment portals [31]. Although all of these studies are based on a small number of events and vary in patient selection or treatment strategy, intra-abdominal recurrences seem to occur predominantly in the peritoneum, tumor bed or LN area.

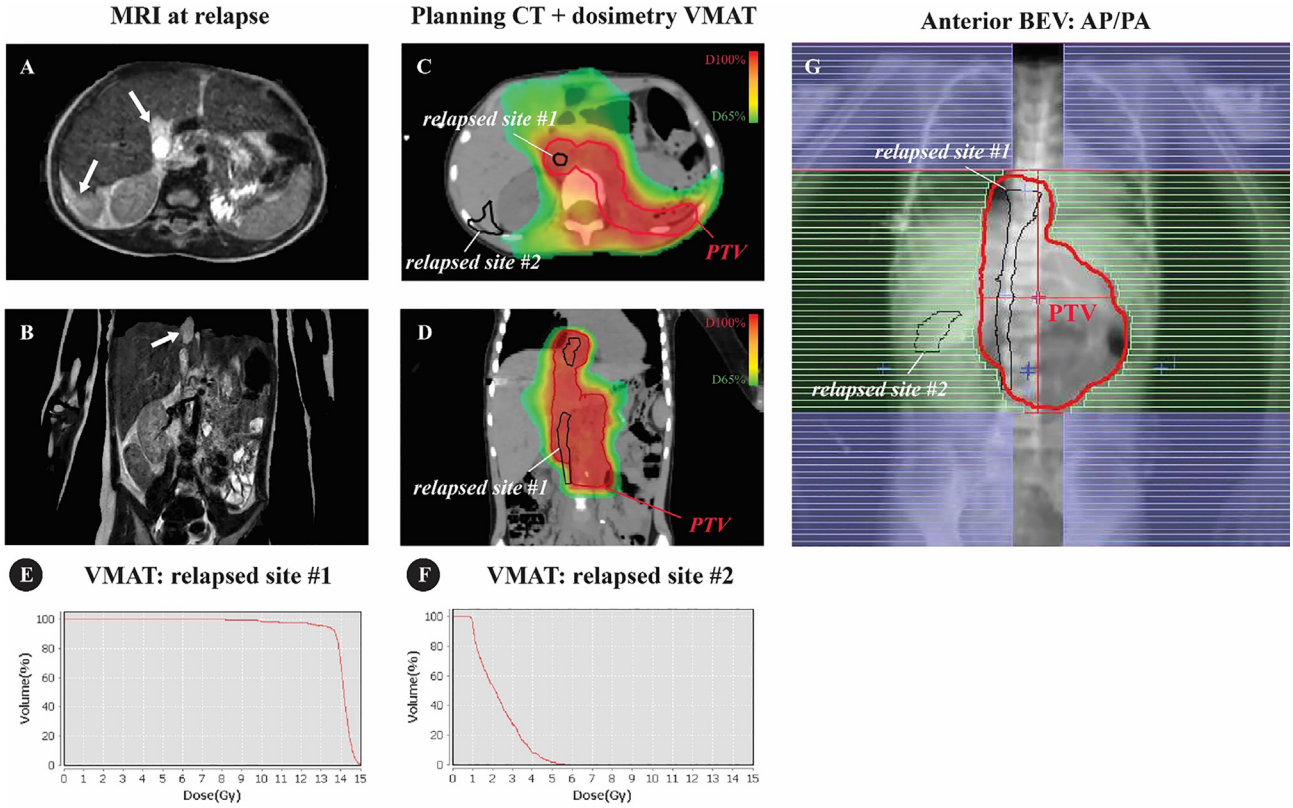

Fig. 3. Dose reconstruction of the locoregional relapses for the second patient, who was irradiated for an intermediate risk stage III WT due to a viable tumor thrombus in the IVC and right atrium after preoperative chemotherapy. The relapses at the inferior vena cava (site #1) and the contralateral retroperitoneal space (site #2), visible on an axial (2A) and coronal (2B) MRI-scan, are reconstructed on the planning CT-scan with dose distributions (2C and 2D), while dose coverage is depicted in dose volume histograms (2E and F). Both relapsed sites are projected on a Beam's Eye View (anterior to posterior beam) with the conventional Planning Target Volume indicated in red (2G). Abbreviations: VMAT, Volumetric-Modulated Arc Therapy; RT, radiotherapy; Gy, Gray. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article).

Besides, more than 80% of the locoregional relapses occurred within 24 months from diagnosis [26,28,30].

To investigate whether highly conformal flank irradiation caused unexpected abdominal recurrences in our cohort, we performed an in-depth dosimetric analysis of each locoregional relapse. Although, in the first patient, the recurrence at the paravertebral space extended beyond the conventional radiation field, the origin of this recurrence may have been adequately covered. Nevertheless, neither LN invasion according to the pathology report nor an indication to include the contralateral paravertebral retrocrural region due to primary tumor extension, can explain the recurrence at the contralateral paravertebral space. In the second patient, the IVC relapse was defined as a marginal failure. However, it is more likely that this lesion had expanded more caudally in the IVC after becoming therapy-resistant, considering that over 90% of the relapsed volume had been infield at primary irradiation. Moreover, the BEV showed that the caudal part of this lesion would also not have been included in conventional AP/PA RT fields. Overall, the pattern of abdominal relapses in our cohort does not seem to be correlated with the highly conformal target volume definition.

Ultimately, the main reason to implement highly conformal RT techniques is to spare healthy organs surrounding the target volume and thus to reduce the risk of late adverse effects. Recent childhood cancer survivor studies have provided evidence of a dose–response relationship between radiation exposure of the pancreas and the risk of diabetes, especially when the tail of the pancreas receives a mean dose of $\geq$10 Gy [8,9]. Also, the SIOP-Europe Radiation Oncology Working Group now recommends antibiotic prophylaxis or (re)vaccination in children receiving a mean dose above 10 Gy to the spleen, because this is associated with an increased rate of late infection-related mortality [10,11]. In patients with tumor extension in major blood vessels, VMAT may contribute to a risk reduction of cardiac disease or invasive breast cancer in later life by sparing or decreasing the dose to the heart and mammary buds [12-15]. Since highly conformal flank RT maximizes normal tissue preservation during first-line therapy, opportunities for re-irradiation with acceptable toxicity increase for the rare cases with locoregional or peritoneal relapse. Besides that, cardiac-sparing whole lung RT, as described by Kalapurakal et al., and highly conformal flank irradiation can be delivered synchronously as it was the case in five out of six patients from our cohort [32–34].

It is true that rotational IMRT techniques, like VMAT, may increase the low dose exposure during flank irradiation when compared to conventional AP/PA irradiation. However, in literature and daily practice, secondary malignancies are nearly exclusively observed in the intermediate to high radiotherapy dose areas [35]. Consequently, high dose irradiation to a smaller volume by using VMAT is likely to counterbalance the increase of low dose to a larger volume, when compared to a high dose to a large volume by using AP/PA beams. Unfortunately, no clinically validated models are available to predict what the effect of low dose irradiation on secondary tumor induction in pediatric renal tumor survivors may be [36]. Proton therapy could further reduce the low-dose bath and dose to the OARS when compared to VMAT, as it was shown by Guerreiro et al and others [18,20,37]. However, time to onset of radiotherapy per protocol, but also technical issues, like diaphragmatic and organ motion as well as bowel density changes,

are current challenges for referral to proton therapy centers on a routine base. A better prediction of the real clinical benefit of proton therapy compared to rotational IMRT techniques is essential to consider regular patient referral.

In conclusion, this analysis provides encouraging evidence that excellent locoregional control of pediatric renal tumors can be achieved using highly conformal flank irradiation with VMAT. Dose reconstruction demonstrates that all locoregional failures in our cohort were unavoidable by using conventional volumes and AP/PA beams. In the next step, the oncological safety and clinical benefit of highly conformal flank irradiation will be validated during a SIOP-RTSG multicenter prospective study with focus on locoregional control and registration of radiotherapy-related morbidity.

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.04.005.

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