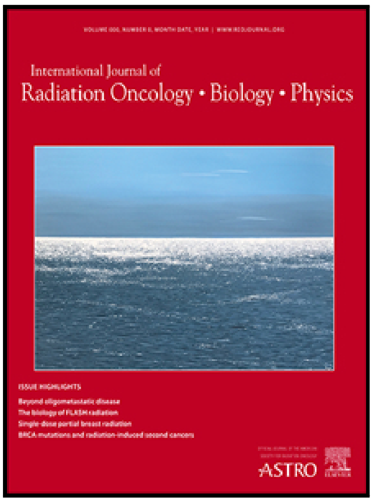

Long-term locoregional control and pattern of recurrences after implementation of highly conformal flank target volumes and image-guided Intensity-Modulated Arc Therapy for pediatric Wilms tumors

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RUNNING TITLE

Highly conformal flank irradiation for Wilms Tumors

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Abstract

Introduction

Excellent outcomes in Wilms tumors (WT) have allowed efforts to reduce toxicity and treatment burden while sustaining effectiveness. Concerning radiotherapy, ‘conventional’ flank target volumes combined with two opposing photon beams are now being replaced by highly conformal flank target volumes combined with image-guided Intensity Modulated Arc Therapy (IMAT), allowing better sparing of the organs at risk, but outcome descriptions based on large cohorts are scarce.

Previously a cohort of 36 patients with excellent locoregional control at 2 years from diagnosis using ‘modern’ flank irradiation has been described. This study aims to investigate locoregional control outcomes, patterns of recurrence, and toxicity in an extended national cohort of WT with a longer follow-up period.

Materials and methods

Newly-diagnosed patients with a WT, irradiated on the flank between 01-2015 and 08-2025 using highly conformal target volumes, as defined by the SIOP-RTSG consensus statement, combined with IMAT were eligible for analysis. Four-year locoregional control rate (LCR), disease-free interval (DFI), event-free survival (EFS), overall survival (OS), acute and estimated late toxicity were assessed. For each locoregional recurrence, image co-registration and dose reconstruction were performed to classify each recurrence as 'infield' ($V95\%_{recurrence-IMAT}$: ≥99%), 'marginal' ($V95\%_{recurrence-IMAT}$:20.0-98.9%) or 'outfield' ($V95\%_{recurrence-IMAT}$: ≤19.9%).

Results

Seventy patients received post-operative flank irradiation only (n=50) or combined with metastatic site irradiation (n=20). With a median follow-up of 4.7 years, the estimated 4-year LCR, DFI, EFS, and OS were 93.7%, 86.4%, 83.7% and 93.7%, respectively. Four patients developed a locoregional recurrence, of whom one (marginal recurrence) could have been better covered by the conventional approach. Nausea ± vomiting requiring anti-emetics developed in 34/63 (54%) patients. In 24/70 (34%) patients, major constraints violations, mainly involving pancreatic tail and spleen, were observed.

Conclusion

This extended national cohort of WT patients confirms the excellent locoregional control rate, using modern flank irradiation, even after a long-term follow-up.

Keywords:

Wilms tumors; IMAT; highly conformal flank target volumes; tumor recurrence; locoregional recurrences; flank irradiation.

Introduction

Renal tumors account for 5-6% of all pediatric malignancies, 73-90% of these are reported to be nephroblastoma or Wilms tumor (WT) [1,2,3]. In the Netherlands, all children diagnosed with a renal tumor are treated according to the guidelines of the International Society for Pediatric Oncology - Renal Tumor Study Group (SIOP-RTSG) [4]. Postoperative radiotherapy (RT) of the flank during first-line treatment is required in approximately 20% of children with a WT [4,5].

Since the SIOP-RTSG radiotherapy consensus statement has been published, highly conformal flank target volumes combined with modern radiotherapy techniques (onwards named modern flank irradiation) are being stepwise introduced across the affiliated countries to replace conventional volumes treated with two opposing anterior-posterior/posterior-anterior (AP/PA) photon beams [6,7]. This revised target volume definition accounts for postoperative changes and intra-fraction motion and allows better sparing of the surrounding healthy tissue when combined with intensity-modulated arc therapy (IMAT) or proton therapy [8,9]. However, using smaller radiation volumes may increase the rate of locoregional recurrences compared with conventional flank RT. Initial single-center experience in the first series of 36 patients in the Netherlands treated with highly conformal flank volumes and IMAT, as well as a multi-center experience in a group of 40 patients in France treated with a mix of conventional and highly conformal flank volumes combined with modern radiotherapy techniques, demonstrated no abnormal recurrence pattern [5,7]. However, data on long-term disease control with this new approach has not yet been reported so far.

Therefore, the aim of this project is to show the long-term loco-regional control and pattern of recurrence after flank irradiation using highly conformal volumes combined with image-guided IMAT in the extended national cohort of WT, with a longer follow-up.

Materials and methods

Patient selection

From January 2015 to August 2025, all children diagnosed with a renal tumor at the Princess Máxima Center (Utrecht, Netherlands) and who received radiotherapy at the affiliated University Medical Center Utrecht (Utrecht, Netherlands) were eligible for analysis. From this cohort, patients with non-Wilms tumors and patients with Wilms tumor who received whole-abdomen irradiation, non-flank irradiation only, flank re-irradiation, or flank irradiation for a locoregional recurrence were excluded. Patients with a local stage II WT with diffuse anaplastic histology, or a local stage III WT (without intraperitoneal rupture) intermediate-/high-risk (IR/HR) histology were treated with flank irradiation according to the SIOP 2001 (EudraCT number 2007-004591-39), or the SIOP-RTSG UMBRELLA-2016 (EudraCT number 2016-004180-39) protocol and were included in the current descriptive analysis (institutional review board approval number: PMCLAB2025.0728). The current analysis also includes WT patients from the previous paper, but with a longer follow-up period [5].

SIOP-RTSG policy for Wilms Tumors

All patients aged between 6 months and 16 years with typical clinical and radiological features of a Wilms tumor receive preoperative chemotherapy without a prior biopsy. In patients with unilateral tumors pre-operative chemotherapy consists of 4 weeks of vincristine-actinomycin or 6 weeks of vincristine-actinomycin-doxorubicin, respectively depending on the absence or presence of distant metastases. This approach assesses tumor chemosensitivity, allows downstaging of the primary tumor, and reduces the number of per-operative tumor ruptures and therefore, the subsequent need for more intensive chemotherapy and/or whole abdomen irradiation. Afterwards, a pre-operative MRI is performed followed by a nephrectomy with lymph node (LN) sampling. Based on the response to preoperative chemotherapy, cell type, and tumor volume WT are classified into three risk groups: low risk (cystic partially differentiated, completely necrotic), intermediate risk (regressive, mixed, epithelial, stromal, and focal anaplasia), and high risk (blastemal and diffuse anaplasia). The postoperative chemotherapy regimen is determined by tumor stage and risk group, and since SIOP-RTSG UMBRELLA-2016 also by preoperative tumor volume (≤500 ml vs. >500 ml) in selected intermediate-risk subtypes (mixed, regressive, and focal anaplasia).

Regarding radiotherapy indications, flank irradiation is indicated for WT local stage III intermediate- and high risk and for local stage II (with diffuse anaplasia only). Whole abdomen irradiation (WAI) is indicated in cases of major rupture of the tumor or LN pre- or during surgery, or in the presence of macroscopic peritoneal deposits at presentation, regardless of the response to preoperative chemotherapy. Whole-lung irradiation (WLI) is recommended for all high-risk patients with initial pulmonary metastases, as well as for intermediate-risk patients with initial pulmonary metastatic disease who either have viable tumor in resected lung metastases after preoperative chemotherapy or incomplete radiological remission of pulmonary metastases at week 10 of postoperative chemotherapy.

The doses prescribed in the SIOP-RTSG approach take into account the risk group (intermediate- vs. high risk), volume (flank vs. whole abdomen), metastatic site (lung), and the age of the patient (younger or older than 2 years). More information about dose prescriptions and fractionation schemes for flank irradiation, WAI, and WLI can be found in the supplementary data **(Table S1)**.

Highly conformal flank irradiation

Magnetic resonance imaging (MRI, T1-weighted ± intravenous Gadolinium contrast and T2-weighted images, slice thickness of 1.5 mm, Achieva 1.5T, Philips Medical Systems, Best, the Netherlands,) obtained after preoperative chemotherapy were rigidly co-registered to a postoperative 4D planning computed tomography (CT, Brilliance, Philips Medical Systems, Best, the Netherlands, slice thickness of 2-3 mm) with the patient in a supine position in a vacuum mattress (Bluebag, Elekta, Stockholm, Sweden) and the arms wide along the body. During nephrectomy, four surgical clips were placed in each patient to mark the borders of the operative field, in accordance with the standard of care at our institution. Target volume delineation is a multistep process that begins with contouring of the primary tumor using the co-registered MRI performed after pre-operative chemotherapy, taking into account the surgical clips and the post-operative organ shift (**Table S2)** [6, 10]. Specifically, after delineation of the GTV and CTV, an Internal Target Volume (ITV) margin, defined as the maximum intra-fraction motion registered by the 4D-CT, was generated. Since no primary tumor is visible at the time of flank irradiation, and intrafraction motion is most pronounced in the subdiaphragmatic area, motion of the superior clip is considered as a surrogate for intra-fraction tumor bed motion [10]. When performing 4D-CT imaging, each complete respiratory cycle during spontaneous breathing is registered as a series of ten phases acquired at equally distributed time intervals. Additionally, a reference CT is created by calculating the mean of the voxel intensity values from all phases of the breathing cycle and used to generate the ITV. The superior clip is contoured on the reference scan, also on the phases corresponding to maximum inspiration and expiration. Differences (in millimeters) between these three positions of the superior clip are considered as indicators of the tumor bed motion during the respiratory cycle and used to personalize the ITV margins for each patient. Depending on the size of the ITV (<10 cm or ≥10 cm in craniocaudal direction), a 0.3 cm or 0.5 cm isotropic margin, respectively, was added to the ITV to generate the Planning Target Volume (PTV).

The prescribed doses for flank irradiation were based on the SIOP 2001/SIOP-RTSG UMBRELLA-2016 protocols **(Table S1)**. A boost dose was indicated only in cases of macroscopic residual disease [11]. Target volume coverage was considered adequate if 95% of the prescribed dose was given to at least 99% of the CTV (CTV V95%: ≥99%) and 95% of the PTV (PTV V95%: ≥95%), respectively. During plan optimization, dose constraints were considered for the kidney(s), spleen, pancreatic tail, liver, intestines, heart, lungs, and mammary buds, as defined in the SIOP-2001/UMBRELLA-2016 protocol and additional papers [12-20]. To avoid steep dose gradients across the vertebrae adjacent to the PTV, potentially increasing the risk of asymmetrical vertebral growth due to the fact that the primary ossification centers and growth plates are in the vertebral body and in the left and right side of the vertebral arch, the left-to-right and ventral-to-dorsal dose gradients must be respected [21]. For patients younger vs. older than 2 years, a RT dose gradient up to 3 Gy and 5 Gy is allowed, respectively. The prescribed dose was delivered five days per week using an IMAT with a full-arc 6 MV or 10 MV photon beam (Elekta Synergy, Elekta, Stockholm, Sweden). Daily pre-treatment Cone Beam CT (CBCT) images (on-board Elekta XVI system, version 4.5.1, Elekta, Stockholm, Sweden) were acquired for patient position verification and correction.

Acute and Estimated Late Toxicity

Acute toxicity, in particular nausea ± vomiting, was assessed weekly during radiotherapy, and within the first 2 weeks via telephone and it was classified into three categories: category 1, no toxicity during RT; category 2, toxicity during RT not requiring anti-emetics; and category 3, toxicity during RT requiring at least one anti-emetic. Additionally, the association between the incidence of nausea ± vomiting and the laterality of flank irradiation (right vs. left) was investigated.

To make an estimation of the potential late toxicity, the mean dose on the contralateral kidney, heart, spleen, pancreatic tail, bowel, liver, and mammary buds was collected. Organ constraint violations were classified into four categories: no violation; minor violation (constraint exceeded by ≤ 2.0 Gy); major violation (constraint exceeded by >2.0 Gy) and not applicable (e.g., risk of breast hypoplasia in male patients) [12-17, 19-20]. The analysis considered the laterality of flank irradiation (left vs. right), the risk group (intermediate risk vs. high risk) and whether flank and whole lung irradiation were combined or not.

Follow-up and analysis of outcome

Follow-up (FU) of patients included routine physical examination, chest X-ray, and abdominal ultrasound, according to the SIOP 2001/SIOP-RTSG UMBRELLA-2016 protocols. Recurrences were classified as local, regional, abdominal or distant. Tumor recurrence at the primary tumor bed (nephrectomy site) was classified as a local recurrence. Tumor recurrence in the para-aortic LN or in an area with tumor extension *per continuitatem*, e.g., tumor thrombus in the inferior vena cava (IVC), was classified as a regional recurrence. The occurrence of either of the two above-mentioned types of recurrence represents locoregional recurrence. A recurrence caused by tumor spillage was classified as an abdominal recurrence. Disease recurrence in a LN outside the abdomen and/or metastases to the lungs, liver, brain, or bone/bone marrow was considered distant recurrence.

For patients with a locoregional recurrence, MR-imaging at the time of recurrence was rigidly co-registered with the CT in treatment position and the dose distribution from first-line RT. Subsequently, each recurrence was delineated, and a dose reconstruction was conducted to calculate the dose delivered to each recurrent site. Based on the dose reconstruction, a recurrence was categorized as *'infield'* if ≥ 99.0% of its volume received adequate coverage (at least 95% of the prescribed dose), as '*marginal recurrence*' if it was between 20–98.9%, and as *'outfield recurrence'* if it was less than 20%; '*progression*' was defined as continuous growth of residual tissue already present at the time of radiotherapy [5]. In addition, flank radiotherapy plans were generated using CT-based conventional target volumes combined with AP/PA photon beam arrangements, following the conventional approach of the SIOP-RTSG UMBRELLA-2016 protocol [4]. The aim of this approach was to determine whether the observed locoregional recurrences would have been more adequately covered by the prescribed dose that would have been administered in case of combining conventional volumes with two opposing photon beams ($V95\%_{\text{recurrence-AP-PA}} \geq 99\%$).

End points and statistical analysis

The primary endpoint was the Locoregional Control rate (LRC), defined as the absence of a first local or regional recurrence. Secondary endpoints were Disease-Free Interval (DFI), defined as the time to any recurrence (locoregional, abdominal, and distant), Event-Free Survival (EFS), as the time to the first occurrence of any progressive disease or death from any cause, Overall Survival (OS), as the time to death from any cause, incidence of nausea ±vomiting, and an estimation of potential late toxicity.

All intervals were calculated from the date of diagnosis and censored at the event or the last date of follow-up. The Kaplan-Meier method was used to estimate the 2- and 4-year probabilities of LRC, DFI, EFS, and OS, with Greenwood 95% confidence intervals. Analysis was performed using the R package version 4.4.0. Fisher's exact test was used to assess whether the incidence of nausea ±vomiting differed between left and right flank irradiation.

Results

A group of 137 patients with a renal tumor underwent radiotherapy and were eligible for the study. Sixty-seven patients were excluded because of a non-Wilms tumor (n=17), whole abdomen irradiation or non-flank irradiation only (n=43), flank re-irradiation for a locoregional recurrence (n=4) or flank irradiation for a locoregional recurrence (n=3) (**Figure 1**). A total of 70 WT patients, including 32 previously described [5], received flank radiotherapy for an intermediate-risk (n=51) or high-risk (n=19) type of WT. Initially, 31/70 (44.3%) patients presented with metastatic disease, of which 20/70 (28.6%) received flank combined with metastatic site irradiation. The main indications for post-operative flank irradiation were positive section margins in 35/70 (50.0%) patients and LN involvement in 34/70 (48,6%) patients. An indication for RT based on LN involvement only was observed in 20/70 (28.6%) patients. **Table 1** depicts the patient and tumor characteristics, and **Table 2** summarizes the treatment details.

With a median follow-up duration of 4.7 years (range, 0.1–10.0 years), the estimated 2 and 4-year LCR were 93.7% (95% CI: [87.5–99.9]) and 93.7% (95% CI: [87.5–99.9]), respectively (**Figure 2A**). In the entire cohort, disease recurrence was observed in 8/70 (11.4%) patients, of whom 4/70 (5,7%) developed a locoregional recurrence. One patient had an isolated local recurrence, one experienced concurrent regional and abdominal recurrence, and two presented with simultaneous locoregional and distant recurrence. All locoregional recurrences occurred within 0.9 years from diagnosis.

The estimated 2-year DFI, EFS, and OS rates were 90.6% (95% CI: [83.6–98.0]), 87.5% (95% CI: [79.8–96.0]), and 93.7% (95% CI: [87.9–99.9]), respectively **(Figure 2B-D)**. The corresponding 4-year estimates were 86.4% (95% CI: [78.0–95.8]), 83.5% (95% CI: [74.6–93.5]), and 93.7% (95% CI: [87.9–99.9]), respectively**.**

Table 3 illustrates detailed information about the four patients who developed a locoregional recurrence. Patient one, with an initial indication for flank irradiation due to a positive section margin, developed an infield local recurrence, in the ipsilateral adrenal gland region ($V95\%_{recurrence\text{-}IMAT}$: 100%) and an outfield regional recurrence ($V95\%_{recurrence\text{-}IMAT}$: 1.2%) in the contralateral retro-crural region at level T12 corresponding to the para-aortic LN area, combined with distant pulmonary recurrence. Patient two, who initially had received flank irradiation due to a viable tumor thrombus in the IVC after preoperative chemotherapy, experienced a marginal regional recurrence in the IVC ($V95\%_{recurrence\text{-}IMAT}$: 93%) combined with a synchronous abdominal recurrence, laterally to the contralateral remaining kidney. In the third patient, flank irradiation was indicated because of a positive surgical margin within the diaphragm and an incompletely resected IVC tumoral thrombus. Eleven months after diagnosis, the patient experienced an infield local recurrence dorsal to the right liver lobe, just adjacent to the lateral insertion of the diaphragm ($V95\%_{recurrence\text{-}IMAT}$: 100%). Patient four had received right flank irradiation due to the involvement of para-aortic LN simultaneously with whole-lung irradiation. Eight months after diagnosis, the patient developed an ipsilateral local recurrence at the inferior rim of the liver, just ventral to the hepatic flexure, with prominent invasion in the hepatic parenchyma. The recurrence was classified as a marginal recurrence ($V95\%_{recurrence\text{-}IMAT}$: 32,1%). At the time of recurrence, all patients with a locoregional recurrence underwent second-line therapy, including reirradiation. Doses and volumes are specified in **Table 3**. At the last follow-up, all patients with a locoregional recurrence were alive and without evidence of disease since reirradiation (range 0.9-8.9 years).

Data on acute toxicity was available for 63/70 patients included in the cohort. Nausea ±vomiting with or without the need for anti-emetics was observed in 34/63 (54 %) and 10/63 (16 %) patients, respectively. Left flank irradiation (± WLI) was associated with higher odds of toxicity compared to right flank irradiation (± WLI) (OR = 2.56, 95% CI: 0.74–9.82; p = 0.10).

Table 4 depicts the constraint violations of the organs at risk for each patient. Major constraint violations were observed in 24/70 (34%) patients of whom 11, 9, 2, 1 and 1 patients had respectively 1, 2, 3, 4, 5 violations. The pancreatic tail (13/24) and spleen (11/24) constraints were most violated. When comparing left vs. right flank only RT in patients treated with 14.4 Gy and 25.2 Gy, major violations were observed in 3/18 vs. 0/22 and 4/4 vs. 2/7 patients, respectively. When left vs. right flank RT was combined with WLI, major violations were observed in 3/4 vs. 4/7(for 14.4 Gy) and 6/6 vs. 2/2 (for 25.2 Gy) patients, respectively. Mean doses for every organ at risk for patients with an intermediate- and high-risk WT can be found in the supplementary data **(Table S3**).

Discussion

The 4-year locoregional control rate of 93.7% in this extended national cohort of 70 pediatric patients with a WT confirms the oncological safety of using highly conformal flank target volumes combined with IMAT. With an additional follow-up time of 4.2 years of the initial cohort of 36 renal tumor patients, of which 32 were WT, no additional locoregional events have been observed in this group [5]. Of the four locoregional recurrences, one could potentially have been avoided by using the conventional volumes combined with AP/PA-beams.

The LRC rate observed in our cohort since the introduction of highly conformal flank target volumes and IMAT is in line with the international series using conventional volumes and techniques. A study from the UK Children's Cancer and Leukaemia Group (UK-CCLG) and German Society for Pediatric Oncology and Hematology (GPOH) Wilms tumor trials, focusing on stage III patients with positive resection margins and registered in the SIOP-2001 protocol, reported a 5-year local recurrence-free survival probability of 95.7% among 195 patients [22]. Also, a retrospective study of the GPOH involving 2386 patients with unilateral WT enrolled over 32 years (1989-2020) in SIOP-9, SIOP-93-01, and SIOP-2001 reported a locoregional recurrence rate of 4.9% with a median follow-up of 14.6 years [23]. Recently, an analysis of the French PediaRT cohort demonstrated a 3-year LRC rate of 97.4 % in 40 pediatric renal tumor patients treated with modern photon radiotherapy combined with a mix of conventional and highly conformal flank volumes, compared to 94.7 % in 39 patients treated with conventional 3D-RT mostly combined with conventional target volumes [7].

Highly conformal flank target volumes combined with modern RT approaches can reduce the dose to the surrounding structures at risk such as the pancreas, spleen, contra-lateral kidney and colon and have the potential to decrease the incidence of late effects like diabetes mellitus, metabolic syndrome, functional asplenia, chronic kidney disease and secondary colorectal carcinomas as observed in long-term childhood cancer survivors [14,24-29], as reported in a recent in silico study [8] in which twenty renal tumor cases were planned twice using highly conformal flank volumes in combination with VMAT, and conventional flank target volumes in combination with AP-PA. In 12/20 cases, the modern approach demonstrated a potential clinical benefit by fulfilling the dose constraint of at least one organ at risk otherwise violated by the conventional approach. The most notable differences between the two approaches were observed for the pancreatic tail and the spleen. Nonetheless, the same approach may inadvertently increase the risk of locoregional recurrences. Therefore, in the current study, flank RT plans using conventional target volumes and AP/PA beams were developed according to the SIOP-RTSG UMBRELLA-2016 protocol to investigate whether the four loco-regional recurrences could have been avoided by using the conventional approach. The analysis is especially important for the outfield and marginal recurrences observed in this cohort. For the recurrent patients one, two, and three, it is clear that the outfield and marginal locoregional recurrences would not have been avoided using conventional target volumes combined with AP/PA beams ($V95\%_{\text{recurrence-AP-PA}} < 99\%$). In patient four, a right-sided WT, intermediate-risk stage IV, the initial irradiated field included the flank and para-aortic LNs due to LN involvement and was combined with whole-lung irradiation. The patient developed a marginal recurrence at the inferior rim of the right hemi-liver, ventral to the hepatic flexure of the colon ($V95\%_{\text{recurrence-IMAT}}$: 32.1%), which would have been more adequately covered by the prescribed dose using the conventional approach ($V95\%_{\text{recurrence-AP-PA}}$: 100%). However, to assess the potential origin of the voluminous recurrence, the MRI performed after re-induction chemotherapy (SIOP-RTSG UMBRELLA

2016 protocol, BB-regimen) and before surgery was analyzed in depth (volume reduction from 197.6 ml to 14.7 ml). Although the recurrence remained a marginal one ($V95\%_{recurrence-IMAT}$: 25%), a clear regression pattern of the local recurrence towards the inferior rim of the liver, which was covered by the 95% isodose of the first RT course, was noticed (**Figure S1**). Considering this regression trend, it remains unclear whether the origin of the recurrence is a result of an underestimation of the target volume or a consequence of a radioresistant infield clone of the initial tumor.

The majority of the locoregional recurrences in this extended cohort was confined to the retroperitoneum, aligning with the patterns observed in the French study [7]. Notably, 3/4 locoregional recurrent patients in our cohort presented with synchronous abdominal or distant recurrence. Similar combined locoregional and distant recurrences were reported in 2/3 cases in the PediaRT cohort [7] and 5/8 cases in the UK-CCLG/GPOH-study [22].

All four locoregional recurrences occurred within the first year after diagnosis, which is consistent with findings from the French PediaRT cohort [7]. In the UK-CCLG/GPOH cohort, 81.5% of recurrences (including other types of recurrences) were reported within two years of treatment [22], and 77% of locoregional recurrences occurred within 24 months after diagnosis in the GPOH cohort [23]. The latter report confirmed that age >48 months at diagnosis represents a significant risk factor for developing a locoregional recurrence in WT. This was also illustrated by Hol et al. in a retrospective study which included 5631 patients registered prospectively in the SIOP-93-01 and SIOP-2001 trials [30]. In the present paper, three cases with a locoregional recurrence are older than 48 months. In contrast to previous literature, which emphasizes the increased risk of locoregional recurrence among patients with a WT and high-risk histology [23], none of the patients who developed a locoregional recurrence in this study had intermediate-risk histology.

Implementing highly conformal target volumes in a multicenter setting can lead to substantial inter-clinician variability, as demonstrated in a WT contouring study for both highly conformal and conventional flank target volumes [31, 32]. To address this inter-clinician variability, COG- and more recently the SIOPE-affiliated initiatives such as the QUARTET project (Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials), launched in 2016, provide a centralized, prospective radiotherapy quality assurance program for pediatric solid tumor patients participating in clinical trials [33,34]. In the first report from six QUARTET-affiliated trials, a rejection rate of 38% was observed, mainly due to major deviations in target volume delineation [35]. To help bridge this gap in delineation variability, deep learning-based auto-contouring may offer a promising complementary approach. Currently, efforts are ongoing to develop a reliable AI-based auto-contouring model for the flank target volumes. Previously, a robust auto-contouring model has been developed for pediatric upper abdominal structures at risk, reducing delineation time by up to 59%, improving delineation accuracy, and decreasing inter-observer variability in WT [36,37]. The combination of these AI-driven projects, once demonstrated in a research setting, can be implemented in routine clinical practice on an international scale.

`The primary strength of this analysis lies in the inclusion of a uniformly treated national patient cohort and the homogeneity and consistency of the protocol regarding target volumes and technique, applied within a single high-volume institution. Moreover, for all consecutively included patients, data regarding tumor, treatment, and imaging characteristics obtained during treatment and follow-up were complete and available for this analysis. Nevertheless, several limitations can be identified. The dosimetric analysis of recurrences within the cohort was conducted based on rigid co-registration between the MRIs used to identify the recurrences and the initial RT treatment plans. This approach may have led to inaccuracies in the calculation of the V95%$_{\text{recurrence-IMAT}}$ due to inherent limitations of this type of co-registration, particularly in the subdiaphragmatic region. At the same time, this single-institution study cannot account for multicenter variability, particularly regarding the implementation of highly conformal target volumes in routine clinical practice, which may affect locoregional control rates.

In conclusion, our extended analysis of a larger national WT cohort with extended follow-up further supports the evidence that highly conformal flank target volumes combined with IMAT can achieve excellent long-term locoregional control rates. No aberrant locoregional recurrence patterns were identified that can be unequivocally related to the use of this new approach.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019; 69: 7–34.

[2] Brok J, Treger TD, Gooskens SL, van den Heuvel-Eibrink MM, Pritchard-Jones K. Biology and treatment of renal tumors in childhood. Eur J Cancer 2016; 68: 179–95.

[3] Roy P, van Peer SE, de Witte MM, Tytgat GAM, Karim-Kos HE, van Grotel M, van de Ven CP, Mavinkurve-Groothuis AMC, Merks JHM, Kuiper RP, Hol JA, Janssens GOR, de Krijger RR, Jongmans MCJ, Drost J, van der Steeg AFW, Littooij AS, Wijnen MHWA, van Tinteren H, van den Heuvel-Eibrink MM. Characteristics and outcome of children with renal tumors in the Netherlands: The first five-year's experience of national centralization. PLoS One. 2022 Jan

13;17(1):e0261729. doi: 10.1371/journal.pone.0261729. PMID: 35025887; PMCID: PMC8757983.

[4] Van Den Heuvel-Eibrink MM, Hol JA, Pritchard-Jones K, et al. Position Paper: Rationale for the treatment of Wilms tumor in the UMBRELLA SIOP-RTSG 2016 protocol. Nat Rev Urol. 2017;14:743–752.

[5] Mul J, van Grotel M, Seravalli E, et al. Locoregional control using highly conformal flank target volumes and volumetric-modulated arc therapy in pediatric renal tumors: Results from the Dutch national cohort. Radiother Oncol. 2021;159:249-254.

[6] Janssens GO, Melchior P, Mul J, et al. The SIOP-Renal Tumour Study Group consensus statement on flank target volume delineation for highly conformal radiotherapy. Lancet Child Adolesc Health. 2020 Nov;4(11):846-852.

[7] Le Quellenec G, Bernier-Chastagner V, Sellami N, et al. Post-operative flank irradiation using conformal versus highly conformal radiotherapy techniques for paediatric renal tumours: Results from the French registry PediaRT. Pediatr Blood Cancer. 2023;70:e30627.

[8] Mul J, Seravalli E, Bosman ME, et al. Estimated clinical benefit of combining highly conformal target volumes with Volumetric-Modulated Arc Therapy (VMAT) versus conventional flank irradiation in pediatric renal tumors. Clin Transl Radiat Oncol. 2021;29:20-26.

[9] Vogel J, Lin H, Both S, et al. Pencil beam scanning proton therapy for treatment of the retroperitoneum after nephrectomy for Wilms tumor: A dosimetric comparison study. Pediatr Blood Cancer. 2017;64:39–45.

[10] Mul J, van de Ven CP, Seravalli E, Littooij AS, Wijnen MHWA, van Grotel M, vaden Heuvel-Eibrink MM, Janssens GO. The contribution of surgical clips for optimizing highly-conformal image-guided flank irradiation in pediatric renal tumors: A single center experience. Radiother Oncol. 2021 Mar;156:62-68. doi: 10.1016/j.radonc.2020.12.010. Epub 2020 Dec 11. PMID: 33310005.

[11] Dávila Fajardo R, Oldenburger E, Rübe C, et al. Evaluation of boost irradiation in patients with intermediate-risk stage III Wilms tumor with positive lymph nodes only: Results from the SIOP-WT-2001 Registry. Pediatr Blood Cancer. 2018;65:1–7.

[12] Poppe MM, Tai A, Li XA, et al. Kidney Disease in Childhood Cancer Survivors Treated with Radiation Therapy: A PENTEC Comprehensive Review. Int J Radiat Oncol Biol Phys. 2024 Jun 1;119(2):560-574.

[13] Arunagiri N, Kelly SM, Dunlea C, et al. The spleen as an organ at risk in pediatric radiotherapy: A SIOP-Europe Radiation Oncology Working Group report. Eur J Cancer. 2020; 143:1-10. doi: 10.1016/j.ejca.2020.10.025

[14] De Vathaire F, El-Fayech C, Ben Ayed FF, et al. Radiation dose to the pancreas and risk of diabetes mellitus in childhood cancer survivors: A retrospective cohort study. Lancet Oncol. 2012;13:1002–1010.

[15] Weil BR, Murphy AJ, Liu Q, et al. Late Health Outcomes Among Survivors of Wilms Tumor Diagnosed Over Three Decades: A Report from the Childhood Cancer Survivor Study. J Clin Oncol. 2023 May 10;41(14):2638-2650.

[16] Hall MD, Howell RM, Jackson A, et al. Liver Late Effects in Childhood Cancer Survivors Treated With Radiation Therapy: A PENTEC Comprehensive Review. Int J Radiat Oncol Biol Phys. 2024 Jun 1;119(2):575-587.

[17] Bates JE, Rancati T, Keshavarz H, et al. Cardiac Disease in Childhood Cancer Survivors Treated With Radiation Therapy: A PENTEC Comprehensive Review. Int J Radiat Oncol Biol Phys. 2024 Jun 1;119(2):522-532.

[18] Briere TM, Agrusa JE, Martel MK, et al. Acute and Late Pulmonary Effects After Radiation Therapy in Childhood Cancer Survivors: A PENTEC Comprehensive Review. Int J Radiat Oncol Biol Phys. 2024 Jun 1;119(2):533-548.

[19] Lo AC, Ronckers C, Aznar MC, et al. Breast Hypoplasia and Decreased Lactation From Radiation Therapy in Survivors of Pediatric Malignancy: A PENTEC Comprehensive Review. Int J Radiat Oncol Biol Phys. 2024 Jun 1;119(2):549-559.

[20] Mulder RL, Hudson MM, Bhatia S, et al. Updated Breast Cancer Surveillance Recommendations for Female Survivors of Childhood, Adolescent, and Young Adult Cancer From the International Guideline Harmonization Group. J Clin Oncol. 2020 Dec 10;38(35):4194-4207.

[21] Hoeben BA, Carrie C, Timmermann B, Mandeville HC, Gandola L, Dieckmann K, Ramos Albiac M, Magelssen H, Lassen-Ramshad Y, Ondrová B, Ajithkumar T, Alapetite C, Balgobind BV, Bolle S, Cameron AL, Davila Fajardo R, Dietzsch S, Dumont Lecomte D, van den Heuvel-Eibrink MM, Kortmann RD, Laprie A, Melchior P, Padovani L, Rombi B, Scarzello G, Schwarz R, Seiersen K, Seravalli E, Thorp N, Whitfield GA, Boterberg T, Janssens GO. Management of vertebral radiotherapy dose in paediatric patients with cancer: consensus recommendations

from the SIOPE radiotherapy working group. Lancet Oncol. 2019 Mar;20(3):e155-e166. doi: 10.1016/S1470-2045(19)30034-8. PMID: 30842059.

[22] Groenendijk A, van Tinteren H, de Krijger RR, Vujanic G, Al-Saadi R, Pritchard-Jones K, Ramírez-Villar GL, Melchior P, Godzinski J, Schenk JP, Graf N, Segers H, Sudour-Bonnange H, Verschuur AC, Drost J, Perotti D, Al-Jilaihawi S, Brok J, van den Heuvel-Eibrink MM, Spreafico F, Mavinkurve-Groothuis AMC. Outcome of patients with a first relapse after intermediate- or high-risk Wilms tumor, treated according to SIOP WT 2001/UK-IMPORT study; A report from the SIOP renal tumor study group. Urol Oncol. 2025 Sep;43(9):525.e19-525.e32. doi: 10.1016/j.urolonc.2025.05.018. Epub 2025 Jun 21. PMID: 40545412.

[23] Meier CM, Fuchs J, von Schweinitz D, Stein R, Wagenpfeil S, Kager L, Schenk JP, Vokuhl C, Melchior P, Welter N, Furtwängler R, Graf N. Surgical Factors Influencing Local Recurrence and Outcome in the Treatment of Unilateral Nephroblastoma. Ann Surg. 2023 Aug 1;278(2):e360-e367. doi: 10.1097/SLA.0000000000005690. Epub 2022 Aug 26. PMID: 36017935.

[24] Wens FSPL, Zonca F, van Tinteren H, Timmermann B, Laprie A, Boterberg T, Gaze M, Lim P, Jazmati D, Dieckmann K, Vennarini S, Melchior P, Weber B, Albiac MR, Szulc A, Grigorenko V, Magelssen H, van Beek K, Graf N, Papadakis V, Neggers SJCMM, van den Heuvel-Eibrink MM, Janssens GO, Polak R. Late toxicity after upper abdominal radiotherapy in pediatric Wilms tumor and neuroblastoma survivors. A systematic review on behalf of SIOPEN and SIOP-RTSG. Radiother Oncol. 2025 Aug;209:110961. doi: 10.1016/j.radonc.2025.110961. Epub 2025 May 27. PMID: 40441488.

[25] Owens CA, Ludmir EB, Liu Q, Qiu W, Gupta AC, Smith SA, Rigaud B, Brock KK, Bates JE, Meyers TG, Paulino AC, Peterson CB, Kry SF, Teepen JC, Ronckers CM, Neglia JP, Leisenring

WM, Oeffinger KC, Nathan PC, Turcotte LM, Hodgson DC, Hudson MM, Robison LL, Moskowitz CS, Armstrong GT, Henderson TO, Yasui Y, Howell RM. Colorectal-Specific Radiation Dose and Chemotherapy Risk for Subsequent Colorectal Malignancies in Childhood Cancer Survivors: A Childhood Cancer Survivor Study (CCSS) Report. J Clin Oncol. 2025 Nov;43(31):3403-3421. doi: 10.1200/JCO-25-00531. Epub 2025 Oct 1. PMID: 41032739; PMCID: PMC12573684.

[26] Weil BR, Madenci AL, Liu Q, Howell RM, Gibson TM, Yasui Y, Neglia JP, Leisenring WM, Smith SA, Tonorezos ES, Friedman DN, Constine LS, Tinkle CL, Diller LR, Armstrong GT, Oeffinger KC, Weldon CB. Late Infection-Related Mortality in Asplenic Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study. J Clin Oncol. 2018 Jun 1;36(16):1571-1578. doi: 10.1200/JCO.2017.76.1643. Epub 2018 Apr 17. PMID: 29664715; PMCID: PMC5978467.

[27] Meacham LR, Sklar CA, Li S, Liu Q, Gimpel N, Yasui Y, Whitton JA, Stovall M, Robison LL, Oeffinger KC. Diabetes mellitus in long-term survivors of childhood cancer. Increased risk associated with radiation therapy: a report for the childhood cancer survivor study. Arch Intern Med. 2009 Aug 10;169(15):1381-8. doi: 10.1001/archinternmed.2009.209. PMID: 19667301; PMCID: PMC3529471.

[28] Dieffenbach BV, Liu Q, Murphy AJ, Stein DR, Wu N, Madenci AL, Leisenring WM, Kadan-Lottick NS, Christison-Lagay ER, Goldsby RE, Howell RM, Smith SA, Oeffinger KC, Yasui Y, Armstrong GT, Weldon CB, Chow EJ, Weil BR. Late-onset kidney failure in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Eur J Cancer. 2021 Sep;155:216-226. doi: 10.1016/j.ejca.2021.06.050. Epub 2021 Aug 11. PMID: 34391054; PMCID: PMC8429192.

[29] Green DM, Wang M, Krasin M, Srivastava D, Onder S, Jay DW, Ness KK, Greene W, Lanctot JQ, Shelton KC, Zhu L, Mulrooney DA, Ehrhardt MJ, Davidoff AM, Robison LL, Hudson MM. Kidney Function after Treatment for Childhood Cancer: A Report from the St. Jude Lifetime Cohort Study. J Am Soc Nephrol. 2021 Apr;32(4):983-993. doi: 10.1681/ASN.2020060849. Epub 2021 Mar 2. PMID: 33653686; PMCID: PMC8017532.

[30] Hol JA, Lopez-Yurda MI, Van Tinteren H, Van Grotel M, Godzinski J, Vujanic G, Oldenburger F, De Camargo B, Ramírez-Villar GL, Bergeron C, Pritchard-Jones K, Graf N, Van den Heuvel-Eibrink MM. Prognostic significance of age in 5631 patients with Wilms tumour prospectively registered in International Society of Paediatric Oncology (SIOP) 93-01 and 2001. PLoS One. 2019 Aug 19;14(8): e0221373. doi: 10.1371/journal.pone.0221373. PMID: 31425556; PMCID: PMC6699693.

[31] Mul J, Melchior P, Seravalli E, Saunders D, Bolle S, Cameron AL, Gurtner K, Harrabi S, Lassen-Ramshad Y, Lavan N, Magelssen H, Mandeville H, Boterberg T, Kroon PS, Kotte ANTJ, Hoeben BAW, van Rossum PSN, van Grotel M, Graf N, van den Heuvel-Eibrink MM, Rübe C, Janssens GO. Inter-clinician delineation variation for a new highly-conformal flank target volume in children with renal tumors: A SIOP-Renal Tumor Study Group international multicenter exercise. Clin Transl Radiat Oncol. 2021 Mar 11;28:39-47. doi: 10.1016/j.ctro.2021.03.001. PMID: 33796796; PMCID: PMC7995478.

[32] Padovani L, Huchet A, Claude L, Bernier V, Quetin P, Mahe M, Laprie A, Kerr C, Bondiau PY, Delarue A, Coze C, Gibon D, Barteau C, Maire JP, Carrie C, Muracciole X. Inter-clinician variability in making dosimetric decisions in pediatric treatment: a balance between efficacy and late effects. Radiother Oncol. 2009 Nov;93(2):372-6. doi: 10.1016/j.radonc.2009.05.024. Epub 2009 Aug 3. PMID: 19647884.

[33] Kelly SM, Effeney R, Gaze MN, Bernier-Chastagner V, Blondeel A, Clementel E, Corning C, Dieckmann K, Essiaf S, Gandola L, Janssens GO, Kearns PR, Lacombe D, Lassen-Ramshad Y, Merks H, Miles E, Padovani L, Scarzello G, Schwarz R, Timmermann B, van Rijn RR, Vassal G, Boterberg T, Mandeville HC; QUARTET Project and the SIOPE Radiation Oncology Working Group. QUARTET: A SIOP Europe project for quality and excellence in radiotherapy and imaging for children and adolescents with cancer. Eur J Cancer. 2022 Sep;172:209-220. doi: 10.1016/j.ejca.2022.05.037. Epub 2022 Jun 30. PMID: 35780527.

[34] Fitzgerald TJ, Followill D, Laurie F, Boterberg T, Hanusik R, Kessel S, Karolczuk K, Iandoli M, Ulin K, Morano K, Bishop-Jodoin M, Kry S, Lowenstein J, Molineu A, Moni J, Cicchetti MG, Prior F, Saltz J, Sharma A, Mandeville HC, Bernier-Chastagner V, Janssens G. Quality assurance in radiation oncology. Pediatr Blood Cancer. 2021 May;68 Suppl 2(Suppl 2):e28609. doi: 10.1002/pbc.28609. PMID: 33818891; PMCID: PMC10578132.

[35] Kelly SM, Turcas A, Corning C, Bailey S, Cañete A, Clementel E, di Cataldo A, Dieckmann K, Gaze MN, Horan G, Jenney M, Ladenstein R, Padovani L, Valteau-Couanet D, Boterberg T, Mandeville H. Radiotherapy quality assurance in paediatric clinical trials: first report from six QUARTET-affiliated trials. Radiother Oncol. 2023 May;182:109549. doi: 10.1016/j.radonc.2023.109549. Epub 2023 Feb 23. PMID: 36828140.

[36] Ding M, Maspero M, Littooij AS, van Grotel M, Fajardo RD, van Noesel MM, van den Heuvel-Eibrink MM, Janssens GO. Deep learning-based auto-contouring of organs/structures-at-risk for pediatric upper abdominal radiotherapy. Radiother Oncol. 2025 Jul;208:110914. doi: 10.1016/j.radonc.2025.110914. Epub 2025 May 4. PMID: 40328363.

[37] Ding M, Maspero M, Harrabi S, Jouglar E, Vennarini S, Spencer T, Weber B, Magelssen H, Van Beek K, Stoica R, Saldi S, Boterberg T, Melchior P, van den Heuvel-Eibrink MM, Janssens

GO. Impact of deep learning on CT-based organ-at-risk delineation for flank irradiation in paediatric renal tumours: a SIOP-RTSG radiotherapy committee study. Clin Transl Radiat Oncol. 2025 Sep 19;56:101051. doi: 10.1016/j.ctro.2025.101051. PMID: 41141653; PMCID: PMC12553021.

Figure captions

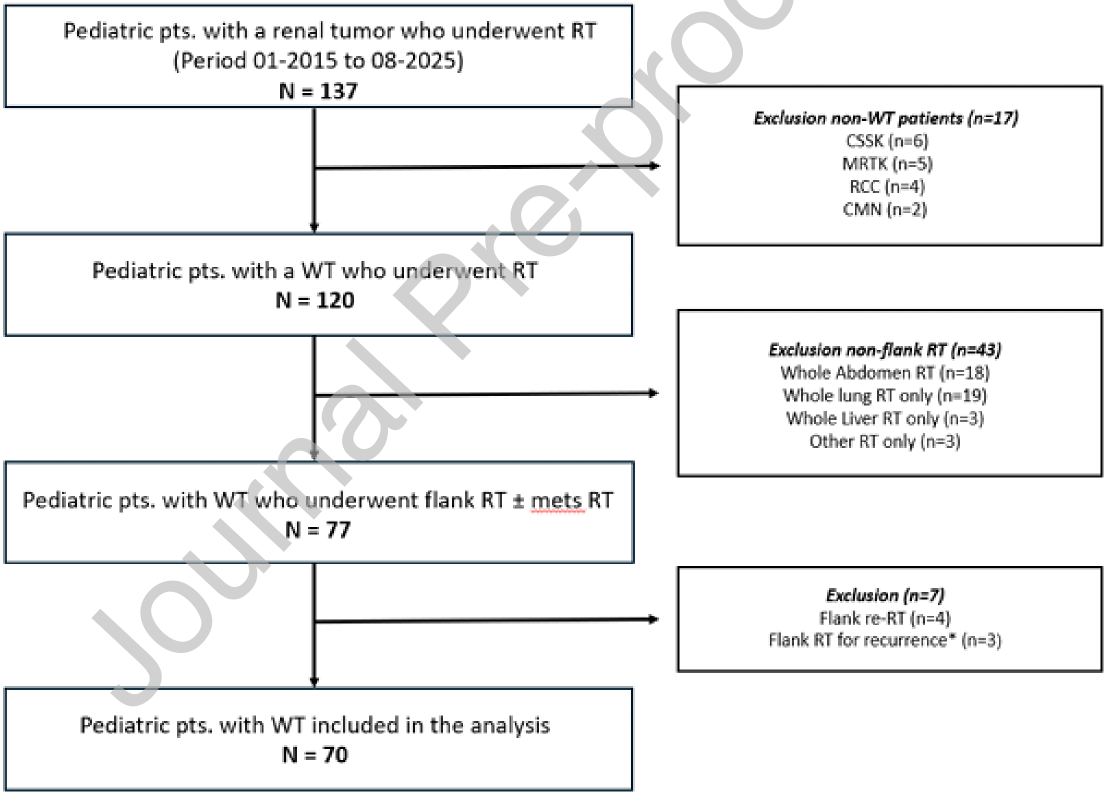

Figure 1. Flowchart

Abbreviations: Pts. = patients; RT = radiotherapy; N,n = number; WT = Wilms Tumor; CSSK= Clear Cell Sarcoma of the Kidney; MRTK = Malignant Rhabdoid Tumor of the Kidney; RCC = Renal Cell Carcinoma; re-RT = re-irradiation.

* Patients who initially didn't have an indication for flank irradiation and who developed a local recurrence.

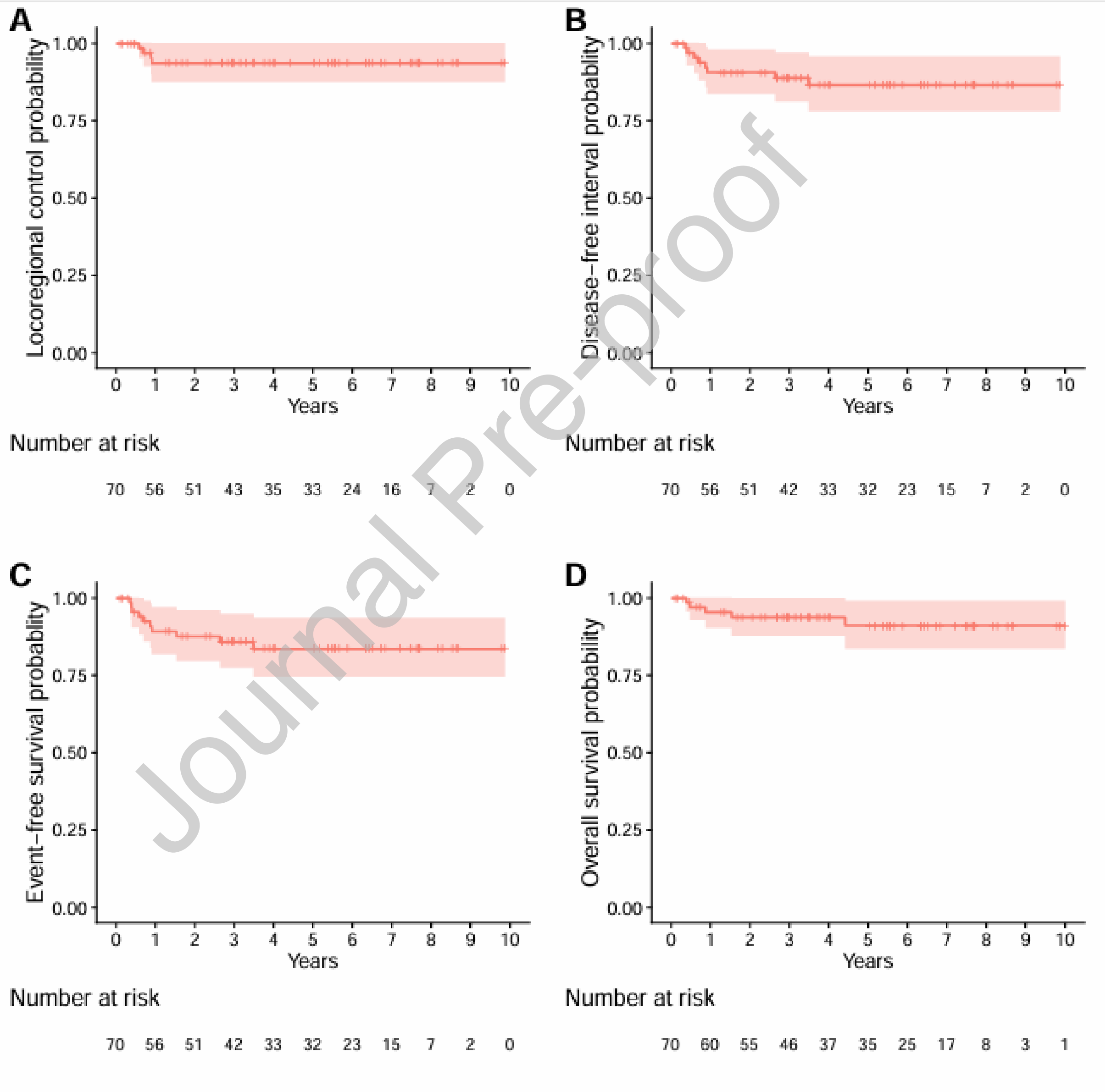

Figure 2. The estimated survival curves (with confidence intervals) of locoregional control (A), disease-free interval (B), event-free survival (C), and overall survival (D).

Table 1. Patient and tumor characteristics of the irradiated cohort (n=70).

	Number (n=70)	Percentage (%)
Patient Characteristics		
Gender		
Male	37	52.9
Female	33	47.1
Age at diagnosis (years)		
Median (range)	3.7 (0.6-18.9)	
Follow-up (years)		
Median (range)	4.7 (0.1-10.0)	
Tumor Characteristics		
Overall Stage		
II	6	8.6
III	26	37.1
IV	29	41.4
V without metastasis	7	10.0
V with metastasis	2	2.9
Local Highest Stage		
II	11	15.7
III	59	84.3

Histology		
IR-Epithelial type	1	1.4
IR-Stromal type	8	11.4
IR-Mixed type	20	28.6
IR-Regressive type	22	31.4
HR-Blastemal type	3	4.3
HR-Diffuse anaplasia type	16	22.9
Reason for Local Stage III		
SM+ only	15	21.4
LN+ only	20	28.6
IVC thrombus +	2	2.9
IVC thrombus+ and SM+	8	11.4
IVC thrombus+ and LN+	2	2.9
LN+ and SM+	11	15.7
LN+ and SM+ and IVC thrombus+	1	1.4

Abbreviations: WT = Wilms Tumor, IR = Intermediate-risk, HR = High-risk, RT = Radiotherapy, Gy = Gray, LN = Lymph Node, SM = Section Margin, IVC = Inferior Vena Cava.

Table 2. Treatment characteristics of the irradiated cohort (n=70).

	Number (n=70)	Percentage (%)
Surgery		
Total nephrectomy	65	92.9
Partial nephrectomy	5	7.1
Radiotherapy		
Time from surgery to start of RT (weeks)		
Flank ± para-aortic LN		
Median (range)	4.1 (2.7-16.7)	
Flank ± para-aortic LN and lungs		
Median (range)	12.6 (2.6-19.6)	
Radiotherapy volume		
Flank only	29	41.4
Flank + Para-aortic LN	21	30.0
Flank ± Para-aortic LN and Lung		
Synchronous	15	21.4
Metachronous	2	2.9
Flank ± Para-aortic LN, Lung and Liver		
Synchronous	1	1.4
Flank ± Para-aortic LN and Vertebrae		
Synchronous	2	2.9

Radiation elective dose		
Flank ± para-aortic LN		
14.4 Gy	51	72.8
25.2 Gy	19	27.2
Lung		
12 Gy	12	17.1
15 Gy	6	8.5
Vertebra		
14.4 Gy	2	2.9
Liver		
14.4 Gy	1	1.4
Radiation boost dose		
Flank ± para-aortic LN		
SEQ 25.2 Gy	3	4.2
SIB 22 Gy	2	2.9
32.2 Gy	1	1.4
Lung		
SIB 22 Gy	9	12.8
27.5 Gy	3	4.2
32 Gy	2	2.8
Liver		
22 Gy	1	1.4

Abbreviations: RT = Radiotherapy, Gy = Gray, LN = Lymph Node, SEQ = sequential boost, SIB= simultaneous integrated boost.

Table 3. Patients with a locoregional failure as first event.

Patient (Number)	Stage + Risk group (Overall, local)	Target Volumes-RT1	Dose-RT1 (Gy)	Failure (Site, interval)	Locoregional failure analysis				Dose-RT2 (Gy)	Outcome (Type, interval)
					(Location)	(Type)	(V95%: recurr-IMAT)	(V95%: recurr-AP-PA)		
1	III, III + IR	Flank L	14.4/1.8	LF + RF + DF (M1PUL), 0.9 y	Ipsilateral adrenal gland	Infield	100%	100%	WLI 12/1.5 SIB 22/2.75*	NED, 8.9 y post-RT2
					Contralateral paravertebral space	Outfield	1,2%	81,0%		
2	III, III + IR	Flank L, IVC	14.4/1.8	RF + AF, 0.6 y	VCI	Marginal	93%	97%	WAI 15/1.5 SIB 20/2*	NED, 4.8 y post-RT2

3	III, III + IR	Flank R, IVC	14.4/1.8 SIB 22/2.75	LF + DF (M1PUL), 0.9 y	Dorsally to the right liver lobe	Infield	100%	100%	WLI 12/1.5 SIB 22/2.75*	NED, 2.4 y post-RT2
4	IV, III + IR	Flank R, Para-Ao LN, WLI	WLI 12/1.5 14.4/1.8	LF, 0.7 y	Inferior rim of the liver	Marginal	32,1%	100%	25.2/1.8	NED, 0.9 y post-RT2

Abbreviations: L = Left, R = Right, IR = Intermediate-risk, IVC = Inferior Vena Cava, RT1 = Radiotherapy Course 1, Gy = Gray, Para- Ao LN = Para-aortic lymph nodes, WLI = Whole Lung Irradiation, SIB = Simultaneous Integrated Boost, LF = local failure, RF= regional failure, DF = distant failure, AF = abdominal failure, y = years, M1 PUL = pulmonary metastasis, WAI = whole abdomen irradiation, V95% recurr- IMAT = volume of the GTV at recurrence receiving 95% of the prescribed dose in the IMAT planning technique during course 1, V95% recurr- AP-PA = volume of the GTV at recurrence receiving 95% of the prescribed dose when using conventional volumes in combination with a AP-PA planning technique, NED = no evidence of disease.

[*] The dose received by all sites of macroscopic recurrence.

Table 4. Organ at risk constraint violations per patient in the cohort (N=70)

PATIENT	**GENDER**	**FLANK**	**WLI**	**DOSE FIANK** (elective dose + boost)	**KIDNEY CONTRA** (CKD)[12]	**HEART** (cardiac effects)[17]	**SPLEEN** (functional asplenia)[13]	**PANCREAS TAIL** (diabetes)[14]	**BOWEL** (obstruction) [15]	**LIVER** (SOS)[16]	**MAMMA LEFT** (hypoplasia)[19]	**MAMMA RIGHT** (hypoplasia)[19]	**MAMMA LEFT** (SMN)[20]	**MAMMA RIGHT** (SMN)[20]
					<8 Gy	<10 Gy	<10 Gy	<10 Gy	<20 Gy	<10 Gy	<1Gy	< 1Gy	<10 Gy	<10 Gy
1	M	L	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟦	🟦	🟩	🟩
2	F	L	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
3	M	L	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟦	🟦	🟩	🟩
4	F	L	0	14,4	🟩	🟩	🟨	🟩	🟩	🟩	🟩	🟩	🟩	🟩
5	F	L	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
6	F	L	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟨	🟩	🟩
7	M	L	0	14,4	🟩	🟩	🟥	🟩	🟩	🟩	🟦	🟦	🟩	🟩
8	M	L	0	14,4	🟩	🟩	🟩	🟨	🟩	🟩	🟦	🟦	🟩	🟩
9	F	L	0	14,4	🟩	🟩	🟩	🟨	🟩	🟩	🟨	🟨	🟩	🟩
10	M	L	0	14.4	🟩	🟩	🟩	🟩	🟩	🟩	🟦	🟦	🟩	🟩
11	M	L	0	14,4	🟩	🟩	🟩	🟨	🟩	🟩	🟦	🟦	🟩	🟩
12	F	L	0	14,4	🟩	🟩	🟩	🟨	🟩	🟩	🟨	🟨	🟩	🟩
13	M	L	0	14,4 + 10,8	🟩	🟩	🟩	🟥	⬜	🟩	🟦	🟦	🟩	🟩
14	M	L	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟦	🟦	🟩	🟩
15	M	L	0	14,4 + 10,8	🟩	🟩	🟩	⬜	🟩	🟨	🟦	🟦	🟩	🟩
16	F	L	0	14,4	🟩	🟩	🟩	🟨	🟩	🟩	🟩	🟩	🟩	🟩
17	F	L	0	14,4	🟩	⬜	🟨	🟥	🟩	🟩	⬜	⬜	⬜	⬜
18	M	L	0	14,4	🟩	🟩	🟩	⬜	⬜	🟩	🟦	🟦	⬜	⬜
19	M	L	1	14.4	🟩	🟩	🟩	🟩	🟩	🟩	🟦	🟦	🟩	🟩
20	F	L	1	14,4 + 10,8*	🟩	🟩	🟨	🟥	🟩	🟩	🟥	🟥	🟩	🟩
21	M	L	1	14,4	🟩	🟩	🟨	🟥	🟩	🟩	🟦	🟦	🟩	🟩
22	M	L	1	14,4	🟩	🟨	🟥	🟥	🟩	🟩	🟦	🟦	⬜	⬜
23	M	L	0	25.2	🟩	🟩	🟥	🟩	🟩	🟩	🟦	🟦	🟩	🟩
24	M	L	0	25.2	🟩	🟩	🟩	🟥	🟩	🟩	🟦	🟦	🟩	🟩
25	M	L	0	25.2	🟩	🟩	🟥	🟥	⬜	🟥	🟦	🟦	🟩	🟩
26	F	L	0	25.2	🟩	⬜	🟥	⬜	⬜	🟩	⬜	⬜	⬜	⬜
27	M	L	1	25.2	🟨	🟨	🟥	🟥	🟩	🟨	🟦	🟦	🟩	🟩
28	M	L	1	25.2	🟩	🟩	🟥	🟥	🟩	🟩	🟦	🟦	🟩	🟨
29	M	L	1	25.2	🟩	🟨	🟥	🟥	🟩	🟨	🟦	🟦	🟩	🟩
30	M	L	1	25.2	🟩	🟩	🟥	🟥	🟩	🟩	🟦	🟦	🟩	🟩
31	F	L	1	25.2	🟩	🟩	🟥	🟥	🟩	🟨	🟥	🟥	🟩	🟩
32	M	L	1	25.2	🟩	🟨	🟥	🟥	🟩	🟥	🟦	🟦	🟥	🟥
33	M	R	0	14.4	🟩	🟩	🟩	🟩	🟩	🟩	🟦	🟦	🟩	🟩
34	F	R + L	0	12 L, 14,4 R	🟦	🟩	🟩	🟨	🟩	🟩	🟩	🟩	🟩	🟩
35	M	R	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟦	🟦	🟩	🟩
36	F	R	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
37	M	R	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟦	🟦	🟩	🟩
38	M	R	0	14,4 + 10,8 *	🟩	🟩	🟩	🟩	🟩	🟨	🟦	🟦	🟩	🟩
39	M	R	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟦	🟦	🟩	🟩
40	F	R	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
41	F	R	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
42	M	R	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟦	🟦	🟩	🟩
43	F	R	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
44	F	R	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
45	F	R	0	14,4	🟩	🟩	🟩	🟩	⬜	🟩	🟩	🟨	🟩	🟩
46	F	R	0	14,4 + 10,8	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
47	F	R	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟨	🟩	🟩
48	M	R	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟦	🟦	🟩	🟩
49	M	R	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟦	🟦	🟩	🟩
50	F	R	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
51	F	R	0	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
52	F	R	0	14,4	🟩	🟩	🟩	🟩	🟩	🟨	🟨	🟨	🟩	🟩
53	F	R	0	14,4	🟩	🟩	🟩	⬜	⬜	🟩	⬜	⬜	⬜	⬜
54	F	R	0	14,4	🟩	🟩	🟩	⬜	⬜	🟩	🟩	🟩	🟩	🟩
55	F	R	1	14,4	🟩	🟨	🟩	🟩	🟩	🟦	🟥	🟥	🟩	🟩
56	`M	R	1	14,4	🟩	🟩	🟩	🟨	🟩	🟨	🟦	🟦	🟩	🟩
57	F	R	1	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟥	🟥	🟩	🟩
58	M	R	1	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟦	🟦	🟩	🟩
59	M	R	1	14,4	🟩	🟩	🟩	🟩	🟩	🟩	🟦	🟦	🟩	🟩
60	F	R	1	14,4	🟩	🟨	🟩	🟨	⬜	🟨	🟥	🟥	🟩	🟩
61	F	R	1	14,4	🟩	🟩	🟩	⬜	🟩	🟩	🟥	🟥	🟩	🟩
62	F	R	0	25,2	🟩	🟩	🟩	🟩	🟩	🟥	🟩	🟩	🟩	🟩
63	M	R	0	25,2	🟩	🟩	🟩	🟩	🟩	🟩	🟦	🟦	🟩	🟩
64	M	R	0	25,2	🟩	🟩	🟩	🟩	🟩	🟥	🟦	🟦	🟩	🟩
65	F	R	0	25,2	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
66	F	R	0	25,2	🟩	🟩	🟩	🟩	🟩	🟨	🟩	🟩	🟩	🟩
67	F	R	0	25,2	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
68	M	R	0	25,2	🟩	🟩	🟩	🟨	🟩	🟩	🟦	🟦	🟩	🟩
69	M	R	1	25,2 + 10,8*	🟩	🟨	🟨	🟩	🟩	🟥	🟦	🟦	🟩	🟩

70	M	R	1	25,2	🟩	🟩	🟩	🟩	🟩	🟥	🟦	🟦	🟩	🟩

Green cell = no violation; Orange cell = minor violation (≤2.0 Gy); Red Cell = major violation (> 2.0 Gy); Blue cell = Not applicable; White cell = D_{mean} of organ not available

Abbreviations: M = male; F = female; L = left; R = right; WLI = whole lung irradiation; Gy = Gray; CKD = chronic kidney disease; SMN = secondary malignant neoplasm; SOS = Sinusoidal Obstruction Syndrome.

* Boost dose for the flank residue was delivered using an equivalent simultaneous integrated boost fractionation scheme.

**Patient received also concomitantly whole liver irradiation (14.4 Gy).