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The Effect of Uterine Motion and Uterine Margins on Target and Normal Tissue Doses in Intensity Modulated Radiation Therapy of Cervical Cancer

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Abstract

In intensity modulated radiation therapy (IMRT) of cervical cancer, uterine motion can be larger than cervix motion, requiring a larger clinical target volume to planning target volume (CTV-to-PTV) margin around the uterine fundus. This work simulates different motion models and margins to estimate the dosimetric consequences.

A virtual study used image sets from 10 patients. Plans were created with uniform margins of 1cm (PTV_A) and 2.4cm (PTV_C), and a margin tapering from 2.4cm at the fundus to 1cm at the cervix (PTV_B). Three inter-fraction motion models (MM) were simulated. In MM1, all structures moved with normally distributed rigid body translations. In MM2, CTV motion was progressively magnified as one moved superiorly from the cervix to the fundus. In MM3, both CTV and normal tissue motion was magnified as in MM2, modeling the scenario where normal tissues move into the void left by the mobile uterus. Plans were evaluated using static and percentile DVHs (PDVHS).

For a conventional margin (PTV_A), quasi-realistic uterine motion (MM3) reduces fundus dose by about 5Gy and increases normal tissue volumes receiving 30-50Gy by ~5%. A tapered CTV-to-PTV margin can restore fundus and CTV dose, but will increase normal tissue volumes receiving 30-50Gy by a further ~5%.

Keywords

cervical cancer; radiation therapy; IMRT; margins; uterine motion

1 Introduction

For radiation therapy of cervical cancer, intensity modulated radiation therapy (IMRT) is increasingly used as an alternative to traditional four-field box and 3D conformal radiation therapy (3DCRT) treatments.^{1,2,3,4,5} IMRT produces more conformal dose distributions, and therefore has the potential to deliver higher tumor dose for the same normal tissue dose. However, IMRT presupposes that one has accurate knowledge of geometric uncertainties, including internal tissue motion, and that one uses this knowledge to build appropriate margins into treatment plans. Use of IMRT without accurate geometric uncertainty models and accurate margins risks tumor under-dosing and / or normal tissue over-dosing.

The cervix and the gross tumor originating from the cervix exhibit relatively little motion because the cervix is connected to surrounding structures and to the bony pelvis by ligaments. Similarly, the motion of iliac and paraaortic nodes is limited. In contrast evidence is accumulating that, at least in some patients, the body and fundus of the uterus exhibit substantial inter- and intra-fractional mobility relative to the cervix.^{6,7,8} The body and fundus are connected to the bony pelvis laterally via broad ligaments, which constrain right-left (RL) motion, but permit significant motion in the anterior-posterior (AP) and superior-inferior (SI) directions. Notably, the uterus can rotate from ante-flexed to retro-flexed positions, possibly influenced by bladder, bowel and rectal filling, and may exhibit shrinkage over the course of treatment. This type of motion is a challenge for all radiation therapy strategies, but especially for IMRT because its success strongly depends on quantifying the motion and translating it into adequate margins.

In this work, inter-fraction uterine motion is addressed within the margin framework proposed by van Herk et al.^{9,10}, which derives margins from the standard deviations (SDs) Σ and σ of systematic and random components. The magnetic resonance imaging (MRI) study by Taylor and Powell⁶ provides data that directly fits the van Herk framework. That study registered bony anatomy in patient MRI images taken on consecutive days. In each image, points were identified on the anterior uterine body (point U), posterior cervix (point C) and upper vagina (point V). Separation of the same point on consecutive days was used to estimate that point's inter-fraction positional uncertainty relative to the treatment field, if bony anatomy was used for patient positioning. This data could reasonably be expected to provide an upper bound on the cervix and vagina's inter-fraction positional uncertainty relative to the treatment field, and a good estimate of the uterus' inter-fraction positional uncertainty, if daily images were used for patient positioning.

The Taylor and Powell study provides data only on random uncertainty. Because only two MRI images were acquired per patient, nothing could be deduced regarding systematic uncertainty. However, in the absence of data it would be reasonable to assume, as did Taylor and Powell, that systematic uncertainties have similar SDs to random errors. For the fundus (point U), σ was estimated to be 9.0 mm in the AP direction, 6.8 mm in the SI direction, and 1.3 mm in the RL direction. For the cervix (point C), σ was 4.4 mm AP, 2.8 mm SI and 0.8 mm RL. For the upper vagina (point V), σ was 3.0 mm AP and 1.0 mm RL. The method did not give σ in the SI direction for point V.

Other recent cervix motion studies include the following: Van de Bunt et al.¹ investigated the merits of IMRT versus 3DCRT and traditional treatment, and looked at tumor regression during treatment, concluding that the primary gross tumor on average shrinks 46% after 30 Gy, from 71 cc to 39 cc. Van de Bunt et al.⁸ used weekly MRI images to find the margins around the clinical target volume (CTV) that would geometrically cover the CTV for 95% of uncertainties. The study notes extensive internal organ motion and variations in the volumes of organs at risk (OAR). Significant gross tumor regression was found, but the authors concluded that this had little effect on overall size of the CTV or margins. Also, correlation of GTV and CTV motion with rectum and bladder filling status was characterized as weak. Counter-examples are presented of patients in which a substantial change in bladder volume produced either no change, or a significant change, in CTV position.

Chan et al.⁷ used weekly cinematic MRI to measure inter-and intra-fractional positional variations relative to bony landmarks of three points on the uterus: the fundus, isthmus and external cervical os. Results are presented in terms of means and 90th percentile confidence intervals for motion in the AP and SI directions. A follow-up study by Lim et al.¹¹ used the same image sets to evaluate the effect of anatomic variations on the cumulative dose delivered to the GTV, CTV and OAR by three plans: four-field box, large margin (20 mm)

IMRT, and small margin (5 mm) IMRT. With the exception of one patient, the small margin IMRT plans were found to deliver adequate target coverage, while significantly reducing dose to the bladder, sigmoid colon and rectum. Relevant earlier studies are cited in these papers.

Direct comparison of Taylor and Powell's data with those of other studies is difficult due to the different approaches taken to motion measurement and reporting. An exception is the work of Chan et al.⁷ Chan's points F (fundus) and O (os) are comparable to Taylor and Powell's points U and V. Chan gives 90th percentiles for inter-scan and intra-scan motion in the AP and SI directions, of which the inter-scan numbers are comparable to Taylor and Powell's data. If one assumes that shifts are normal, one can divide Chan's inter-scan 90th percentile range by 3.28 (i.e., the 90th percentile range for the standard normal distribution) to estimate the SDs of AP and CC shifts. This produces estimated fundus SDs of 9.1 mm (AP) and 18.1 mm (SI), and cervix SDs of 8.5 mm (AP) and 8.3 mm (SI). Except for the fundus AP SD, these estimates disagree with Taylor and Powell's, possible reasons being the inclusion of systematic volume changes during treatment in Chan's data, inadequate sampling by one or both studies, or non-normality of AP and SI shifts. Reconciling the estimates is beyond the scope of this work. Taylor and Powell's numbers are used here.

A majority of published studies suggest that internal motion of the cervix and upper vagina is modest (SDs ≤ 3 mm), but that uterine motion can be significantly larger. This applies to both inter- and intra-fractional motion. However, there is a wide range of estimates for uterine motion and margins. Roeske² and Mundt⁴ employ 1 cm margins. Chan et al.⁷ derive margins of 1-4 cm for the fundus, 1-2.5 cm for the cervical canal and 1-1.5 cm for the os. Van de Bunt⁸ has margins in the range 8-24 mm, and Taylor and Powell⁶ have CTV to planning target volume (PTV) margins of 7 mm laterally and 15 mm in the AP and SI directions. The dose accumulation study by Lim et al.¹¹ concludes that dosimetric analysis is required in order to obtain accurate margin estimates.

Of the cited studies, only Taylor and Powell⁶ uses the established van Herk margin formula in conjunction with measured motion SDs to determine treatment margins for the uterus, and that study does not evaluate the dosimetric effect of larger uterine margins on organs at risk. The goal of the present study is to perform this evaluation. This work assumes normally distributed motion with systematic and random SDs Σ and σ consistent with those obtained by Taylor and Powell⁶. Three motion models are investigated. Margins appropriate to each case are obtained from the van Herk margin formula, and the effect of margins which either allow or do not allow for increased uterine motion is evaluated. Specifically, the study quantifies the falloff in uterine dose if one uses margins appropriate to cervix motion when in fact the uterus is moving with greater amplitude. It also quantifies the increase in OAR doses if one uses margins that properly account for the larger magnitude of uterine motion observed in some patients. A novel aspect of this study is the use of a margin that tapers from the fundus to the cervix, to accommodate uterine motion.

2 Methods and Materials

2.1 Treatment Planning

Ten cervical cancer patients, treated with an in-house Phase I/II SIB-IMRT protocol for intermediate-risk cervix cancer were retrospectively analyzed for this study. Patients were scanned on supine position using a Philips AcQsim (PQ5000, Philips Medical Systems, Cleveland, OH) CT simulator with a 3mm slice spacing.

All patients had intact cervix and uterus, and were scheduled for primary radiotherapy combined with chemotherapy. (Patients received a brachytherapy boost, which is not

considered in the present work.) Tumor stages according to FIGO were IB – IIIB. CT image sets were contoured by the same physician (EW). The primary CTV (denoted CTV) consisted of the cervix including the primary tumor, upper vagina and uterus. The uterus excluding cervix was further divided into uterine body (lower two thirds) and fundus (upper third). Subdivisions of the CTV were irrelevant for clinical treatment planning, but were employed in the subsequent analysis. The nodal CTV (CTVnodes) consisted of internal iliac, external iliac and common iliac nodes. OAR consisted of the bladder, rectum, small bowel and femoral heads. PTV expansions of CTV and CTVnodes — denoted PTV and PTVnodes — are discussed below.

The prescription dose was 48.75 Gy to the primary PTV and 45 Gy to PTVnodes, delivered in 25 fractions. Simultaneous integrated boost (SIB) IMRT plans utilized seven 6MV beams equi-spaced in the patient's transverse plane, for delivery via a Varian 21 EX linear accelerator equipped with a 120-leaf Millennium MLC (Varian Medical Systems, Palo Alto, CA). Optimization was performed using Pinnacle DMPO version 8.0m (Philips Medical Systems, Fitchburg, WI).¹² Optimization criteria (doses in Gy) were PTV: $D_{\min} \geq 49.8$, $D_{\max} \leq 52.2$; PTVnodes excluding PTV: $D_{\min} \geq 45.5$, $D_5 \leq 48.75$, $D_{\max} \leq 50$; bladder excluding target (PTV+PTVnodes): $D_{45} \leq 38$, $D_{25} \leq 40$, $D_{\max} \leq 52.2$; rectum excluding target: $D_{50} \leq 30$, $D_{25} \leq 40$, $D_{\max} \leq 52.2$; small bowel: $D_{50} \leq 25$, $D_{\max} \leq 52.2$; femoral heads: $D_{\max} \leq 25$. A ring structure around the targets was used to limit peripheral dose.

2.2 Motion Models

Motivated by published studies of inter-fraction uterine motion, three motion models — MM1, MM2, MM3 — were employed for the primary CTV and OAR. These had the same RL motion, but differed in the magnitudes of AP and SI motion. CTV and OAR motion in the AP and SI directions was as follows:

- **MM1 (*uniform motion*)** MM1 was a baseline model against which the other models could be compared. AP and SI displacements of the CTV and OAR (bladder, rectum, small bowel) were normally distributed rigid body translations with SDs $\Sigma = \sigma = 3$ mm. (Rotations were not modeled.) That is, the CTV and OAR moved with the same parameters as the cervix. Note that for cervix point C (see Introduction), Taylor and Powell⁶ found $\sigma_{AP} = 4.4$ mm and $\sigma_{SI} = 2.8$ mm. Allowing for measurement-related variation in published data, the choice $\Sigma_{AP} = \sigma_{AP} = \Sigma_{SI} = \sigma_{SI} = 3$ mm is consistent with cervix motion reported by Taylor and Powell and others.
- **MM2 (*scaled uncoupled motion*)** OAR AP and SI displacements were the same as in MM1. CTV AP and SI displacements were normally distributed with $\Sigma = \sigma = 3F$ mm, where F was a scale factor that was (i) 1.0 for any voxel inferior to the cervix center-of-mass (COM), (ii) 2.5 for any voxel superior to the fundus COM, and (iii) varied linearly from 1.0 to 2.5 for SI coordinates between the cervix and fundus COMs. Note that resulting CTV AP and SI displacement SDs for voxels superior to the fundus COM were $\Sigma = \sigma = 3 \times 2.5 = 7.5$ mm, which is roughly consistent with the point U SDs obtained by Taylor and Powell.
- **MM3 (*scaled coupled motion*)** Both CTV and OAR AP and SI displacements were normally distributed with $\Sigma = \sigma = 3F$ mm, where F was the same scale factor as in MM2. In contrast to MM2, normal tissues move together with the CTV in MM3, filling space vacated by the CTV.

In all models, CTV and OAR RL displacements were assumed to be normally distributed with $\Sigma = \sigma = 1.5$ mm. (Taylor and Powell⁶ found $\sigma_{RL} \leq 1.3$ mm for the cervix, vagina and uterine points.) Also, in all models nodal structures were assumed to be anchored to the

abdominal wall and so have motion statistically similar to the cervix: $\Sigma_{RL} = \sigma_{RL} = 1.5\text{mm}$ and $\Sigma_{AP} = \sigma_{AP} = \Sigma_{SI} = \sigma_{SI} = 3\text{mm}$.

Motion models 1-3 are illustrated in cartoon form in Figure 1. Figure 2 shows the extent of modeled MM3 organ motion for one patient. Panels (a) – (c) show structure contours as thick lines: CTV (pink), CTVNodes (red), bladder (yellow), rectum (dark blue), small bowel (light blue). Envelopes encompassing 90% of MM3 motion are shown using corresponding thin lines. These envelopes characterize motion with respect to the beam (isocenter), not with respect to the bony anatomy. Bony anatomy can be assumed to be subject to simultaneous motion, including both setup errors and pelvic bone rotation, though this motion will be smaller in magnitude than the deformation of internal organs such as the uterus. Bony anatomy motion is not modeled or shown in the figure.

In MM3, motion of the CTV is assumed either to push adjacent OAR in front of it, or pull them behind it. For example, CTV displacement towards the patient's posterior is modeled as pushing the rectum, and pulling the bladder, towards the sacrum (Figure 2, panel c). As modeled in MM3, this could result in parts of the rectum moving into space occupied by the sacral vertebrae in the planning image. Clearly, to the extent that MM3 models the OAR as moving into bone, it is unrealistic. In reality, OAR would be compressed or displaced in this scenario. However, affected voxels of the rectum and bladder are distant from the high dose region, and so the dosimetric effect of this modeling inaccuracy is assumed to be small. Dosimetric conclusions depend most strongly on modeled tissue motion in and around the high dose regions. They are less dependent on modeled motion at the periphery of the high dose regions.

In motion simulations and plan evaluation — discussed more fully in sections 2.4 and 2.5 — the effect of the assumed motion on each structure was evaluated independently of other structures. So, for example, while this work assumed that nodes moved with the same parameters as the cervix, it did not assume that their motions were correlated. Results presented below capture the aggregate effect of the assumed motion model on each structure, but say nothing about correlations (of motion or dose) between the structures.

2.3 PTV Expansions

In the van Herk framework, treatment course uncertainties are categorized as systematic or random. The systematic uncertainty is the average uncertainty over a large number of fractions. Random uncertainties are those occurring in each fraction, once the systematic error is subtracted. Given the standard deviations (SDs) Σ (systematic) and σ (random) of geometric uncertainties, van Herk et al.⁹ proposed the following formula for estimating the required treatment margin to ensure CTV coverage for 90% of uncertainties: $M = 2.5 \Sigma + 0.7 \sigma$. Consistent with this formula, the following three PTV expansions of the primary CTV were employed for this study:

- PTV_A was obtained by expanding the CTV by 1cm in all directions. According to the van Herk margin formula, a 1cm expansion will absorb motion having $\Sigma = \sigma \leq 3\text{mm}$, i.e., the motion assumed for all structures in MM1.
- PTV_C was obtained by expanding CTV by 1cm in the RL direction and 2.4cm in the AP and SI directions. According to the van Herk margin formula, a 2.4cm expansion will absorb motion having $\Sigma = \sigma \leq 7.5\text{mm}$, i.e., the motion assumed for the uterine fundus in MM2 and MM3.
- PTV_B interpolated between PTV_A and PTV_C . Inferior to the cervix COM PTV_B is identical to PTV_A . Superior to the fundus COM it is identical to PTV_C . Between the COMs it varies linearly with SI position from PTV_A at the cervix to PTV_C at the

fundus. PTV_B is tailored to target motion as in MM2 and MM3 that increases linearly from $\Sigma = \sigma = 3$ mm at the cervix to $\Sigma = \sigma = 7.5$ mm at the fundus.

The above PTVs are illustrated in Figure 3. PTV_A and PTV_C were generated using Pinnacle's standard rolling ball expansion algorithm. For each anatomy, PTV_B was generated outside of Pinnacle, by interpolating between PTV_A and PTV_C contours in each axial CT slice. Specifically, PTV_A and PTV_C contours were exported from Pinnacle as text files, and a program was employed to read these files and interpolate the contours in each slice. The interpolated contours were then imported into the Pinnacle plan as a new structure. In all plans PTVnodes was a uniform 1cm expansion of CTVnodes. No planning-at-risk volumes (PRVs) were employed for OARs.

2.4 Motion Simulations

For each of the 10 'patients' (i.e., CT image sets), three IMRT plans were generated using PTV_A , PTV_B and PTV_C . The effect on each plan of motion models MM1, MM2 and MM3 was then simulated. In the following we refer to the combination of the PTV_A plan with motion model 1 as 'scenario A1', the combination of the PTV_A plan with motion model 2 as 'scenario A2', and so on.

Inter-fraction motion simulation was performed as follows. A treatment 'series' was pre-generated, consisting of 1000 treatment courses. Each treatment course was characterized by a normally distributed vector systematic offset, representing the average offset of the cervix COM with respect to the isocenter, and 25 normally distributed vector per-fraction offsets, representing the additional perfraction offsets of the cervix COM with respect to the isocenter. Each systematic vector offset consisted of pseudo-randomly generated RL, AP and SI components having SDs $\Sigma_{RL} = 1.5$ mm and $\Sigma_{AP} = \Sigma_{SI} = 3$ mm. Each per-fraction vector offset consisted of pseudo-randomly generated RL, AP and SI components having SDs $\sigma_{RL} = 1.5$ mm and $\sigma_{AP} = \sigma_{SI} = 3$ mm.

In each fraction of a treatment course, the sum of the systematic offset and one of the 25 random offsets was applied directly to the cervix COM, but was also used to determine the offsets applied to other voxels in the patient anatomy. In the case of motion model 1, all voxel offsets were equal to the cervix COM offset. That is, patient motion was modeled as rigid body translations. In the case of motion model 2, uterine voxel offsets were equal to the cervix COM offset multiplied by the scale factor F , described in section 2.2. F was equal to 1.0 inferior to the cervix COM, increased linearly from 1.0 to 2.5 as one moved superiorly from the cervix COM to the fundus COM, and was equal to 2.5 superior to the fundus COM. (Offsets for all voxels in the same transverse plane were the same multiple F of the cervix COM offset.) In the case of motion model 3, both uterine and OAR voxel offsets were equal to the cervix offset multiplied by the scale factor F . Note that MM2 modeled uterine motion with respect to the treatment head as a combination of shear and stretching motion: shearing in RL and AP directions and stretching in the SI direction. MM3 used the same shear/stretch model for both uterus and OAR.

For each fraction, the dose in a displaced voxel was determined by assuming shift invariance of the dose distribution. That is, voxel dose was obtained by determining the static (i.e., planned) dose at the displaced voxel position. For each voxel, dose for a treatment course was obtained by determining the shifted dose for each of the 25 fractions, and averaging. To calculate DVHs for a treatment course, it was necessary to use the above approach to calculate dose for all voxels in the CTV, CTVNodes, rectum, bladder and small bowel structures.

The series of 1000 treatment courses was ‘delivered’ (i.e., applied to each patient and scenario), resulting in 1000 DVHs for each structure, from which PDVHs were obtained. (See section 2.5 for the definition of percentile DVH.) Final results therefore consisted of 9 PDVH sets for each patient, one set for each of the 9 scenarios, each set consisting of 9 PDVHs for the CTV and OARs. Results below — e.g., Figure 4 — are presented according to scenario (A1, A2, etc). Results for each of the 9 scenarios represent a population average of PDVHs over the 10 patients.

2.5 Plan Evaluation

Inter-fraction motion is random and is not known prior to treatment delivery. Each possible motion will produce a different set of DVHs for the CTVs and OAR. In order to rigorously evaluate the effect of motion on a treatment plan, one therefore needs to capture the probabilistic nature of DVHs. In this work this is done using percentile DVHs (PDVHs), which were used in Gordon et al¹³ and are now briefly summarized.

The dose received by $v\%$ of a structure's volume is conventionally denoted by D_v , and the volume receiving dose d by V_d . If one considers only the nominal or ‘static’ treatment plan (i.e., the plan presented by the treatment planning system), D_v and V_d have unique values. However, when one accounts for motion D_v and V_d assume a range of values. They become random variables characterized by a statistical distributions. We use $D_{v,q}$ to denote the q th percentile of D_v : $\Pr[D_v \geq D_{v,q}] = q$. Similarly, $V_{d,q}$ denotes the q th percentile of V_d : $\Pr[V_d \geq V_{d,q}] = q$.

The quantity q was referred to in Gordon et al¹³ as a coverage probability. If, for a fixed value of q , one plots $D_{v,q}$ as a function of v , one obtains a pseudo-DVH that is denoted by DVH_q and is referred to as a percentile DVH. The value of $V_{d,q}$ can be read off DVH_q in the same way that V_d is read off a conventional DVH. DVH_q is an envelope DVH such that $q\%$ of realized DVHs fall above DVH_q (on a pointwise basis). Specifically, 95% of realized DVHs fall above DVH_{95} and 5% of realized DVHs fall above DVH_5 , which means that 90% of realized DVHs fall between DVH_{95} and DVH_5 . Percentile DVHs are therefore statistical confidence intervals for realized DVHs.

PDVHs can be generated for all structures. In cases where one is interested in the structure exceeding a minimum dose constraint, one will typically want to look at DVH_q corresponding to a high value of q (e.g., $q = 95\%$). Such a DVH gives a lower confidence interval for the realized values of D_v . In cases where one is interested in the structure staying below a maximum dose constraint, one will typically want to look at DVH_q corresponding to a low value of q (e.g., $q = 5\%$). Such a DVH gives an upper confidence interval for the realized values of D_v . In this work, CTV and CTVnodes doses will be evaluated using DVH_{95} and corresponding metrics $D_{v,95}$ and $V_{d,95}$, while OAR doses will be evaluated using DVH_5 and corresponding metrics $D_{v,5}$ and $V_{d,5}$. A more detailed explanation of PDVHs may be found in Gordon et al¹³.

3 Results

The top row of Figure 4 shows static DVHs for the primary PTV (P), nodal PTV (N), bladder (B), rectum (R) and small bowel (SB), for PTVs A, B and C. Rows 2-4 of Figure 4 show PDVHs for the primary CTV (P), nodal CTV (N), bladder (B), rectum (R) and small bowel (SB), for scenarios A1 – C3. Each DVH (PDVH) is a population average over 10 DVHs (PDVHs) obtained from the 10 patients.

The circles on Figure 4 indicate the prescription dose plus optimization constraints that were applied to the non-target parts of the OAR (see Methods and Materials). Note that the OAR

DVHs shown in Figure 4 are for the whole OAR, rather than the non-target portion. All plans were able to meet or closely approach the constraints on non-target OAR. Specifically, for each patient, the static DVHs for the non-target parts of OAR showed little variation in going from PTV_A to PTV_B to PTV_C. Consequently, in Figure 4 the displacement of OAR DVHs towards high dose as one moves from column 1 (PTV_A) to column 2 (PTV_B) to column 3 (PTV_C) reflects the progressively greater volumes of OAR being included in the PTV.

When combined with PTV_A, motion models 2 and 3 result in a falloff of the dose to the primary CTV. This is shown by the rounding of the CTV PDVH shoulder in scenarios A2 and A3. The sharp edge of the CTV PDVH can be restored by going to a larger margin, as in scenarios B2, B3, C2 and C3. However, the price for restoring the target dose is increased dose to the normal structures. In comparison to scenarios A* (column 1), scenarios B* (column 2) show a modest rise in normal tissue dose, particularly the percentage of the structures receiving high doses around 50 Gy. Scenarios C* (column 3) show a larger increase in normal tissue doses.

Figure 5 shows PDVHs for the primary CTV (P), cervix (C), vagina (V), uterine body (B) and fundus (F), for scenarios A3 and B3. This figure indicates that, when PTV_A is combined with motion models 3, it is the fundus dose that is most significantly eroded. This is not surprising, given that the fundus has the largest range of motion. The larger margin associated with PTV_B restores the sharp shoulder to the PDVHs for all target structures. The higher maximum doses to the vagina and cervix in scenario B3 are attributed to increased dose heterogeneity (i.e., hotter hot spots), due to the target optimization criterion for expanded PTV_B pushing more strongly against the OAR criteria.

Dose metrics $D_{v,q}$ for target and normal tissue structures are given in Table 1 for scenarios A1, A3 and B3. Target doses are quantified in terms of $D_{98,95}$, though $D_{95,95}$ shows similar behavior. In going from scenario A1 to A3, fundus doses decrease by ~5 Gy. That is, application of a realistic motion model (MM3) to a plan which does not account for the variable motion (PTV_A) results in a fundus under-dosage of ~5 Gy. This dose deficit is restored by going to the larger PTV_B margin (i.e., scenario B3). Table 1 suggests little change in bladder and rectum metrics between these 3 scenarios, except that bladder and rectum $D_{50,5}$ increase by ~2–3 Gy in going from scenario A1 to B3. The small bowel experiences larger dose increases. Between scenarios A1 and B3 small bowel $D_{15,5}$ and $D_{25,5}$ increase by 6–7 Gy while $D_{5,5}$ and $D_{50,5}$ increase by 3–4 Gy.

Note that in motion model 3, both the uterus and normal structures experience a larger range of motion as one moves superiorly. Increases in normal tissue doses between scenarios A1 and B3 may be attributed to two effects: (a) in scenario A3, the normal tissues' larger range of motion makes them more likely to move into the radiation field, and (b) in scenario B3, the expanded PTV_B margin encompasses more normal tissues. Comparison of the A3 and B3 doses in Table 1 suggests that approximately half of the noted dose increases are due to magnified normal tissue motion in motion model 3, the other half being due to margin expansion.

Table 2 gives dose metrics $V_{d,q}$ for target and normal tissue structures. The percent volume of the CTV receiving the prescription dose of 48.75 Gy falls from 99% to 95% in going from scenario A1 to A3. Most of this dose falloff is due to the fundus. The percent volume of fundus receiving the prescription dose falls from 100% to 82%. Use of PTV_B restores the fundus and CTV doses. However, in doing so the volumes of bladder, rectum and small bowel receiving higher doses are increased. In going from scenario A1 to A3 — i.e., increased target and OAR motion, but no increase in margin — the volumes of bladder,

rectum and small bowel receiving doses in the range 30-50Gy increase by up to 7%. In going from scenario A1 to scenario B3 — i.e., increased target and OAR motion, and increased margin — OAR volumes receiving doses in the range 30-50Gy increase by up to 13%.

4 Discussion

The goals of this paper were to quantify: (a) the reduction of target doses due to large uterine motion, if that motion is not addressed through expanded CTV-to-PTV margins, and (b) in the case where uterine motion is addressed via expanded margins, the corresponding increase in normal tissue doses. The results most relevant to these goals are for scenarios A1, A3 and B3. Note that scenarios A3 and B3 incorporate motion model 3, which assumes that both CTV and OAR motion increases towards the fundus. In MM3, the OAR are assumed to 'fall into' the void left by the mobile uterus. Scenarios A2 and B2 are more conservative, because in MM2 OAR motion is assumed to have the same parameters as the cervix, i.e., to be uncoupled from the uterus. Further clinical data is required in order to determine how tightly or loosely the pelvic OAR are coupled to uterine motion. Published data are ambiguous on this point. Results for scenarios A3 and B3 are emphasized here because they provide an upper bound on dose effects. Plans utilizing PTV_C are unrealistic, as few practitioners would contemplate a full 2.4 cm expansion. They are included here to illustrate the effect of using large margins which are not tapered from the fundus to cervix.

Presented with large uterine motion, scenario A3 represents the strategy of leaving margins unchanged, and allowing target dose to simply be eroded. Figure 5 shows that the main adverse consequences are for the fundus. Scenario B3 represents the opposite strategy of using whatever margins are necessary to fully preserve target dose. This strategy accepts the increase in normal tissue doses as an inevitable consequence of preserving target dose. For cervical cancer, uterine involvement is mostly limited to the lower uterus. Consequently, for scenario A3, the 5Gy dose reduction to the fundus may be clinically acceptable. For scenario B3, an increase in the volumes of rectum and bladder receiving 30-50 Gy might also be clinically acceptable, given the higher tolerance doses of these organs. However, this will not necessarily be the case for the small bowel, which has a lower tolerance dose. In practice, physicians may opt for a strategy somewhere in between A3 and B3: some margin expansion around the fundus, but not the full 2.4 cm expansion assumed by scenario B3. This is essentially what Taylor and Powell⁶ recommend. They opt for a CTV margin expansion of 1.5 cm AP and SI, which does not fully compensate for measured fundus motion, and allows some degradation of fundus dose.

We note that the conclusions of this study are dependent on the assumed motion models, specifically on the assumption in motion models 2 and 3 that fundus motion is a combination of shearing and stretching motion of the type described in section 2. To first order one would not expect the results of the study to be sensitive to the precise motion model, as long as the correct magnitude of fundus motion is reproduced. However, more elaborate motion models will become possible as clinical data accumulates, allowing more accurate modeling. Given the imprecision with which population uterine motion parameters can presently be estimated, the assumed motion models provide an acceptable estimate of target / normal tissue dose tradeoffs.

A full dosimetric study would incorporate brachytherapy dose. This would involve simulating different motion models for IMRT versus brachytherapy treatments, then combining the biological equivalent doses for the two modalities. This was beyond the current study, which sought only to characterize effect of uncertainties on IMRT treatment.

A full characterization of the effect of geometric uncertainties would also include the effect of tumor shrinkage, which was not considered in the present work.

Previous studies of uterine motion have recommended CTV-to-PTV margins that range widely from 1 cm^{2,4} to 4 cm⁷. This could be due to differences in measurements technique (e.g., whether measurements capture tumor shrinkage over a course of treatment) and treatment protocol (e.g., whether the protocol attempts to achieve reproducible rectum and bladder filling). It could also be due to inadequate statistical sampling. Several studies arrive at margins by sampling a relatively small number of image sets, and / or setting the PTV equal to the convex hull of CTV positions. The disadvantage of using a small number of samples is that it creates significant uncertainty in the estimated motion parameters, and therefore also in the margins. Assume that a motion parameter — e.g., the SD of fundus displacements — is normally distributed. A sample of 20 patients will produce an estimate $\hat{\sigma}$ whose 90% confidence intervals are $[0.73 \sigma, 1.25 \sigma]$, where σ is the true value. By chance, it may happen that the 20 images produce an estimate that is significantly low: e.g. $\sim 0.73 \sigma$. This will lead to the erroneous conclusion that small margins are sufficient. Alternatively, the 20 images could produce an estimated SD that is significantly high: e.g. $\sim 1.25 \sigma$. This will also lead to an erroneous conclusion, that margins must be large.

The confidence intervals become even wider if one uses 20 image sets to estimate a percentile of the fundus displacement. Suppose one is interested in the 95th percentile τ_{95} of the fundus displacement. This is the value such that 95% of fundus displacements are less than τ_{95} . A sample of 20 patients will produce an estimate $\hat{\tau}_{95}$ whose 90% confidence intervals are $[0.57 \tau_{95}, 1.44 \tau_{95}]$, where τ_{95} is the true value. A small sample can under- or over-estimate this parameter by up to $\sim 45\%$, leading to a similar under- or over-estimate of the required margin. The convex hull of a CTV measures the sample minimum or sample maximum of the CTV displacement. The sample minimum and maximum are surrogates for percentiles such as τ_{95} , and so are subject to similar estimation uncertainties.

Clinical datasets are typically small, up to a few tens of patients. Statistical uncertainties in the resulting motion estimates should ideally be reported. Meta-analyses of comparable studies can then progressively refine estimates of population motion parameters. We note that the SD estimates provided by Taylor and Powell are derived from 33 patients. The uncertainty in these estimates, and therefore in the corresponding margins, is approximately $\pm 25\%$.

5 Conclusions

Some, perhaps many, cervical cancer patients will experience internal uterine motion that is significantly larger than cervix motion. For the models assumed here, uterine motion reduces fundus dose by about 5Gy and increases normal tissue volumes receiving doses in the range 30-50Gy by $\sim 5\%$, relative to scenarios where the uterus is assumed to have limited motion, i.e., motion comparable to the cervix. Use of a tapered CTV-to-PTV margin that increases around the fundus can restore fundus and CTV dose to the desired levels, but will increase normal tissue volumes receiving doses in the range 30-50 Gy by a further $\sim 5\%$. Altogether, when uterine motion is large and compensated for with a tapered margin, normal tissue volumes receiving doses in the range 30-50 Gy increase by up to 13%.

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References

1. van de Bunt L, van der Heide UA, Ketelaars M, de Kort GA, Jurgenliemk-Schulz IM. Conventional, conformal, and intensity-modulated radiation therapy treatment planning of external beam radiotherapy for cervical cancer: The impact of tumor regression. *Int J Radiat Oncol Biol Phys*. 2006; 64(1):189–196. [PubMed: 15978745]
2. Roeske JC, Lujan A, Rotmensch J, et al. Intensity-modulated whole pelvic radiation therapy in patients with gynecologic malignancies. *Int J Radiat Oncol Biol Phys*. 2000; 48(5):1613–1621. [PubMed: 11121668]
3. Portelance L, Chao KS, Grigsby PW, Bennet H, Low D. Intensity-modulated radiation therapy (IMRT) reduces small bowel, rectum, and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation. *Int J Radiat Oncol Biol Phys*. 2001; 51(1):261–266. [PubMed: 11516876]
4. Mundt AJ, Lujan AE, Rotmensch J, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys*. 2002; 52(5):1330–1337. [PubMed: 11955746]
5. Heron DE, Gerszten K, Selvaraj RN, et al. Conventional 3D conformal versus intensity-modulated radiotherapy for the adjuvant treatment of gynecologic malignancies: a comparative dosimetric study of dose-volume histograms small star, filled. *Gynecol Oncol*. 2003; 91(1):39–45. [PubMed: 14529660]
6. Taylor A, Powell ME. An assessment of interfractional uterine and cervical motion: implications for radiotherapy target volume definition in gynaecological cancer. *Radiother Oncol*. 2008; 88(2):250–257. [PubMed: 18538873]
7. Chan P, Dinniwell R, Haider MA, et al. Inter- and intrafractional tumor and organ movement in patients with cervical cancer undergoing radiotherapy: a cinematic-MRI point-of-interest study. *Int J Radiat Oncol Biol Phys*. 2008; 70(5):1507–1515. [PubMed: 18164850]
8. van de Bunt L, Jurgenliemk-Schulz IM, de Kort GA, et al. Motion and deformation of the target volumes during IMRT for cervical cancer: what margins do we need? *Radiother Oncol*. 2008; 88(2):233–240. [PubMed: 18237798]
9. van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. *Int J Radiat Oncol Biol Phys*. 2000; 47(4):1121–35. [PubMed: 10863086]
10. van Herk M. Errors and margins in radiotherapy. *Semin Radiat Oncol*. 2004; 14(1):52–64. [PubMed: 14752733]
11. Lim K, Kelly V, Stewart J, et al. Pelvic radiotherapy for cancer of the cervix: is what you plan actually what you deliver? *Int J Radiat Oncol Biol Phys*. 2009; 74(1):304–312. [PubMed: 19362250]
12. Lof, J.; Rehbinder, H.; McNutt, T.; Johnson, S. P3IMRT: Inverse Planning Optimization, Philips White Paper No 4535 983 02479. 2003.
13. Gordon JJ, Sayah N, Weiss E, Siebers JV. Coverage optimized planning: Probabilistic treatment planning based on dose coverage histogram criteria. *Med Phys*. 2010; 37(2):550. [PubMed: 20229863]

Figure 1.

Sagittal views illustrating AP and SI displacements in motion models MM1 (uniform motion), MM2 (scaled uncoupled motion) and MM3 (scaled coupled motion). The primary CTV consists of cervix (C), upper vagina (V), uterine body (B) and fundus (F). OAR of interest are the bladder (B), rectum (R) and small bowel (SB). The centers of mass (COM) of the cervix and fundus are represented by gray dots. The magnitude of AP and SI motion is indicated by the size of the arrows. In MM1, CTV and OAR displacements are normally distributed with the same SDs $\Sigma = \sigma = 3\text{mm}$ regardless of position. In MM2, uterine motion (but not OAR motion) increases linearly as one moves superiorly from the cervix COM to the fundus COM. In MM3, uterine and OAR (B, R, SB) motion increase linearly as one moves superiorly from the cervix COM to the fundus COM. In all models, RL motion is independent of position with $\Sigma = \sigma = 1.5\text{mm}$.

Figure 2.

Extent of motion model 3 (MM3) organ motion for one patient. In panels (a)-(c) structure contours are shown using thick lines: CTV (pink), CTVNodes (red), bladder (yellow), rectum (dark blue), small bowel (light blue). Envelopes encompassing 90% of MM3 motion are shown using corresponding thin lines. In panel (b), contours for the bladder and small bowel are turned off in order to de-clutter the picture. In panel (d), the CTV is shown as a pink colorwash, and bladder, rectum and small bowel contours are shown as thick brown lines. Other colored lines show sampled deformations of the CTV. These deformations are at the 90th percentile of motion. A sufficiently large sample would 'trace out' the envelopes shown in panels (a)-(c).

Figure 3.

A sagittal view of the three PTV expansions of the primary CTV. PTV_A was obtained by expanding the CTV by 1cm in all directions. PTV_C was obtained by expanding CTV by 1cm in the RL direction and 2.4 cm in the AP and SI directions. PTV_B interpolates between PTV_A and PTV_C . Inferior to the cervix center of mass (COM) PTV_B is identical to PTV_A . Superior to the fundus COM it is identical to PTV_C . Between the COMs it varies linearly with SI position from PTV_A at the cervix to PTV_C at the fundus.

Figure 4.

Dose volume histograms (DVHs) for the small bowel (SB), rectum (R), bladder (B), nodal CTV/PTV (N) and primary CTV/PTV (P). Row 1 (top) gives static DVHs (no motion). Target DVHs are for the nodal PTV and primary PTV. Rows 2-4 give percentile DVHs for motion models 1–3. Target DVHs are 95th percentile DVHs (DVH_{95}) for the nodal CTV and primary CTV. Normal tissue DVHs are 5th percentile DVHs (DVH_5). Circles indicate prescription dose and optimization constraints that were applied to the *non-target* parts of OAR. Note that the OAR DVHs / PDVHs shown here are for the *whole* OAR.

Figure 5.

95th percentile DVHs (DVH_{95}) for the primary CTV (P), uterine fundus (F), uterine body (UB), cervix (C) and vaginal CTV (V). DVHs on the left are for PTV_A and motion model 3. DVHs on the right are for PTV_B and motion model 3.

Table 1

D_v (dose to volume v in Gy) for: (i) scenario A1 (PTV_A plus motion model 1), (ii) scenario A3 (PTV_A plus motion model 3), and (iii) scenario B3 (PTV_B plus motion model 3). The table gives the average value and the range of D_v . The average value is averaged over 10 patients. The range is the range of values encountered across the 10 patients.

ROI / metric	scenario A1 (PTV _A + MM1)	scenario A3 (PTV _A / MM3)	scenario B3 (PTV _B / MM3)
CTVNodes D _{98,95}	45.9 [45.4, 46.9]	45.9 [45.4, 46.9]	45.9 [45.4, 46.9]
CTV D _{98,95}	49.7 [49.4, 50.0]	46.9 [41.7, 48.9]	49.7 [48.9, 49.9]
Vagina D _{98,95}	50.0 [48.9, 50.8]	50.0 [49.0, 50.8]	49.4 [47.8, 50.6]
Cervix D _{98,95}	49.8 [49.2, 50.5]	49.8 [49.1, 50.5]	49.7 [48.9, 50.4]
Uterine Body D _{98,95}	49.7 [49.1, 50.1]	48.7 [46.6, 49.6]	49.7 [49.3, 50.1]
Uterine Fundus D _{98,95}	49.8 [49.4, 50.7]	44.5 [39.4, 47.4]	49.7 [49.0, 50.0]
Bladder D _{0,5}	53.6 [52.1, 55.2]	53.5 [52.2, 54.5]	53.6 [53.1, 54.3]
Bladder D _{5,5}	52.0 [51.1, 52.7]	52.0 [51.1, 52.7]	52.0 [51.3, 52.7]
Bladder D _{15,5}	51.2 [49.9, 52.1]	51.2 [50.1, 52.1]	51.2 [50.0, 51.9]
Bladder D _{25,5}	50.2 [47.6, 51.5]	50.3 [48.1, 51.5]	50.6 [48.1, 51.6]
Bladder D _{50,5}	45.9 [41.4, 49.9]	46.6 [42.8, 50.1]	47.6 [43.3, 50.6]
Rectum D _{0,5}	53.9 [52.7, 54.6]	53.7 [52.7, 54.5]	53.8 [53.3, 55.3]
Rectum D _{5,5}	52.2 [51.3, 52.7]	52.1 [51.3, 52.7]	52.2 [51.7, 53.1]
Rectum D _{15,5}	51.3 [50.2, 51.9]	51.2 [50.3, 51.8]	51.4 [50.9, 52.3]
Rectum D _{25,5}	50.3 [48.6, 51.2]	50.4 [48.8, 51.2]	50.9 [49.5, 51.8]
Rectum D _{50,5}	45.2 [38.5, 49.5]	46.2 [40.7, 49.8]	48.3 [41.8, 50.7]
Small Bowel D _{0,5}	52.8 [49.4, 54.5]	52.2 [49.7, 52.9]	52.4 [51.7, 53.3]
Small Bowel D _{5,5}	47.0 [41.3, 49.3]	48.0 [44.5, 49.8]	49.6 [47.7, 50.2]
Small Bowel D _{15,5}	38.4 [26.9, 46.1]	41.5 [32.9, 46.8]	44.6 [37.9, 47.9]
Small Bowel D _{25,5}	28.6 [5.1, 43.6]	33.3 [12.8, 44.6]	35.9 [12.2, 46.2]
Small Bowel D _{50,5}	14.9 [1.1, 31.1]	17.8 [1.3, 36.0]	19.0 [1.3, 37.5]

Table 2

Columns 2-4 give V_d (percent volume receiving dose d) for: (i) scenario A1 (PTV_A plus motion model 1), (ii) scenario A3 (PTV_A plus motion model 3), and (iii) scenario B3 (PTV_B plus motion model 3). Column 5 is the difference between columns 2 and 3. Column 6 is the difference between columns 2 and 4. The table gives the average value of V_d over 10 patients.

ROI / metric	scenario A1 (PTV _A + MM1)	scenario A3 (PTV _A + MM3)	scenario B3 (PTV _B / MM3)	% change A1 → A3	% change A1 → B3
CTVNodes $V_{45,95}$	99	99	99	0	0
CTV $V_{48,75,95}$	99	95	99	-4	0
Vagina $V_{48,75,95}$	100	100	99	0	-1
Cervix $V_{48,75,95}$	99	99	99	0	0
Uterine Body $V_{48,75,95}$	100	98	99	-2	0
Uterine Fundus $V_{48,75,95}$	100	82	100	-18	0
Bladder $V_{30,5}$	99	99	99	0	0
Bladder $V_{35,5}$	92	94	95	2	3
Bladder $V_{40,5}$	70	74	78	4	8
Bladder $V_{45,5}$	54	57	62	3	8
Bladder $V_{50,5}$	30	32	37	2	7
Rectum $V_{30,5}$	81	84	86	3	5
Rectum $V_{35,5}$	72	76	80	4	8
Rectum $V_{40,5}$	63	67	74	4	11
Rectum $V_{45,5}$	52	56	65	4	13
Rectum $V_{50,5}$	32	33	44	1	12
Small Bowel $V_{30,5}$	27	34	37	7	10
Small Bowel $V_{35,5}$	21	27	30	6	9
Small Bowel $V_{40,5}$	16	20	24	4	8
Small Bowel $V_{45,5}$	10	12	17	2	7
Small Bowel $V_{50,5}$	2	2	5	0	3