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ORIGINAL RESEARCH

Assessment of intact cervix motion using implanted fiducials in patients treated with helical tomotherapy with daily MVCT positioning

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Abstract
Objectives This study assesses the relative motion of the cervix during the course of treatment in patients with intact cervical cancers treated with pelvic intensity modulated radiation therapy (IMRT).
Methods Nineteen patients with intact cervical cancer were treated definitively with tomotherapy using daily megavoltage (MV) CT positioning to pelvic bony anatomy. Textured gold fiducials were placed in three of four quadrants of the cervix prior to CT simulation. Daily MVCTs were registered to the planning CT based on bony anatomy. The center of mass (COM) of the fiducials was used to assess interfractional cervical motion by comparing the relative positions of the COMs. Tumor regression was indirectly assessed by calculating the contraction in the relative distance between fiducial pairs.
Results Fourteen patients were evaluable. Average vector motion of the COM was 7.0 mm (SD=5.7 mm; range of 0 to 34 mm). Ninety-five percent of fiducial excursions were encompassed by 8 mm right–left, 12 mm anterior–posterior, and 11 mm superior–inferior. Ninety-five percent of all measured COM motions were ≤18 mm. Contraction was observed in 9 out of 12 patients that were analyzable. In those nine patients, the average distances between the fiducial pairs were 23 mm (range, 5.8 to 48 mm) and 18 mm (range, 3.8 to 41 mm) in the planning CT and in the last daily MVCT, respectively. On average, fiducials moved 23 % closer together.
Conclusion Quantification of the excursions of the intact cervix using daily imaging of implanted fiducials was feasible and useful to define appropriate clinical target volume–planning target volume (CTV–PTV) margins for IMRT. Nonuniform CTV–PTV margins may be appropriate based on differential directional motion.

Keywords IMRT · Fiducials · Cervix motion · Margins

Introduction

Pelvic irradiation, in combination with brachytherapy has commonly been used in the definitive treatment of cervical cancer. Radiation is typically given with concurrent chemotherapy, as several randomized trials have shown a significant improvement in local control and survival with combination therapy [1]. Radiation field arrangements traditionally have been large open fields, either anterior-posterior (AP), posterior-anterior (PA) or four-field box techniques, with little capability of sparing normal tissues. Combination therapy also exposes patients to increased risk of side effects to the bladder, bowel, and bone marrow. There has been interest in recent years in using intensity modulated radiation therapy (IMRT) in gynecologic cancer patients receiving definitive radiation in order to reduce normal tissue doses and thereby decrease acute and long-term toxicity, and possibly to dose escalate gross disease.

In intact cervix cancer patients, there is a fixed nodal target volume and mobile cervix and uterus target volumes. Therefore, when aligning to bony anatomy for daily positioning, clinical target volume–planning target volume (CTV–PTV) margins must allow for the motion of the involved cervix and uterus. This study was undertaken to assess cervical organ motion during the course of pelvic irradiation using pelvic IMRT delivered with helical tomotherapy. Uterine motion was not part of this study. Organ motion assessment was accomplished by the placement of fiducial markers in the cervix prior to simulation and daily megavoltage (MV) CT imaging of the pelvis and fiducials

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through a 5-week course of treatment. The primary objective was to determine average directional and aggregate motion so that recommendations for PTV margins could be developed, in order to address a relative paucity of inter- and intrafraction 3D and longitudinal motion data across an entire course of treatment for the use of pelvic IMRT for intact cervix patients.

Methods

This was an IRB approved retrospective study of 19 patients treated with pelvic IMRT for intact clinical stage IB1 to IIIB cervical cancer. The main endpoint of the study was to measure cervical organ motion on daily image sets during the 5-week course of pelvic irradiation in order to estimate appropriate margins for pelvic IMRT. Pelvic dose was 45 or 50.4 Gy given with concurrent cisplatin-based chemotherapy, followed by appropriate brachytherapy and parametrial boost as indicated. All patients included in this series were treated with helical tomotherapy from June 2008 through December 2009 and had daily MVCT scan images for the purposes of positioning. These daily images comprised the data set for the study. MVCT assessment of organ motion throughout the course of treatment was based on the relative motion of gold fiducial markers that were implanted prior to CT simulation.

IMRT treatment planning parameters

This study predated the publication of the contouring atlas for definitive cervix [2]. We developed a standardized in-house standard protocol for IMRT in intact cervix patients. All patients were staged with PET-CT, which was also used to aid target volume delineation. Pelvic MRI was not routinely used for planning the pelvic fields during this era. Three textured gold fiducials (X-Mark, ONC Solutions) were placed into the cervix in three of four quadrants using preloaded needle inserters under direct visualization prior to CT simulation.

The following contouring and dose parameters were used during this time period: paracervical gross tumor volume (GTV) included all gross cervical, uterine, vaginal, and parametrial diseases as seen on PET-CT and CT simulation studies plus full bilateral parametrium and upper half of the vagina (or gross disease+3 cm of the vagina). Pelvic nodal volumes were contoured to include all PET-positive disease plus the visible vascular bundle from the bifurcation of the aorta or the bifurcation of the common iliac vessels (depending on stage) on intravenous contrast-enhanced CT. The presacral nodes were drawn as a 1.5-cm contour along the presacral hollow from S1 to S4. CTV=[paracervical GTV+20 mm]+[(pelvic nodes+7 mm)]+presacral nodes excluding bone, PTV=CTV+7 mm. Prescription dose was to cover 97 % of the PTV. Homogeneity goals included <20 % PTV to receive >110 % of prescribed dose and <1 % PTV to receive <93 % of prescribed dose. Because all patients were treated on tomotherapy, oral contrast could not be used. As our routine practice for patients treated with tomotherapy, daily MVCT image sets aligned to pelvic bony anatomy and including the cervical fiducial markers were obtained in all patients for daily setup purposes.

Study data sets and analyses

Fourteen out of 19 patients were available for fiducial identification and analysis; in five patients, two of the fiducials were lost during the treatment course. In addition, two patients were not used for analysis of motion between fiducials because of the loss of one fiducial.

An average of 23 daily MVCT image sets were analyzable per patient for a total of 316 daily image sets analyzed. The planning CT image set and the daily MVCT image sets were transferred to the Pinnacle treatment planning system (Philips Medical Systems, Madison, WI). The planning CT was the primary image set. Each MVCT set was subsequently registered to the corresponding primary image set by alignment of the bony anatomy. Each individual fiducial was contoured on all daily image sets (Fig. 1). The coordinates of the center of each fiducial were calculated by the treatment planning software and the coordinates for each fiducial for every image set were recorded. Since the secondary image sets were all aligned to the primary set solely based on bony anatomy alignment, the changes in daily position of the fiducials were calculated directly from the fiducial coordinates.

Paracervical motion was described using two metrics. The first was the global motion of the cervix, which was measured by examining the motion of the fiducials as a group for each patient. This was accomplished by calculating coordinates of the center of mass, or COM_i, of the fiducials of the i^{th} image set using Eq. 1 as follows:

$$COM\,X_i = \sum_{j=1}^{3} X_{ij} \ / \ 3 \tag{1}$$

$$COM\ Y_i = \sum_{j=1}^{3} Y_{ij} \ / \ 3$$

$$COM\ Z_i = \sum_{j=1}^{3} Z_{ij} \ / \ 3$$

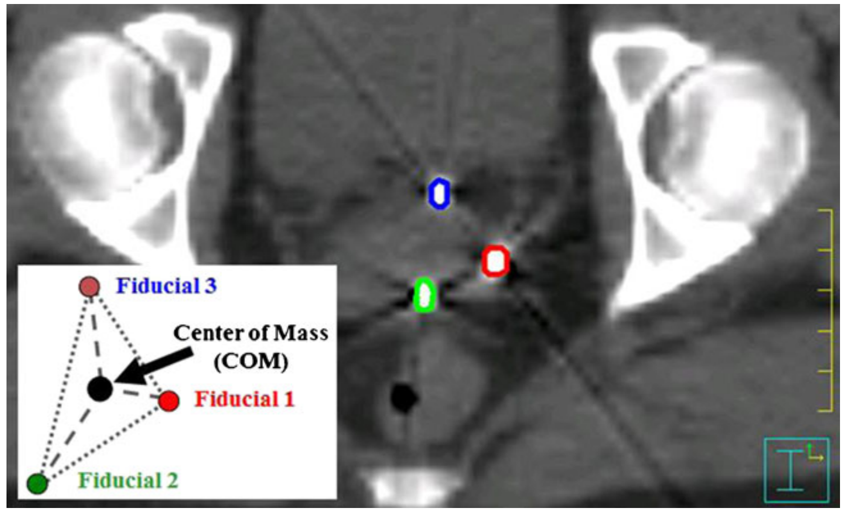
for the left–right (+X direction), anterior–posterior (+Y direction), and the inferior–superior (+Z direction) directions, respectively.

The change in position of the COM_i for the i^{th} image set relative to the COM_p of the primary image set was a vector difference as follows:

$$\begin{aligned}\Delta COM \ = \ & (COMX_i - COMX_p)\bar{x} \\ & + (COMY_i - COMY_p)\bar{y} \\ & + (COMZ_i - COMZ_p)\bar{z}\end{aligned} \tag{2}$$

where $\bar{x},\ \bar{y},\ and\ \bar{z}$ are unit vectors.

Fig. 1 An example showing an axial slice of the CT of pelvis with three contoured fiducials implanted prior to CT simulation. The inset shows a representation of the center of mass (COM) of the fiducials. In this figure, all fiducials appeared in the same slice but this was not normally the case



The second metric can be considered a local measurement of motion, namely the change in distance between pairs of fiducials (1 and 2, 2 and 3, 1 and 3) of each daily MVCT set relative to the corresponding primary CT (ΔS_{ijk}). The distance between two fiducial markers in the kth image set was calculated by

$$S_{ijk} = \sqrt{(x_i - x_j)^2 + (y_i - y_j)^2 + (z_i - z_j)^2} \quad (3)$$

consequently ΔS_{ijk} was calculated by

$$\Delta S_{ijk} = S_{ijk} - S_{ijp} \quad (4)$$

where the subscript p refers to the primary CT set. Since there are three fiducial pairs, the daily intracervix motion was defined by the average of the changes in the distance between fiducial pairs from each daily image set relative to the primary image set. Expansion/contraction was defined as an increase/decrease in the average interfiducial distance. Significant distortion was defined as any fiducial pair demonstrating greater than 10 mm change in interfiducial distance between the daily image set and the primary set.

Characterization of the directional motion (Eq. 1) due to global cervix motion and/or intracervix motion (Eq. 4) during a course of pelvic radiation were used to estimate appropriate CTV–PTV margins for the cervix.

Results

Nineteen consecutive cervical cancer patients treated with helical tomotherapy who had implanted fiducials on daily MVCT image sets comprise the data set for this study. Twelve of these patients had three fiducials that remained through the course of treatment, two patients only had two fiducials, and the remaining five patients only had one fiducial retained through the entire course of therapy.

Interfraction cervical organ motion

The vector of interfraction motion of the center of mass (COM) was calculated to determine the directional and total change in cervical organ position over a 5-week course of pelvic irradiation. Figure 2 summarizes the aggregate interfraction directional motion of the COM of three fiducials from each daily MVCT set relative to the planning CT set. The right–left motion (mean= 2.2 mm, standard deviation (SD)=1.9 mm) was less than either anterior–posterior (mean=4.4 mm, SD=2.1) or superior–inferior (mean=4.7 mm, SD=2.5 mm) motions. The vector motion of the COM, given by Eq. 2, had a mean magnitude of 7.0 mm (range, 0 to 34 mm); 95 % of all COM positions fell within 18 mm of their original position, while 99 % fell within 25 mm. Directional margins of 8 mm along the right–left axis, 11 mm along the superior–inferior axis, and of 12 mm along the anterior–posterior axis encompassed the fiducials in 95 % of treatments. These data suggest that margins may be applied directionally to the cervix CTV and that right–left margins need not be as wide as superior–inferior or anterior–posterior.

Analysis of interfiducial distances

The mean interfiducial distance across all daily images for all patients was 4.0 mm (range, 0 to 19.5 mm, SD=3.5 mm). Significant distortions, defined as a change in the distance between any fiducial pair of greater than 10 mm, were seen in 21 % of daily image sets. Patients with at least two treatments with significant distortions were observed in 44 % (four of nine) of the cases.

Distortions appeared to be random (Fig. 3), and in only one patient, there seem to be a time trend over time (Fig. 3a). The

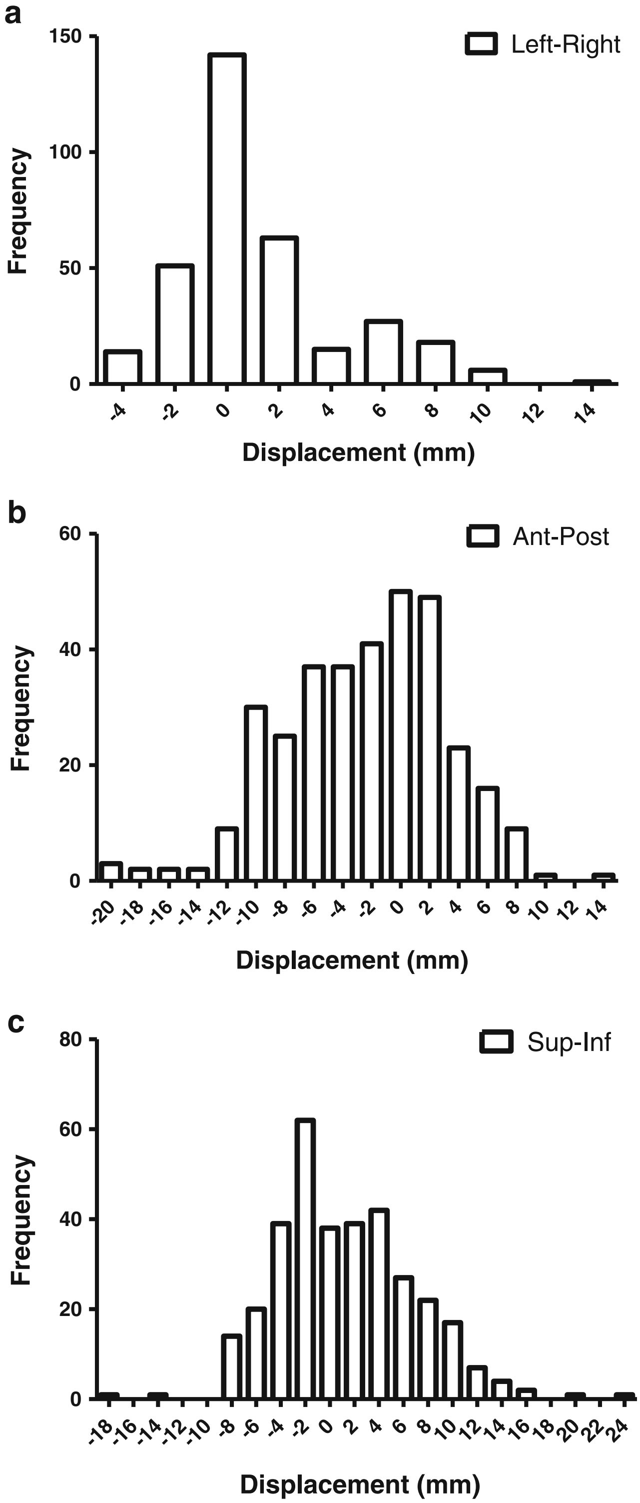


Fig. 2 Histogram of the fiducial COM motion (relative to the CT simulation) for all patients for all daily images by direction: **a** shows the right–left motion, **b** anterior–posterior motion, and **c** superior–inferior motion. The distribution of motion overall seemed nearly random with a slightly higher probability of moving anterior than posterior and a slightly higher probability of moving superior compared to inferior

temporal distribution of maximal distortion also appeared to be random and unpredictable, occurring at a median of day 14 of treatment, but ranging from day 2 to day 30 of treatment.

Cervix contraction was observed in 9 out of 12 patients that were analyzable. In those 9 patients, the average distance between the fiducial pairs in the planning CT was 23 mm (range, 5.8 to 48 mm) and in the last daily CT was 18 mm (range, 3.8 to 41 mm). On average, the fiducials moved 23 % closer together.

Discussion

IMRT may be useful in the treatment of gynecologic cancer patients requiring pelvic irradiation in order to spare normal tissues, thereby reducing the risk of both acute and long-term toxicity. This study was undertaken to attempt to better define appropriate margins around target volumes to account for average cervical organ motion as quantified during an entire course of pelvic irradiation, using 3D daily image guidance.

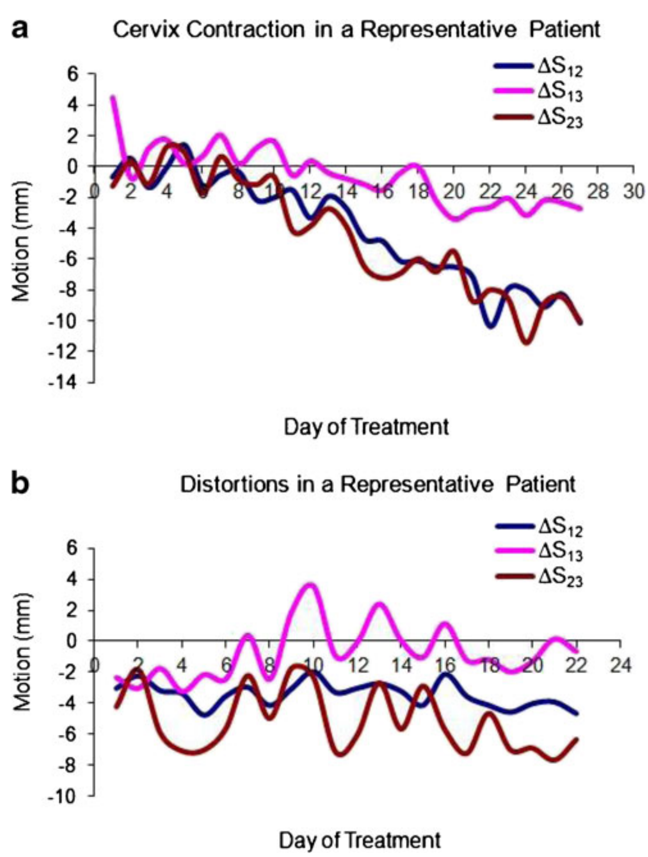


Fig. 3 These are the distortions for individual patients as assessed by variations in distances between seed pairs (Eq. 4). The distance between seed pairs is compared to the distance assessed from the CT simulation. In **a** the seeds are moving closer together as the treatment progresses, whereas in **b** the distortions are random demonstrating no clear trend

Pelvic IMRT allows improved target volume conformality while reducing dose to surrounding normal tissues, parameters which cannot be achieved with conventional 3D conformal techniques. IMRT requires precise delineation of target structures. Moreover, target margins must account for organ motion and daily setup variation to avoid target under dosage. Intact cervix cancer represents a challenging disease for IMRT, as the target volumes include the highly mobile cervix and uterus as well as fixed nodal volumes. A number of planning studies comparing conventional and 3D conformal techniques to pelvic IMRT have shown that IMRT can significantly reduce the volume of normal organs irradiated at higher doses, including rectum, bladder, bowel, and bone marrow [3–5]. Maximum PTV doses with IMRT may be higher than with 3D conformal techniques, but higher doses are confined to small PTV subvolumes. However, planning studies based on initial CT simulations alone do not account for the impact of the substantial motion of the uterus and cervix [6].

We used gold fiducials as surrogate to track cervix motion during the course of radiotherapy. The advantage of using metallic fiducials is that they provide an objective marker of organ position that can easily and reproducibly be tracked by imaging. However, the use of fiducials in intact cervical cancer, as opposed to postoperative cervical cancer [7], presented a notable disadvantage. In this study, we found that the rate of fiducial loss was relatively high. Seven of the 19 patients lost at least one of the three fiducials. We suspect that this is likely due to tumor regression and/or the softer tumor tissue not anchoring fiducials as well as the normal tissue. Additionally, fiducials did not reflect the motion of the uterus but only motion of the cervix. Ultimately, we found fiducials to be less than reliable in intact cervix patients and have discontinued applying them in our own clinic. However, we were able to glean valuable data from the study population regarding cervix motion in those patients who retained the fiducials.

Several studies have characterized interfraction organ motion in intact cervix cancer patients. Taylor and Powell performed pelvic MRI scans on two consecutive days in 32 women with intact cervix or uterine cancers and co-registered reference points on the uterus and cervix [8]. They found movements in the uterus up to 7 mm in the anterior–posterior (AP) direction and 7.1 mm in the superior–inferior (SI) direction, with minimal right–left (RL) lateral movement. The cervix and vaginal motion was related to rectal filling, and most likely affected the AP direction, with a median deviation of 4 mm but a maximal deviation of 19 mm. Van de Bunt et al. studied 20 patients with intact cervix cancer who underwent MRI prior to and weekly during pelvic radiation [9]. They found that in order to encompass the CTV and account for bladder and rectal filling, that CTV–PTV margins of 24/17 mm A/P, 12/16 mm RL lateral and 11/8 mm SI were required to include 95 % of the PTV. Rectal filling mostly affected the AP motion, while bladder filling affected primarily the SI motion. Chan et al. also studied 20 patients with intact cervix cancers with MRI pretreatment and weekly during pelvic radiation and traced the motion of points of interest on the uterus and cervix [10]. The margins required to encompass 90 % of the organ volume were 40 mm at the uterine fundus but only 15 mm at the cervical os.

To our knowledge, there is one other study which used daily MVCT obtained from a tomotherapy unit to assess organ motion in cervix cancer. Collen et al. studied ten definitive cervix cancer patients who also had daily MVCT aligned to bony anatomy for positioning [11]. The cervix and uterus were contoured on each MVCT and registered to the planning CT. Cervix and uterus organ position was compared at seven representative levels on 150 MVCTs and shifts measured in six directions. Using these methods, the authors concluded that CTV–PTV nonuniform margins required to encompass 95 % of the CTV when using bony registration for the cervix were as follows: 17, 12, 9, 8, 15, and 9 mm in anterior, posterior, left and right lateral, and superior and inferior directions, respectively. Cervix motion and contraction were also studied by Beadle et al. using contours of the cervix on weekly CTs of 16 patients [12]. All CTs were registered to the planning CT. The change in volume was used to measure cervix regression, and change in the center of mass and the perimeter of the contour were used to measure the motion of the cervix. The authors found that changes in the center of mass of the cervix were as follows: 21, 16, and 8.2 mm in the superior–inferior, anterior–posterior, and right–left lateral dimensions, respectively. Extreme displacements of the perimeter (or edge) of the cervix were 23 and 13 mm in the superior and inferior, 17 and 18 mm in the anterior and posterior, and 7.6 and 9.4 mm in the right and left lateral directions, respectively.

While our study also used daily MVCT on a tomotherapy unit, our objective was to use implanted fiducials as a fixed objective marker of cervix position in order to quantify directional motion. Our results are in agreement with those of Collen et al. and Beadle et al. The lateral motion of the cervix is smaller compared to the other directions. Interestingly, we also saw larger motion toward the right direction compared to the left as did Collen, while Beadle reported a larger motion toward the left. These asymmetries may be due to the limited sample sizes in these studies.

Our study design did not address intrafraction organ motion, which has been assessed by several investigators. Haripotepornkul et al. performed daily pre- and posttreatment orthogonal images in ten patients who had two vaginal seeds placed pretreatment [13]. They noted mean intrafractional motion of the seeds of 1.6 mm RL, 2.6 mm SI, and 2.9 mm AP; mean interfractional seed motion was 1.9 mm RL, 4.1 mm SI, and 4.2 mm AP, and the range was 0–18 mm. Kerkhof et al.

performed two or three offline MRI scans on 22 cervix patients, comparing CTV motion during the 16-min MRI scan (comparable to an IMRT treatment delivery time) with or without registration correction applied [14]. Maximal intrafraction motion on 90 % of the MRI studies without registration was 10.6 mm, with bony registration was 9.9 mm, and with soft tissue registration was 4.0 mm, although soft tissue registration in practice would be challenging if nodal volumes were being simultaneously treated.

Effects of interfraction organ motion on normal tissue volumes and PTV coverage have been assessed in several studies. Lim et al. conducted pretreatment and weekly pelvic MRI in 20 patients under treatment for cervix cancer and compared the impact of interfraction organ motion on delivered dose [15]. The mean vector motion of the upper vagina was 7 mm and of the cervix was 11 mm. Van de Bundt et al. examined the impact of tumor regression on dose to the tumor and normal organs using two MRIs, pretreatment, and at 30 Gy in 14 patients [16]. IMRT plans, which treated smaller volumes of normal tissues than conventional techniques, gave 95 % of prescribed dose to an average volume of bowel of 232 cc, rectum of 60 cc, and bladder of 58 cc. After 30 Gy, the GTV had decreased an average of 46 % but with a large range of 6 to 100 %, and all target volumes remained effectively covered by the 95 % isodose. A second replan further reduced bowel volume treated if the GTV had decreased by more than 30 cc.

IMRT appears to maintain expected local control rates while significantly reducing toxicities. Chen et al. treated 109 patients with stage IB2–IVA cervix cancer using IMRT with concurrent chemotherapy followed by high-dose rate brachytherapy [17]. At a median follow-up of 32.5 months, overall survival was 78 % and disease free survival was 68 %. Grade 3 or 4 acute gastrointestinal toxicity was seen in 2.7 % and acute hematologic toxicity in 24 %. Chronic grade 3 or 4 gastrointestinal toxicity occurred in 4.6 % and chronic urinary toxicity in 6.4 %. Mundt et al. first reported on 40 patients with gynecologic cancers treated with seven to nine-field coplanar IMRT using a 1 cm CTV–PTV margin [18]. On average, the PTV prescription coverage was 98 %. High dose PTV subvolumes were relatively small—on average, the percentage of the PTV irradiated to 110 and 115 % of the prescription dose was 9.8 and 0.2 %, respectively. Outcomes were compared to historical controls treated with conventional techniques. No acute grade 3 toxicity was recorded. Grade 2 acute gastrointestinal toxicity was seen in 60 % of IMRT-treated patients and in 91 % of controls. The impact on acute urinary toxicity was less pronounced (10 vs. 20 % grade 2, respectively). This group published a follow-up study on 111 stage I to IVA patients (including 89 with intact cervix cancer also receiving brachytherapy) treated with IMRT with a median follow-up of 27 months [19]. Three-year overall survival was 78 %, and disease-free survival was 69 %. Pelvic failure was noted in 13.6 % overall, 6.3 % for stage I–IIA, and 29.2 % for stage IIB–IVA. Overall acute grade 3 toxicity was 2 %, and late grade 3 toxicity was 7 % at a median time to symptoms of 15 months. These rates of chronic toxicities are lower than other treatment series, which have reported late grades 3–4 toxicity of about 15 %, with similar pelvic control rates and overall survival. Recent studies have highlighted inclusion of bone marrow-sparing constraints in order to address the high rates of hematologic toxicity [5, 20]. However, there are to date no randomized comparison of conformal and IMRT techniques in gynecologic malignancies.

Conclusion

In this study, fiducials placed into the cervix were used as a fixed surrogate to track motion throughout the course of pelvic irradiation. By using daily MVCTs registered to the planning CT and aligned to bony anatomy, we found the global motion of the fiducials to be 18 and 25 mm in 95 and 99 % of treatments, respectively. These findings are consistent with other studies, as cited above, of cervix motion (not uterus). Our findings reinforce the notion of establishing nonuniform CTV–PTV margins since directional motion was not uniform as reported by others. This study suggests CTV–PTV margins of 11 and 12 mm along the superior–inferior and anterior–posterior directions, respectively, and lateral margins of 8 mm. These margins were derived to encompass the global position of the fiducials in 95 % of treatments. Using smaller lateral CTV–PTV margins may facilitate lower bone marrow (and femoral head) dose using emerging bone marrow-sparing techniques to reduce hematologic toxicity and improve chemotherapy delivery. Standards for pelvis IMRT techniques should be established to ensure good outcomes. This study corroborates previous reports using a different technique and thus contributes to the published body of data for optimizing IMRT treatment planning parameters for intact cervical cancer patients.

Ethical standards This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

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