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Gynaecological radiotherapy

Internal motion of the vagina after hysterectomy for gynaecological cancer

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ABSTRACT

Background and purpose: The purpose of this study was to investigate position changes of the vagina after hysterectomy for early stage cervical or endometrial cancer and their impact on CTV–PTV margins. We also studied their correlation with surrounding organ filling.

Materials and methods: Fifteen patients underwent T2-weighted MR scans before and weekly during the course of their EBRT. The vaginal CTVs and the surrounding organs were delineated. PTV margins were derived from the boundaries of the CTVs in the main directions and correlated with changes in the volumes of organs at risk. Additionally we investigated the impact of margin sizes on CTV coverage.

Results: The vaginal CTVs change their position in the pelvis during time with a maximum in anterior–posterior direction. The 95% confidence level was 2.3 cm into the anterior or posterior direction, 1.8 cm to left or right and 1.5 cm towards the cranial. With a homogenous 1.5 cm CTV–PTV margin $\geqslant$5% inadequately covered vaginal CTV was seen in only 3.3% of the measurements. This increased to 20.6% with a margin of 1.0 cm. Concerning the impact of organ filling on vaginal position changes we found the only significant correlation with rectal volume and shift of the vagina towards anterior–posterior.

Conclusion: To accommodate the changes in the position of the vaginal CTV inhomogeneous PTV margins should be generated with the largest size in the anterior–posterior direction. The position shifts were only weakly related to the volume of the rectum and not at all to the volumes of other parts of the bowel and the bladder.

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Treatment of choice for endometrial cancer and early stage cervical cancer is surgery, often consisting of hysterectomy. In the case of adverse prognostic factors for local or loco-regional recurrence, surgery is followed by radiotherapy (RT) or chemoradiation in order to increase control rates and outcome [1–4]. In the case of adverse prognostic factors like parametrial infiltration, pelvic node pathology or lymph-vascular space involvement, external beam radiotherapy (EBRT) is often preferred over vaginal brachytherapy [1]. Conventionally, EBRT is delivered by large treatment portals encompassing parts of the vagina and the draining lymphatics, as well as the organs at risk located in the pelvis. Control rates are acceptable with these techniques but treatment related toxicity $\geqslant$grade 3 (3–25%) is not negligible [1,5–9]. With the development of image guidance and treatment planning technology in RT, more conformal treatment portals can be produced. Especially multileaf collimators and intensity modulated radiotherapy (IMRT) techniques allow dose tailoring to the defined target volume with the potential to spare the surrounding organs and to increase the target dose [10–19].

However, in the case of a highly conformal treatment set up precise information on the position changes of the RT target during the course of the treatment is mandatory [20–26]. A pitfall in this respect can be internal target motion induced by variations in intra-abdominal organ filling. For advanced stage cervical cancer, primarily treated with (chemo)radiation, target position changes during the course of the treatment and their impact on treatment margins have been investigated [21–23].

The purpose of this study was to investigate position changes of the vagina after hysterectomy for early stage cervical or endometrial cancer and their impact on CTV–PTV margins. We also studied their correlation with surrounding organ filling.

Materials and methods

Fifteen patients with gynaecological cancer, treated at our department between March 2007 and September 2007, were enrolled in the study. Thirteen patients had cancers originating from the uterine corpus and two patients had cervical cancer. Staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) classification [27]. All patients had FIGO stage I disease.

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In accordance with our treatment protocol patients were treated conventionally with 3–4 treatment fields (bilateral portals combined with either AP/PA fields or one single PA field) to a total of 46 Gy in 23 fractions of 2 Gy, irradiating the proximal part of the vagina (vaginal clinical target volume CTV)), the parametria and the draining lymphatics (up to the level of L5/S1). Patients were treated in prone position. To prevent any rotation of the hip, a knee cushion for alignment of the legs was used in each fraction. No further immobilization devices were used. No special measures were taken to minimize the variation in rectum and bladder filling.

Each patient underwent a CT scan (CT aura, Philips Medical Systems, Best, The Netherlands). Contiguous 3 mm slices were made from the iliac crest to the ischial tuberosities. In order to accurately delineate the regions of interest, MR images were made using a 1.5T MRI scanner (Gyroscan NT Intera, Philips Medical Systems, Best, The Netherlands). Patients were scanned in the treatment position, using a flat tabletop insert. Because of its superior soft-tissue contrast, MRI was used to delineate the target volumes as well as organs at risk (OAR). All 15 patients underwent MR imaging before treatment and weekly during EBRT. The first week MRI was performed after about 10 Gy, the second week MRI after about 20 Gy, third week MRI after about 30 Gy and the fourth week MRI after about 40 Gy. Images were acquired using a Synbody coil according to the following protocol: axial Proton Density images (TE 20 ms, TR 1960 ms) with 6.6 mm thick slices of the whole abdomen and pelvis; axial, sagittal and coronal T2-weighted images (TE 100 ms, TR 3000 ms), with 4.5 mm thick slices from the body of L5 to the ischial tuberosities. The images were taken without additional vaginal markers, contrast agents or vaginal fillings.

We used the planning CT scan as the frame of reference for the MRI data sets of all time points. Therefore, we registered the MRI data sets to the CT scan using a mutual information-matching algorithm (VTK CISG Registration Toolkit, Kitware, York). While the original MRI datasets were used, we extracted a dataset containing only the bony anatomy obtained from the CT using a threshold algorithm. This dataset was used so that the bony anatomy of the CT and each of the five MRI datasets could be matched. Structures contoured on the five MR images were transferred to the CT or MRI coordinate frame using the transformation and image fusion functionality available in our in-house developed contouring software package Volume tool [31]. In an earlier study, we showed that the registration accuracy was on average 1.0–1.4 mm [22]. The analysis of the internal motion was carried out using the five sets of delineations overlayed on the CT scan. For display purposes the delineations were overlayed on the pre-treatment MRI scan.

A radiation oncologist delineated the outer contour of the proximal vagina (vaginal CTV) on the T2-weighted pre-treatment and first to fourth week MR images (Fig. 1). The vaginal CT as contoured here is part of the total post-operative CTV. Parametria, surgical bed and draining lymphatics are not part of this investigation. Contouring was performed on the axially sliced datasets using also the information of the sagittal and coronal images to define the extension of the vagina wall in 3 dimensions. In clinical practice the vaginal CTV is defined as vaginal vault and proximal vagina. Depiction of the lower vagina and especially the introitus without using intravaginal contrast is difficult on MRI. We, therefore, set the caudal border of the vaginal volume to the cranial border of the ramus inferior of the Os pubis. This bony reference is used as an indicator for the inferior treatment field border in our clinical practice. A radiologist specialized in gynaecologic

oncology and a gynaecologic oncologist reviewed the delineated vaginal CTVs. The following critical organs were delineated using the outer organ wall: bladder, rectum, sigmoid and bowel (bowel up to the level of the aorta bifurcation). Vaginal volumes were calculated for 14 patients, one case was excluded because of persisting haematoma.

We have chosen a relatively simple and pragmatic approach to analyze the vaginal position changes, along the lines of Van de Bunt et al. [22]: for each of the four weekly MRI scans an inhomogeneous margin was generated around the pre-treatment CTV encompassing the boundaries of the weekly CTV in the six main directions (anterior, posterior, left lateral, right lateral, superior and inferior) (Fig. 1). A consequence of this approach is that a margin of zero in a given direction does not imply the absence of a shift, but that the boundary of the new volume lies inside the pre-treatment volume.

We used the margin sizes derived for the weekly MRI scans as a surrogate for the shift of the target to assess the impact of variation in organ-filling. To this end a margin in the posterior (P) direction is interpreted as positive, in the anterior (A) direction as negative. Similarly left lateral (L) is positive, right lateral (R) negative and cranial positive (S). As the caudal margin was related to the bony anatomy of the pelvis in all the cases we considered the margin to be zero in this direction. Points with a margin equal to zero are removed from this analysis because the value of zero only means that the new structure fell within the pre-treatment structure.

A paired *t*-test was used to compute the differences in vaginal volume between the MRI scans taken in different weeks. A least square linear regression is performed to study the correlation between margin sizes and change in rectum, sigmoid, and bladder volume.

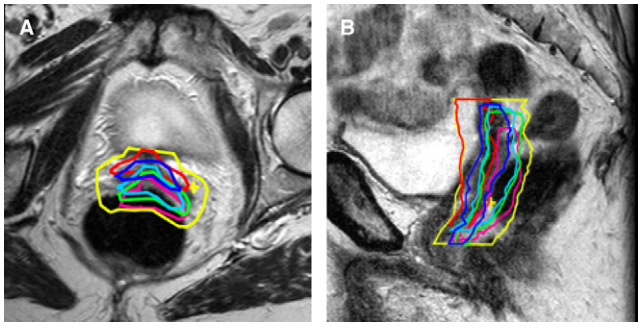

Fig. 1. (A) Transversal view of the pre-treatment vaginal CTV (red) and four CTVs at later time points. The generic PTV, which encloses the pre-treatment en all intra-treatment CTVs is indicated in yellow; (B) analogous for the sagittal direction.

Results

Vaginal and OAR volumes

Post-operative vaginal volumes were easily depicted on the T2 weighted MRI scans before and during radiotherapy and were calculated for 14 patients and five moments. The calculated 70 volumes appeared to be quite comparable with on average 24.9 cm^3 (SD 7.6). We did not see significant changes during the course of treatment with on average 23.6, 24.4, 26.0, 24.3 and 23.3 cm^3 before treatment and in week 1, 2, 3 and 4, respectively. One of the 15 patients was excluded from this analysis because of post-operative haematoma in the vagina vault and an initial vaginal volume of 98 cm^3, which is about 4 times the volume that we saw in the other patients (Fig. 2C). For calculated volumes of rectum, sigmoid and bladder we noticed a decrease from pre-treatment on average 106.7, 142.0 and 153.6 cm^3 to 50.9, 99.6 and 115.3 cm^3 in week 4.

Treatment margins

The impact of vaginal shifts on the coverage of the vaginal volume is depending on the chosen treatment margins. In order to

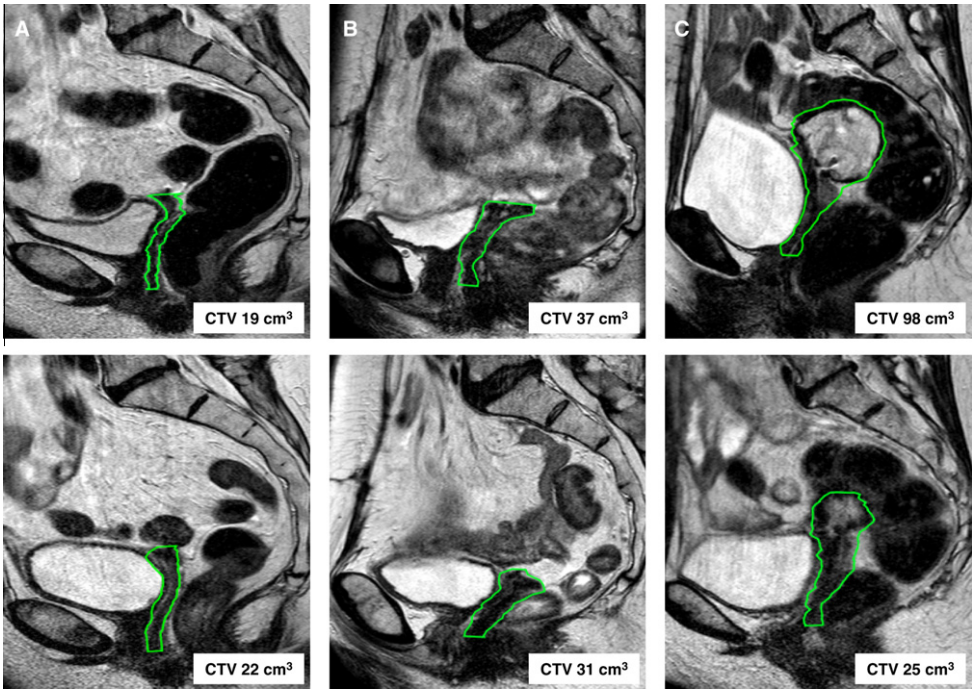

Fig. 2. Changes in volume and position of vaginal CTVs (green contours), T2 weighted sagittal MRI before and in the last week of treatment. (A) Stable volume, no vaginal motion, despite changes in rectum and bladder filling. (B) Vaginal motion and deformation due to changes in organ filling. (C) Substantial volume reduction due to resorption of post-operative haematoma.

determine these margins we used the 4 intra-treatment MRIs for all 15 cases. Around each of the pre-treatment vaginal CTVs inhomogeneous margins were derived to accommodate the changes in the position of the vaginal CTVs and to generate the PTVs on the weekly MRI scans (Fig. 1). This results in 60 margin sizes in the anterior–posterior, left and right lateral, and cranial directions. In these margin sizes the influence of internal organ motion as well as variations in vaginal shape is included. Generic margin sizes that allow complete coverage of 90% and 95% of the vaginal volumes are within the ranges of 1.9–1.1 cm and 2.3–1.5 cm, respectively, and most pronounced in the anterior–posterior direction (2.3 and 1.9 cm anterior–posterior, 1.8 and 1.1 cm left and right and 1.5 cm cranial).

With homogenous CTV–PTV margins of 1.0 and 1.5 cm, as often used in clinical practice, we found that vaginal volumes were not completely covered in 53.3% (32 of 60) and 20.0% (12 of 60) of the intra-treatment situations, respectively. With a margin of 1.0 cm there was quite some amount of vaginal volume that was covered inadequately, up to 5% in 31.7% (19 of 60) of the measurements, more than 5% in 20.6% (13 of 60), respectively (Fig. 3). With a margin of 1.5 cm in all directions the amount of inadequately covered volume was lower, up to 5% in 16.7% (10 of 60) of the measurements, more than 5% in only 3.3% (2 of 60), respectively.

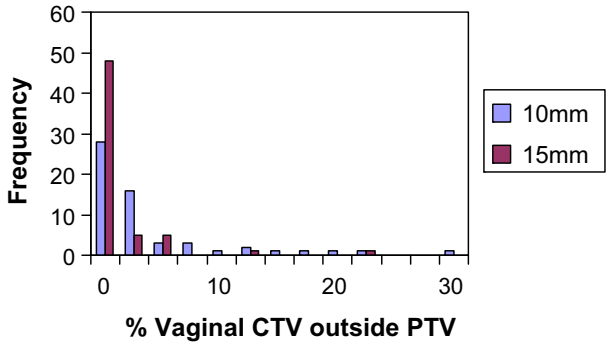

Fig. 3. Influence of clinically accepted CTV–PTV margins on percentage of vaginal CTV coverage.

Impact of organ filling

Concerning the relation between organ filling and vaginal shifts we found no correlation with changes in bladder, sigmoid and bowel volumes. The only significant ($p < 0.001$) but weak correlation (correlation coefficient −0.44) was observed between variations in rectum filling and vaginal motion towards anterior or posterior (Fig. 4). We noticed a trend towards decreased rectal filling over time resulting in a volume reduction from pre-treatment

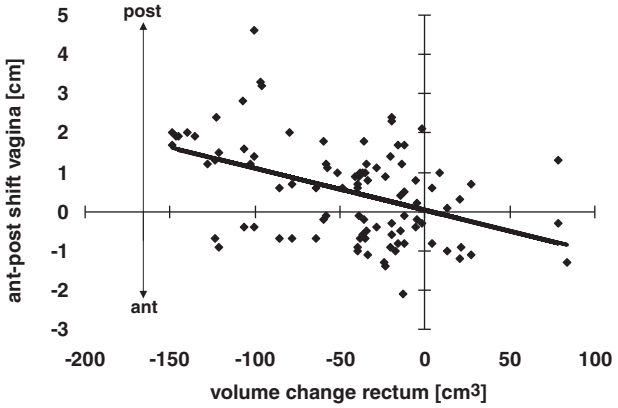

Fig. 4. Correlation of rectal volume changes and vaginal shifts. Point 0 indicates rectal volume and vagina position on the pre-treatment MRI. With decreasing rectal volumes there is a trend towards larger shifts into the dorsal direction. Abbreviations: post = posterior, ant = anterior.

106.7 cm^3 (SD 45.0) to 50.9 cm^3 (SD 20.9). As indicated in Fig. 2B vaginal volumes, and mainly their cranial part, tend to move into the posterior direction if the rectal volume decreases. The required CTV–PTV margins into the posterior direction from pre-treatment to week 1, week 2, week 3 and week 4 were on average 1.0 cm (SD 0.8), 1.3 cm (SD 0.9), 1.1 cm (SD 0.8), 1.5 cm (SD 1.0), respectively. There were no significant relations between organ filling and vaginal shifts towards left–right or cranial (correlation coefficients between 0.25 and −0.03).

Discussion

For patients with cervical or endometrial cancer, post-operative EBRT of the pelvic region is often part of their curatively intended treatment [1–3]. The beneficial effect on tumour control, however, has to be balanced against EBRT related side effects, mainly on bladder and bowel (large and small) [5–9]. Modern radiotherapy techniques, such as IMRT, offer more conformality with potential in either dose escalation or organ at risk sparing. However, the more conformal treatment portals are the more precise the dose is tailored to the target volume, the better one has to be informed about volume or position changes of the target during the course of the treatment. In post-operative radiotherapy for cervical or endometrial cancer risk reduction on tumour recurrence in the vagina is one of the intentions. The proximal part of the vagina is defined as CTV and needs to be identified for treatment planning purposes. MR images are preferable over CT scans in the case of gynaecological cancers [28–30] and we, therefore, used MR images for contouring purposes. The vaginal volumes as calculated from the delineations on T2 weighted scans were overall comparable and stable on the weekly MRI's with small standard deviations. We noticed one exceptional case of post-operative haematoma in which MRI provided additional information for the clinical treatment planning. The dimension of this haematoma would have been underestimated without image guidance (Fig. 2C).

But precise information about the shape and extension of the treatment target before starting highly conformal radiotherapy is not enough. Information on position changes during the course of the treatment is also needed. On the one hand, as indicated in Fig. 1B, the shape of the vaginal CTV can vary over time with some deformations especially in the region of the vagina vault. On the other hand the vagina (and especially the vault) moves within the pelvis during the course of EBRT. A CTV–PTV margin of 2.3 cm towards anterior–posterior would allow complete vaginal coverage in 95% of the operated and non-operated cases. These shifts are in the same order of magnitude as the position changes of the CTVs when the primary tumour is still in situ. For primary cervical cancers we are informed in this respect by studies from Chan et al. [21], Van de Bunt et al. [22] en Taylor et al. [23], which show that essential changes in target positions occur during the course of radiotherapy. The magnitude of the primary CTV shifts lie in the order of 1–2.5 cm with variations into the different directions and maximum towards anterior–posterior. Based on a study of Kerkhoff et al. [32] it can even be expected that position changes occur within a single EBRT fraction. In order to investigate which margins might accommodate the post-operative vaginal position changes we used the approach as described by van de Bunt et al. [22]. This approach is easily applicable in the commercially available planning software. More advanced methods that allow adaptive individualisation for deformable treatment targets are published by Wright et al. [33] and Redpath and Muren [34].

Additional to the directions and magnitude of the vaginal CTVs shifts, we investigated their relation to the filling status of the surrounding organs. Only in case of the rectum we found a significant although weak correlation between CTV shift and organ volume. The smaller the rectal volume was the more pronounced was the shift towards posterior. A weak correlation between target volume shifts and rectal volume changes is also documented by van de Bunt et al. [22]. In contrary, for prostate, a strong relation is found between target volume position and rectal volume changes [35]. The difference between a strong and weak correlation might be due to the limited number of patients that have been investigated in our study. We found no correlation between bladder, sigmoid or bowel filling and the position of the vagina in the pelvis. This might be due to the fact that the complex movements and volume changes of these organs are related to each other. In the example in Fig. 2A the bladder filling has increased between the two moments of investigation. The bowel loops have shifted and the rectum filling has changed, but in the end the vaginal CTV stays in the same place. In Fig. 2B, however, all the differences in organ filling and position changes shift the vagina top towards posterior. These findings help to understand that the measures that are taken to control bladder or rectum fillings do not necessarily reduce position shifts of the radiation targets in the small pelvis in all patients in the same way and do not necessarily allow a safe reduction of treatment margins.

Given herein the presented magnitude of the vaginal shifts one can expect that clinically accepted CTV–PTV generic margins of about 1.0 cm without reliable position verification measures might be too small for an adequate irradiation of the CTVs. And indeed, with 1.0 cm in all directions we found more than 5% of the CTV lying outside the PTV in 20.6% of the measurements. With a margin of 1.5 cm the situation was improved with only at two moments more that 5% of the CTV was inadequately covered. In how far this lack of coverage might have impact on the tumour control probability has not been investigated in this study. It anyhow indicates the need for appropriate position verification procedures during the course of treatment to reduce a possible risk, especially when highly conformal treatment techniques are used.

Conclusion

In gynaecological patients after hysterectomy we found substantial position shifts of the proximal part of the vagina on five consecutive MRIs during the course of post-operative radiotherapy. These shifts were only weakly related to rectal volume and not at all to the volumes of other parts of the bowel and the bladder. To accommodate the position changes of the vaginal CTV inhomogeneous PTV margins should be generated with a maximum in the anterior–posterior directions.

Conflict of interest statement

No conflict of interest exists for the work presented here.

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