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Original Article

The contribution of surgical clips for optimizing highly-conformal image-guided flank irradiation in pediatric renal tumors: A single center experience

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Background and aims: Two-opposing photon beams are considered standard of care for flank irradiation in pediatric patients with renal tumors. Nowadays, Image-Guided Radiotherapy (IGRT) techniques allow high-precision dose delivery to complex flank target volumes taking into account postoperative organ shifts and tumor bed motion. This study examines the contribution of a lateral and superior surgical clip on flank target volume delineation intended for IGRT.

Methods: Between 01-2015 and 09-2019, 30/162 newly-diagnosed pediatric patients with renal tumors, lateral/superior surgical clips (n = 30/30) and available 4D-CT-scans (n = 27/30), underwent postoperative flank irradiation. The lateral and superior clip, as respective markers for the lateral tumor extension and intrafraction motion, were analyzed. The positive and negative values depict the lateral/dorsal/cranial or the medial/ventral/caudal direction, respectively. Planning target volumes (PTV) were generated based on lateral clips ($PTV_{latclip}$), superior clips with 4D-CT technology ($PTV_{supclip}$), and both clips combined ($PTV_{combined}$), and compared to an approach without clips (PTV_{noclip}).

Results: Indicated by clips, the mean lateral tumor bed extension along the posterior wall was 74° (range: 50°–93°), while mean intrafraction motion was +1.2 mm (range: −1.8/+4.8 mm), +0.6 mm (range: +0.6/+4.9 mm), −0.3 mm (range: −3.8/+0.7 mm) in craniocaudal, ventrodorsal, mediolateral direction, respectively. The median PTV_{noclip} (556 mL) was statistically different from the median $PTV_{latclip}$ (454 mL, p = <0.01), median $PTV_{supclip}$ (373 mL, p = <0.01) and median $PTV_{combined}$ (348 mL p = <0.01).

Conclusion: In pediatric patients with renal tumors, surgical clips at the lateral and superior border of the tumor bed can optimize flank target volume delineation and, consequently, reduce the normal tissue volume receiving high-dose irradiation when IGRT techniques are applied.

Around 5–6% of children with cancer are diagnosed with a renal tumor [1]. Recently, the Renal Tumor Study Group (RTSG) of the International Society for Pediatric Oncology (SIOP) initiated the SIOP-RTSG-UMBRELLA 2016 protocol (hereafter the UMBRELLA protocol). In the UMBRELLA protocol, the standard treatment regimen for pediatric renal cancer patients older than 6 months consists of 4–6 weeks of chemotherapy followed by surgery [2,3]. Based on stage and histology, patients with a higher risk of locoregional relapse receive postoperative flank irradiation in addition to postoperative chemotherapy. Indications for flank irradiation are diffuse anaplastic Wilms tumor (WT) stage II, WT stage III with intermediate- and high-risk histology, Malignant Rhabdoid Tumors of the Kidney (MRTK) stage I–III, and Clear Cell Sarcoma of the Kidney (CCSK) stage II–III [2–4]. It is estimated that 20–25% of all patients require postoperative flank irradiation as part of their first line treatment [5].

Since SIOP-1 (1971–1974), the standard technique for abdominal irradiation has been two-opposing or anterior-posterior/posterior-anterior (AP/PA) photon beams [6]. Nowadays, many radiotherapy departments are gaining access to advanced Image-Guided

Abbreviations: SIOP-RTSG, International Society of Pediatric Oncology – Renal Tumor Study Group; WT, Wilms tumor; MRTK, Malignant Rhabdoid Tumor of the Kidney; CCSK, Clear Cell Sarcoma of the Kidney; AP/PA, anterior-posterior/posterior-anterior; IGRT, Image-Guided Radiotherapy; COM, center of mass; $GTV\text{-}T_{pre/post}$, preoperative/postoperative Gross Tumor Volume; CTV, Clinical Target Volume; ITV, Internal Target Volume; PTV, Planning Target Volume.

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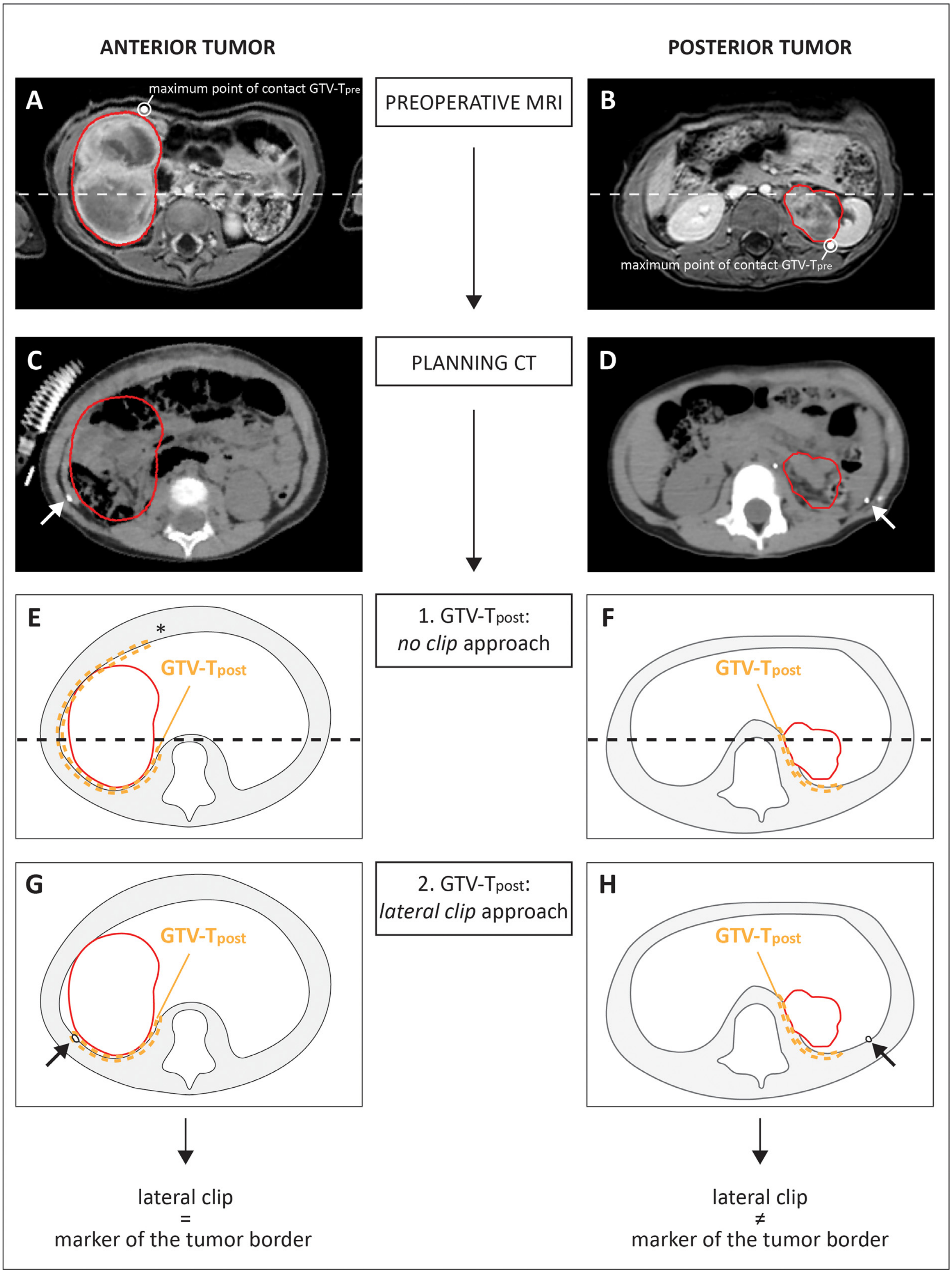

Fig. 1. The benefit of the lateral clip for the GTV-T_{post} reconstruction in case of anteriorly and posteriorly located tumors. Axial abdominal MRI-section before surgery from a patient with a renal tumor arising from the right kidney that occludes the entire hemi-abdomen (anterior tumor) (1A), and a patient with a tumor arising from the left kidney that is located posteriorly (1B), with the corresponding postoperative CT-scan at the level of the lateral surgical clip (1C, 1D). The diagrams illustrate the GTV-T_{post} reconstruction without the use of clips (1E, 1F) and with use of a lateral clip (indicated by a black arrow) (1G, 1H). In case of an anterior tumor, the lateral clip demarcates the tumor border, and can reduce the lateral extension of the GTV-T_{post}. In the posterior tumor, the lateral clip is only an anatomical marker and has no influence on GTV-T_{post} delineation. Red: GTV-T_{pre}; orange: GTV-T_{post}. *Abbreviations*: GTV-$T_{pre/post}$, Gross Tumor Volume of the primary tumor before and after surgery.

Radiotherapy (IGRT) techniques that allow high-precision dose delivery to complex target volumes. Prompted by this development, radiation oncologists affiliated to the SIOP-RTSG reached consensus on a highly-conformal target volume definition for flank irradiation: it was hypothesized that intraperitoneal tumor recurrence is unlikely in patients without major tumor rupture [7]. This was based on the fact that renal tumors are covered by a peritoneal lining and push aside, rather than invade, the intraperitoneal organs and abdominal wall.

Decades ago, four radio-opaque clips were used to indicate the lateral, medial, superior and inferior border of the operative bed in pediatric patients with renal tumors. This enabled the radiation oncologist to reconstruct the preoperative tumor dimensions on postoperative abdominal X-rays [8]. After the introduction of 3D-radiotherapy treatment planning in the late nineties, the primary tumor, visible on the preoperative CT- or MRI-scan, could be reconstructed on the postoperative planning CT-scan using image coregistration. This has diminished the role of surgical clips to demarcate the preoperative tumor in children with renal cancer. However, it is conceivable that surgical clips could be used to optimize highly-conformal target volume delineation for flank irradiation using IGRT techniques.

In a considerable number of patients, the renal tumor remains large after preoperative chemotherapy, and reaches the anterior, ipsilateral abdominal wall without breach of the retroperitoneal fascia. Nevertheless, it is not feasible to determine the anterolateral extension of the retroperitoneal tumor bed on imaging only [9]. To correct for this uncertainty, the radiation oncologist is forced to include a section of the anterior abdominal wall within the target volume. However, when a lateral clip is placed at the level where the retroperitoneal dissection was initiated, the anterolateral extension of the tumor can be reconstructed on imaging. This might allow a safe reduction of the target volume in case of tumors with anterolateral extension preoperatively (Fig. 1). Furthermore, standardized margins for intra-fraction motion of 5 mm are recommended for treatment planning [3]. Evidence suggest that intra-fraction motion of the tumor bed in pediatric patients with an abdominal tumor is limited in most cases [10,11]. Since no macroscopic tumor is visible at the time of flank irradiation, surgical clips may also be used as a surrogate for tumor bed motion when 4D-CT technologies are applied. The largest intra-fraction motion differences are expected near the diaphragm, meaning the superior clip is the most sensitive marker for intra-fraction tumor bed motion [11].

The purpose of this analysis of pediatric patients with renal tumors is to gain insight in the anatomy of the retroperitoneal compartment on postoperative imaging with a lateral clip. In addition, intra-fraction motion of the tumor bed will be measured using a superior clip. Overall, this study aims to define the contribution of a lateral and a superior clip on the flank target volume delineation intended for IGRT.

Material and methods

Patient selection

Between January 2015 and September 2019, 162 newly-diagnosed pediatric patients with a renal tumor were treated in the Princess Máxima Center for Pediatric Oncology (Utrecht, The Netherlands). Those eligible for flank irradiation and treated at the department of radiation oncology of the University Medical Center Utrecht (Utrecht, the Netherlands), were consecutively included in this study (Institutional review board approval (WAG/mb/19/045212)). Prior to flank irradiation, all patients had

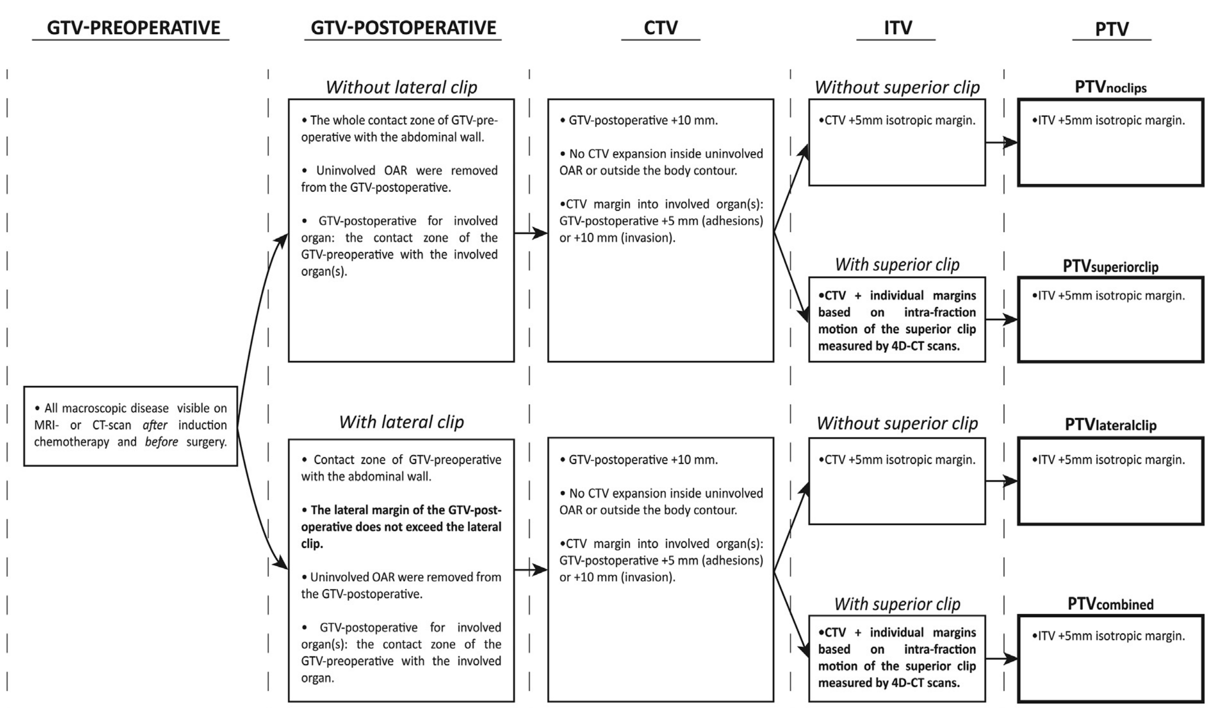

Fig. 2. A stepwise approach for generating PTVs for IGRT with the addition of surgical clips. For the $PTV_{latclip}$, the lateral clip limits the lateral extension of the postoperative GTV, while standardized intra-fraction motion margins of 5 mm are applied. Contrary, for the $PTV_{supclip}$, the postoperative GTV consist of the whole contact zone of the preoperative GTV, while intra-fraction motion margins are based on individual 4D-CT registration of the superior clip. To generate the $PTV_{combined}$, the lateral clip demarcating the lateral tumor extension, and the superior clip measuring intra-fraction motion, are both applied. *Abbreviations:* $GTV_{pre/post}$, Gross Tumor Volume before and after surgery, respectively; CTV, Clinical Target Volume; ITV, Internal Target Volume; PTV, Planning Target Volume; OAR, Organs At Risk; 4D-CT, four-dimensional Computerized Tomography.

received chemotherapy for 4 to 6 weeks, followed by a nephrectomy with lymph node sampling as per protocol. Imaging for flank irradiation consisted of a CT- or MRI-scan directly before surgery, which was rigidly coregistered to a planning CT scan in radiotherapy treatment position (Big Bore CT-scan, Philips Medical Systems, Best, The Netherlands, slice thickness 1 and 3 mm). Patients with incomplete imaging data and patients treated with partial nephrectomy were excluded.

Surgical clip placement

From January 2015, surgeons placed clips at the borders of the operative bed in line with the standard approach described in the UMBRELLA protocol [2]. At the lateral border of the operative bed, at least one clip was placed at the paracolic peritoneal reflection where the retroperitoneal dissection on the posterior wall was initiated. At the superior border of the operative bed, a clip was placed on or close to the diaphragm.

Lateral clip

For each patient, the lateral clip was delineated and analyzed on the postoperative planning CT-scan in radiotherapy treatment position. To allow equal comparison between all patients, the vertebrae were used as a reference landmark. In the axial slide, the position of each lateral clip along the posterior abdominal wall (A) was calculated as an angle ($\angle ABC$) with the anterior border of the corpus vertebrae as center reference point (B) and the dorsal intersection of the midline as zero point (C) and measured in degrees. In the cranio-caudal direction, the lateral clip location was represented by the vertebral level.

Superior clip

For 4D-CT imaging, respiratory trace measurements for pulmonary gating were obtained using a deformable rubber belt fixed to the patient's chest (Philips Bellow System, Best, The Netherlands). Each complete respiratory cycle during spontaneous breathing was registered as a series of ten phases acquired at equally distributed time intervals. In each patient, the superior clip was delineated at the point of maximum inspiration and maximum expiration. The difference between the center of mass (COM) of the superior clip at both breathing phases, with the maximum inspiration as reference phase, was used to calculate the maximum breathing displacement in all orthogonal directions, and measured in millimeter. The positive (+) and negative (−) values depict movement in the lateral, dorsal, and cranial direction or the medial, ventral and caudal direction, respectively.

Target volume comparison

For each patient, four virtual planning target volumes (PTV) were generated to calculate the impact of the lateral clip ($PTV_{latclip}$), the superior clip with 4D-CT imaging ($PTV_{supclip}$), and both clips combined ($PTV_{combined}$) on target volume delineation, compared to an approach without clips (PTV_{noclip}). All PTV's are intended for IGRT and based on the SIOP-RTSG working group delineation consensus for highly-formal flank irradiation [7]. A stepwise delineation approach for the target volumes is described in Fig. 2. The maximum anterior point of contact of gross tumor volume at time of surgery ($GTV\text{-}T_{pre}$) on the abdominal wall was measured as an angle to represent the anterolateral extension of the preoperative tumor. This angle was used as a cutoff value to stratify patients with an anterior tumor (anterolateral extension $GTV\text{-}T_{pre}$ > mean angle of the lateral clips) or with a posterior tumor (anterolateral extension $GTV\text{-}T_{pre} \leq$ mean angle of the lateral clips).

Statistical analysis

Descriptive statistics (mean, range and 95% CI) were used to analyze the lateral clip location and the 4D-CT registration of the superior clip. To compare the PTVs of the four different approaches, paired samples T-test was used for normally distributed variables and Wilcoxon signed-rank test for non-normally distributed variables. The PTV reduction by the lateral clip (i.e. PTV_{noclip} minus $PTV_{latclip}$) in patients with an anterior tumor was compared to patients with a posterior tumor using independent t-test for normally distributed variables and Mann-Whitney U test for non-normally distributed variables. Linear regression was used to determine the PTV reduction by the lateral clip (i.e. PTV_{noclip} minus $PTV_{latclip}$), and the PTV reduction by the superior clip (i.e. PTV_{noclip} minus $PTV_{supclip}$) in relation to the anterolateral extension of the preoperative tumor. A two-tailed *p*-value of <0.05 indicated statistical significance. Milliliters were used as the unit of measurement for PTV volumes. Data were analyzed using statistical software SPSS version 25.0 for Windows (SPSS, INC, Chicago, IL, USA).

Results

Of 162 newly-diagnosed patients with a renal tumor treated at the Princess Máxima Center for Pediatric Oncology, 37 patients received adjuvant radiotherapy of the flank. Seven patients were excluded from this analysis (partial nephrectomy: n = 5;

Table 1
Baseline characteristics.

	Total (n = 30)
Age at RT (in years)	
Median	3.2
Range	0.5 – 14.1
Gender	
Female	17
Male	13
Tumor lateralization	
Left-sided	12
Right-sided	18
Preoperative tumor volume after chemotherapy (mL)	
Median	167
Range	22–1679
Histology	
WT subtypes	
regressive	11
stromal	2
mixed	9
diffuse anaplastic	3
blastemal	1
CCSK	1
MRTK	3
LN positive	
yes	13
no	17
Positive resection margin	
yes	18
no	12
Local stage	
II	4
III	26
Stage	
II	4
III	14
IV	10
V	2

Abbreviations: RT, radiotherapy; WT, Wilms tumor; MRTK, Malignant Rhabdoid. Tumor of the Kidney; CCSK, Clear Cell Sarcoma of the Kidney; LN, lymph node involvement.

age ≥ 18 years old: $n = 1$; incomplete imaging data: $n = 1$). In total, 30 patients treated with flank irradiation using IGRT were included in this analysis. Patient- and tumor characteristics are listed in Table 1. All 30 patients received at least one clip at each of the two predetermined locations. Four dimensional-CT imaging available in 27 of the 30 patients and could not be performed in 3 patients due to very young age (<6 month old: $n = 2$) and logistic reasons ($n = 1$).

In a total of 30 patients, 44 clips were placed at the lateral border of the operative bed (14 of 30 patients received two lateral clips). The mean angle of the lateral clip on the posterior abdominal wall was 74° (range: 50°–93°; 95% CI: [71°, 77°]), with 80% of the clips located between 60° and 87°. Twenty-two of the 44 clips were located at the vertebral level L2 and L3 (Fig. 3).

The 4D-CT analysis of the superior clip showed a mean COM difference of +1.2 mm (range: −1.8 to +4.8 mm; 95% CI: [0.7, 1.8]), +0.6 mm (range: −0.6 to +4.9 mm; 95% CI: [−0.1, 1.0]), and −0.3 mm (range: −3.8 mm to +0.7 mm; 95% CI: [−0.6, 0.01]), for the craniocaudal, ventrodorsal and mediolateral direction, respectively (Fig. 4). Between maximum inspiration and expiration, a COM difference of >1 mm in the craniocaudal, ventrodorsal, and mediolateral direction was found in 17, 5 and 1 of the 30 patients, respectively.

The PTV's generated without the use of clips (median PTV_{noclip}: 556 mL) were statistically different from the PTV's generated with the use of a lateral (median $PTV_{latclip}$: 454 mL, $p = <0.01$), superior (median $PTV_{supclip}$: 373 mL, $p = <0.01$) and both clips combined (median $PTV_{combined}$: 348 mL, $p = <0.01$) (Supplementary Table S1). Compared to an approach without clips, the mean PTV reduction by the lateral, superior and both clips combined was 16%, 25% and 37%, respectively.

In patients with an anterior tumor ($n = 21$, median $GTV\text{-}T_{pre}$: 196 mL) compared to those with a posterior tumor ($n = 9$, median $GTV\text{-}T_{pre}$: 80 mL), the median PTV reduction by the addition of the lateral clip was 164 mL versus 0 mL ($p = <0.01$) (Fig. 5). For each added degree of anterolateral $GTV\text{-}T_{pre}$ extension, the PTV reduction by the lateral clip increased by 4 mL (95% CI: [2.7, 5.6], $p = <0.01$). The PTV reduction obtained by the addition of the superior clip was independent of the anterolateral $GTV\text{-}T_{pre}$ extension of the preoperative tumor (95% CI: [−1.2, 1.6], $p = 0.78$) (Fig. 5).

Discussion

The current study demonstrates that the application of surgical clips significantly reduces the target volume for highly-conformal flank irradiation by IGRT. With the combined use of a lateral clip, defining the lateral border of the postoperative tumor bed in case of large preoperative tumors, and a superior clip with 4D-CT technology, measuring intra-fraction tumor bed motion, a mean PTV reduction of 37% could be obtained. Moreover, the benefit of the lateral clip on target volume delineation increases proportionally with the anterolateral extension of the preoperative tumor above an angle of 74° projected on the abdominal wall, while the addition of a superior clip combined with 4D-CT technology reduces the PTV, independent of anterolateral extension.

For several other types of cancer, surgical clips have also been implemented to optimize radiotherapy treatment planning. In prostate cancer patients, fiducial markers are used for position verification of the target volume during stereotactic radiation therapy, leading to improved target volume coverage [12]. Also, surgical clips placed after breast conserving therapy improve the definition of the irradiated boost volume in patients with breast cancer

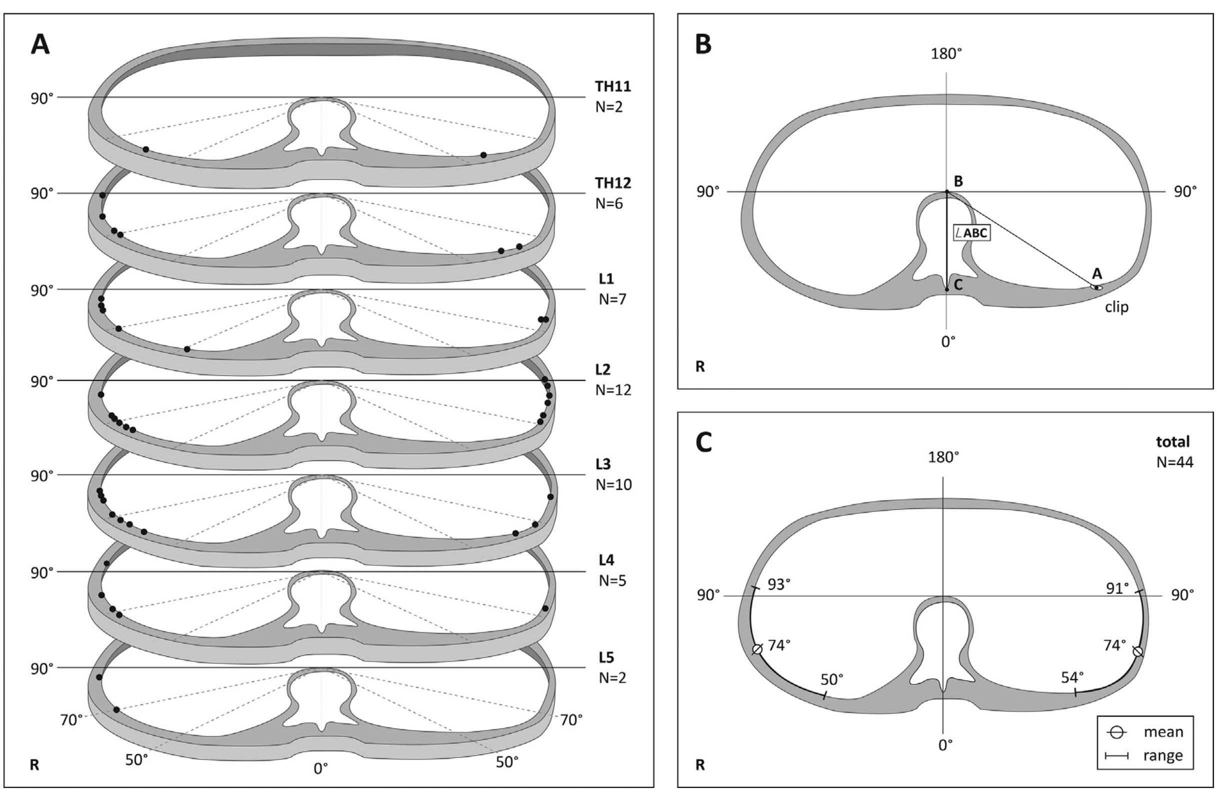

Fig. 3. Schematic representation of abdominal sections from vertebral levels Th11 to L5 with projection of all lateral clips ($n = 44$) on the posterior abdominal wall (3A). Dots depict individual lateral clips at each vertebral level. In the axial slide, the position of the lateral clip along the posterior abdominal wall (point A) was calculated as an angle (∠ABC) with the anterior border of the corpus vertebrae as center reference point (point B) and the dorsal intersection of the midline as zero point (point C) and measured in degrees (3B). The lower-right figure shows the distribution of all lateral clips per side (3C).

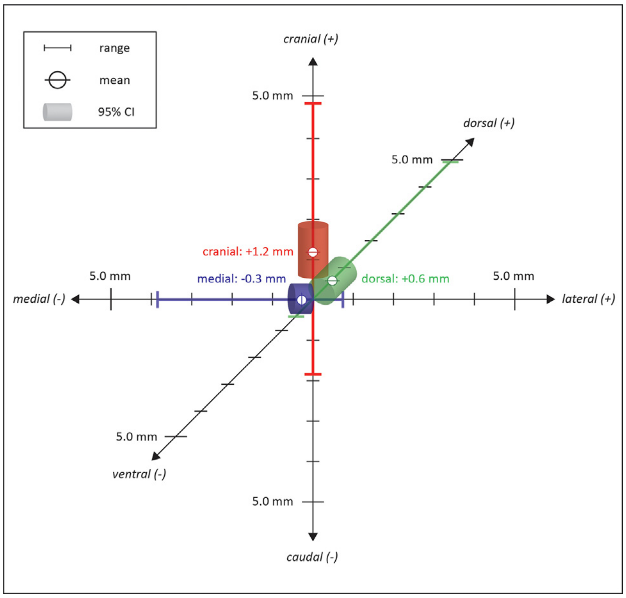

Fig. 4. Maximum displacement of the superior clip from inspiration to expiration in six orthogonal directions measured in 27 patients with a renal tumor using 4D-CT scans.

[13,14]. For pediatric patients with a renal tumor treated with a dose distribution obtained by AP/PA photon beams, the contribution of surgical clips to demarcate the preoperative tumor borders has diminished since the implementation of 3D-image coregistration. When IGRT techniques will be used for flank irradiation, as recommended by the new SIOP-RTSG consensus, the postoperative shift of intraperitoneal organs has to be considered to allow sparing of normal tissue otherwise irradiated by a conventional AP/PA dose distribution [15–19]. However, in patients with a tumor that shrouds most of the hemi-abdomen on preoperative imaging, it is difficult to reconstruct the retroperitoneal tumor bed postoperatively with imaging only. For this reason, the possibility of using surgical clips to optimize flank target volume delineation was evaluated.

In the current study, the lateral clip was placed near the White Line of Toldt to mark the anterolateral extension of tumor bed [20]. The lateral clips were mostly distributed at an angle of 74° measured from the anterior border of the vertebral bodies, showing that postoperative tumor bed is generally confined to the posterior wall. Preoperatively, an anterior tumor (i.e. anterolateral tumor extension > 74° on the abdominal wall) was seen in the majority of patients (n = 21/30), in whom the lateral clip demonstrated to be a useful tool to reduce the target volume. For patients with a smaller, posterior tumor (i.e. anterolateral tumor extension $\leq$ 74° on the abdominal wall), the lateral clip was merely an anatomical marker of the retroperitoneal border and did not contribute to a target volume reduction.

In the current cohort, it was feasible to place surgical clips in all patients over an extended period of time. In other centers, the method of surgical clip placement as described in the current study is likely to be reproducible, because the lateral clip is placed on a distinct anatomical location and the superior clip may be placed anywhere upper pole of the operative bed to remain functional. Furthermore, in 80% of the patients, lateral clips were found within a range of 30° indicating good reproducibility among the five pediatric surgeons in this center.

Nevertheless, using surgical clips might not be preferred in all centers. The current analysis shows that lateral clips were located behind a fictional line parallel to the anterior border of the corpus vertebrae (i.e. 90° on the abdominal wall) in 28 of 30 patients. In two patients, the lateral clip was found in front of this fictional line (i.e. >90° on the abdominal wall), suggesting that the peritoneal fold could be pushed forward by the tumor. Since the 10 mm margin used for microscopic spread (clinical target volume, CTV) compensates for these rare individual outliers, the fictional line can be considered a safe method to determine the lateral margin of the postoperative tumor bed (GTV-T_{post}) in the absence of clips.

To correct for intra- and interfraction motion of the tumor bed and set-up errors, a standardized isotropic margin of 10 mm is recommended by the UMBRELLA protocol [2]. As demonstrated by the current analysis and related publications, motion of retroperitoneal tumors in children as a result of breathing is often limited to 2 mm [10,11,21]. However, an overall reduction of margins for intra-fraction motion in all patients may cause individual outliers, as observed in this analysis, to be missed. Surgical clips as a surrogate for the tumor bed combined with 4D-CT technology can measure intra-fraction motion at an individual level and are translated into an internal target volume (ITV). Incorporating this approach in flank delineation for IGRT allowed a median PTV reduction of 25% compared to standardized isotropic safety margins for intra-fraction motion of 5 mm.

Technical aspects of using surgical clips have to be taken into consideration. Since a clip has to traverse to an adjacent voxel to register a change in position on 4D-CT, a motionless clip cannot be discerned from a clip moving less than the voxel dimensions. Therefore, a minimal ITV margin equal to the resolution of the CT was used in this study, which was ~1 mm for the mediolateral and ventrodorsal direction and 1 to 3 mm in the craniocaudal direction. Also, Guerreiro et al. compared postoperative CT-scans in RT treatment position with the cone-beam CT scans during the treatment course of patients with a WT treated with flank irradiation and found no signs of clip migration [11]. Although evidence on clip migration directly after nephrectomy is lacking, the use of surgical clips at the four borders of the resection field has not been proven unsafe for flank irradiation in the era before image coregistration. In the future, MR-guided radiotherapy is likely to be available, therefore more expensive MRI compatible clips may be needed to replace the regular titanium clips [19]. Finally, the SIOP-RTSG group aims to initiate an international prospective study implementing the new target volume definition with locoregional control as primary endpoint and central review of the target volumes and dosimetry before onset of treatment [7]. In this study, the replicability of surgical clips in a multicenter setting can be analyzed and mapping of locoregional recurrences that may result from target volume optimization by the use of clips can be performed.

In conclusion, this single center study demonstrates that the addition of a lateral clip and a superior clip optimizes highly-conformal target volume delineation applicable for IGRT by marking the lateral border of the postoperative tumor bed in case of large preoperative tumors and acting as a surrogate for tumor bed motion registration during radiotherapy, respectively. Consequently, these smaller and personalized target volumes can reduce the amount of normal tissue volume receiving high-dose irradiation in pediatric patients with renal tumors when advanced radiotherapy techniques are applied.

Author contributions

All authors contributed to the concept and design, acquisition of data, or analysis and interpretation of data, took part in drafting or critically revising the manuscript for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

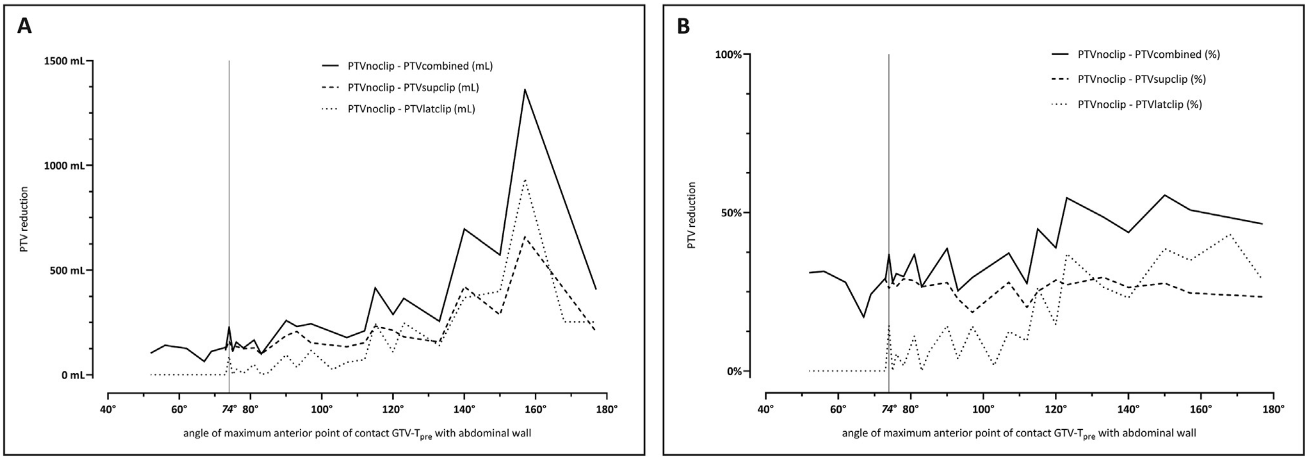

Fig. 5. PTV reduction obtained by the use of surgical clips expressed in mL (*y-axis, 5A*) and percentage (*y-axis, 5B*) in relation to the angle (in degrees) of the preoperative tumor projected on the lateral abdominal wall measured from the anterior border of the vertebral bodies (*x-axis*).

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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.12.010.

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