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FULL PAPER

Vaginal displacement during course of adjuvant radiation for cervical cancer: results from a prospective IG-IMRT study

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Objective: To compare internal target volume (ITV) generated using population-based displacements (ITV_study) with empty and full bladder scan fusion (ITV_EBFB) for organ-at-risk (OAR) doses during adjuvant intensity-modulated radiation therapy (IMRT) for cervical cancer.

Methods: From January 2011 to October 2012, patients undergoing IMRT were included. CT simulation was carried out after inserting vault markers. Planning target volume (PTV)_EBFB received 50 Gy per 25 fractions. Pre-treatment megavoltage CT (MVCT) was performed. MVCTs were registered using bony landmarks with Day 1 MVCT. Displacement of the centre of mass of markers was measured along each axis. Directional ITV was calculated using mean $\pm$ 2 standard deviations (SDs) (ITV_study). Replanning was performed using PTV study, and OAR doses were compared with PTV_EBFB using Wilcoxon test.

Results: A total of 348/386 data sets were evaluable for 16 patients. The median vaginal displacement was 1.2 mm (SD, 1.3 mm), 4.0 mm (SD, 3.5 mm) and 2.8 mm (SD, 3.3 mm) in the mediolateral, superoinferior and anteroposterior directions, respectively. The ITV margins were 4.1, 10.3 and 10.6 mm. ITV_study and ITV_EBFB were 115.2 cm³ (87.7–152.2 cm³) and 151 cm³ (95.7–277.1 cm³) ($p < 0.0001$), respectively. PTV_study and PTV_EBFB were 814 and 881 cm³ ($p < 0.0001$), respectively. Median doses to the bladder were lower with the PTV_study (46.2 Gy vs 43.2 Gy; $p = 0.0001$), and a similar trend was observed in the volume of the small bowel receiving 40 Gy (68.2 vs 60.1 cm³; $p = 0.09$).

Conclusion: Population-based PTV margins can lead to reduction in OAR doses.

Advances in knowledge: Population-based ITV may reduce OAR doses while executing adjuvant IMRT for cervical cancer.

Adjuvant pelvic radiation for cervical and endometrial cancers is recommended in patients with adverse histopathological features following surgery.^{1,2} Although it improves outcomes, it is associated with increased acute and late bowel morbidity.^{1,2} Recently published results of the Radiation Therapy Oncology Group (RTOG) Phase II study demonstrate that the use of pelvic intensity-modulated radiation therapy (IMRT) is associated with reduced treatment-related acute and short-term gastrointestinal (GI) toxicity, and this can be achieved without worsening disease control.³ However, implementing IMRT may be challenging owing to the unpredictable nature of vaginal displacements during the course of external radiation. Therefore, the RTOG recommends that for planning IMRT, both empty and full bladder (EBFB) scans should be obtained for localizing residual vagina and for generating the internal target volume (ITV).⁴ These recommendations are being followed by two ongoing Phase III randomized

controlled trials that aim at reducing acute and late bowel toxicity of adjuvant pelvic radiation.^{5,6} Although this strategy may ensure that all extreme displacements arising out of variations in bladder filling are accounted for, this may result in increased planning target volume (PTV) and thereby increased dose to adjacent organs at risk (OAR). Strong correlation has been reported between the dose received by the bowel and late bowel morbidity after adjuvant pelvic radiation for cervical cancer.⁷ The present study was initiated with an aim of evaluating vaginal displacement for the post-hysterectomy cohort and to investigate if population-based ITV could reduce dose to OARs.

METHODS AND MATERIALS

The present study was conducted on megavoltage CT (MVCT) data sets of patients with cervical cancer scheduled to receive post-operative adjuvant image-guided (IG)-IMRT

with or without chemotherapy and randomized to the tomotherapy arm within the context of ongoing institutional ethics committee-approved Phase III randomized controlled trial.⁵ The study included patients who had undergone simple or Wertheim's hysterectomy and required adjuvant treatment owing to adverse pathological risk factors or suboptimal nodal dissection. Patients with gross residual local or nodal disease, para-aortic disease, history of multiple abdominal surgeries or medical conditions placing patients at high risk of baseline GI dysfunction were excluded.

Fiducial marker placement

All patients underwent silver marker placement in the vaginal apex prior to simulation. Patients were positioned in lithotomy position, and the vaginal apex was identified through per speculum examination. Silver markers (one each) were inserted in the left and right vaginal apex. All patients received 3 days of antibiotics (500 mg of ciprofloxacin twice daily) following marker insertion.

CT simulation

Patients were instructed to report for CT simulation after evacuating bowel contents. No specific dietary modification or stool softeners were prescribed. Radiation planning scans were obtained with EBFB to encompass unpredictable bladder filling.^{4,8} For the EB scan, patients were instructed to void the bladder. Patients were positioned supine with arms above their heads. Three radio-opaque fiducial markers were placed at laser intersection points on the lower abdomen and a radio-opaque marker was placed at the vaginal introitus while obtaining the scan. CT scan was obtained from L2–3 junction to mid-thigh at an interslice thickness of 3 mm. After the EB scan, patients were instructed to consume 500 ml of water and wait for 30 min. Patients were repositioned and imaged after injecting intravenous contrast at approximately 40 min after consuming water. Both the image data sets were exported to the Oncentra® (Nucletron, Stockholm, Sweden) treatment planning system v. 4.1 for target volume delineation.

Target delineation and treatment details

Rigid bony registration was performed for FB and EB data sets. While FB scan formed the primary data set, the EB scan formed the secondary data set. Within these data sets, the vault and introitus markers were used to define the length of the vagina. For each of the data sets, the upper half of the vagina was contoured. As the vesical peritoneum is surgically violated during hysterectomy, the vaginal contour was expanded anteriorly by 1.0–1.5 cm and superiorly by 1.0 cm, posteriorly till the mesorectal fascia and laterally till the pelvic muscles, to generate the clinical target volume EBFB (CTV-EB and CTV-FB). Contours were not edited from distensible or mobile OARs. Boolean operation was used to perform a union of CTV-FB and EB to generate the ITV (ITV-EBFB). Another 7-mm margin was added to ITV to generate PTV for the primary tumour bed. Nodal delineation was carried out using standard guidelines.⁸ Nodal CTV was expanded by 5 mm to generate nodal PTV. Boolean operation was used to perform a union of nodal and primary PTV to generate the final PTV (or PTV EBFB). The OARs except the bowel were delineated using standard guidelines.⁹ The bowel delineation included contouring individual small and large

bowel loops. All patients received 50 Gy per 25 fractions over 5 weeks with or without concurrent chemotherapy. This was followed by vaginal high-dose-rate brachytherapy (12 Gy per two fractions, each fraction delivered 1 week apart).

Image guidance during treatment

Patients were instructed to report after evacuating the bowel and were instructed to repeat the FB regimen, as at the time of the planning scan for daily treatment. A daily pre-treatment MVCT was performed. The daily imaging volume was selected from L4 to the lower extent of the pelvis such that the entire planned target volume was scanned, with some additional margin. The “normal” setting on tomotherapy (4-mm slice thickness) was used for MVCT scanning. Automated registration of the planning kilovoltage CT and daily MVCT images was performed using rigid bony registration. All translations and rotations were recorded but only translational shifts and roll were applied for patient position correction. The pitch and yaw rotations in the patient set-up were recorded but not applied. The treatment was delivered, and a post-treatment MVCT scan was also performed.

Evaluation of vaginal displacement

MVCT images were transferred to the FOCAL® SIM v. 4.3.3 (CMS Medical Systems, Oldham, UK) workstation. The Day 1 MVCT images served as baseline images for evaluation of interfraction vaginal displacement. All subsequent MVCT images were co-registered with Day 1 MVCT using rigid bony registration such that residual displacements of vaginal markers represent internal organ motion. If the vaginal marker was seen in only one MVCT slice, then that particular slice was considered as the reference slice. If, however, the vaginal marker was seen in two slices, then consistently, the caudal slice was used for the purpose of analysis. If two markers were seen on the same slice, then only one marker (right sided) was used to calculate the displacement. If no vaginal marker was identified, then that particular CT data set was excluded from analysis. Vaginal marker in an axial slice was visible as a point or elliptical radio-opaque structure. A three-dimensional (3D) localizer point was placed over the visualized marker to obtain the 3D location or centre of marker (COM). For each fraction, the displacement of this COM from the baseline was recorded. The right, superior and anterior displacements were coded as positive displacements and the left, posterior and inferior displacements as negative displacements from the baseline or Day 1 MVCT. While the medio-lateral (ML) and anteroposterior (AP) displacements could be recorded within an accuracy of <1 mm, the evaluation of the craniocaudal (CC) displacement was limited by the MVCT slice thickness (*i.e.* 4 mm). For each patient, we calculated the mean and standard deviation (SD) of displacement in the ML, AP and CC directions. ITV margins were calculated using various published margin expansion formulae.^{10,11} In addition, ITV was generated using 95% confidence intervals (95% CI) around the directional mean (mean $\pm$ 2SD). This directional expansion was applied to CTV FB and was named as ITV_study for the purpose of this investigation.

Planning target volume and organ-at-risk doses

Using ITV_study and ITV_EBFB, an isotropic expansion of another 7 mm was applied to generate PTV_study and

Table 1. Residual vaginal length at simulation and bladder volumes of patients during the course of radiation

Number	Vaginal length (cm)	Bladder volume Fr 1 (cm ³)	Bladder volume Fr 3 (cm ³)	Bladder volume Fr 6 (cm ³)	Bladder volume Fr 9 (cm ³)	Bladder volume Fr12 (cm ³)	Bladder volume Fr15 (cm ³)	Bladder volume Fr 18 (cm ³)	Bladder volume Fr 21 (cm ³)	Bladder volume Fr 24 (cm ³)	Variation bladder filling (cm ³)
1	6.8	522	323	447	316	180	370	390	228	380	342
2	7.5	490	240	510	446	282	296	200	210	190	320
3	6.3	373	440	570	537	393	452	200	280	400	370
4	6.5	229	230	321	317	280	337	279	238	200	137
5	5.0	254	225	370	170	190	200	230	270	230	200
6	8.3	120	154	133	105	108	70	58	75	73	96
7	6.5	560	285	396	320	290	282	268	330	200	360
8	7.5	290	310	282	382	180	325	386	440	305	260
9	7.0	196	360	358	294	170	80	220	314	181	280
10	9.0	390	260	430	292	300	250	380	307	310	180
11	8.7	503	417	440	455	569	434	555	410	401	168
12	7.0	680	670	515	340	300	456	520	340	293	387
13	8.0	490	240	510	446	282	296	205	210	190	320
14	8.0	290	240	320	220	270	260	311	260	330	110
15	9.0	250	233	430	450	305	400	170	297	220	280
16	6.6	273	380	250	480	440	380	287	308	398	130
Average	7.3	369	313	393	348	284	306	291	282	269	246

Fr, fraction.

The values in bold reflect the minimum and maximum bladder volumes during the course of the radiation treatment.

Table 2. Directional organ motion for the study population (mm)

Direction	Mean	Median	SD	Range	Mean $\pm$ 2 SD (95% confidence interval)
Mediolateral	1.5	1.2	1.3	0–7.6	4.1
Craniocaudal	3.6	4.0	3.5	0–16.0	10.3
Anteroposterior	3.7	2.8	3.3	0–18.3	10.6

SD, standard deviation.

PTV_EBFB, such that the PTV_study represented the PTV with population-based margins and the PTV_EBFB represented the PTV generated using EBFB fusion. A new plan was generated for the PTV_study for each of the patients using dose constraints and iterations as at the time of the original plan (PTV_EBFB). The PTV and OAR doses were compared to evaluate differences if any occurred.

Statistical analysis

All analyses were performed using SPSS® v. 21 (SPSS Inc., Chicago, IL). The displacements in each direction over the course of IMRT are depicted as mean and median. The volume of ITV, PTV and the mean and median doses for all OARs were obtained and compared for the PTV_study and PTV_EBFB using Wilcoxon test for paired samples.

RESULTS

A total of 16 patients received IG-IMRT. Of these, seven had undergone Wertheim's hysterectomy and nine had undergone hysterectomy without pelvic lymph node dissection. A total of 14/16 patients received concurrent chemoradiation (87.5%), and all received brachytherapy. An average of 21 (14–25) data sets were available for the study cohort. Of the available 386 image data sets, 348 (90%) data sets were included for the present study. A total of 37 CT data sets were excluded owing to non-visualization or poor visualization of the vaginal marker. One CT data set was excluded as the vaginal marker had displaced within the overlying small bowel loop. Of the 348 data sets available for analysis, the vaginal marker was visible in more than one slice in almost half of the image sets.

The residual vaginal length for each of the study patients and bladder volumes during the course of radiation are depicted in Table 1. The median displacement of vaginal vault was 1.2, 4.0 and 2.8 mm in the ML, CC and AP directions, respectively. The mean, SD and range of displacements are detailed in Table 2. Figure 1 represents the displacement of vault markers for the entire study population over the course of IG-IMRT. There was no specific trend in directional displacement. The discrete pattern of the CC histogram is explained by the interslice distance of 4 mm. The population systematic error (Σ) in the ML, CC and AP directions was 0.84, 1.91 and 1.69 mm, respectively. The population random error (σ) in the corresponding directions was 1.11, 3.06 and 2.89 mm, respectively. The random errors in our patient cohort were greater than the systematic errors.

Internal target volume margins

ITV margins were calculated using 95% CI, and Stroom's and van Herk's formulae^{10,11} (Table 3). Using the 95% CI formula, the ITV

margin in the ML, CC and AP directions was 4.1, 10.3 and 10.6 mm, respectively. The corresponding values were 2.5, 5.9 and 5.4 mm with the Stroom's formula and 2.9, 6.9 and 6.3 mm with the van Herk's formula (Table 3). Using van Herk's and Stroom's expansion recipe, 72% and 67% of ML, 83.2% and 82.5% for CC and 86.2% and 82.0% of AP displacements could be accounted, respectively. Therefore, 95% CI-based margins were used for generating ITV_study.

The mean of the ITV_study and ITV_EBFB was 115.2 cm³ (87.7–152.2 cm³) and 151 cm³ (95.7–277.1 cm³), respectively, and the difference between the two volumes was statistically significant ($p < 0.0001$). The difference in patient-specific ITVs is depicted in Figure 2. Using the proposed margins, the vault markers were outside the ITV_study in only 4 patients and constituted 21/348 fractions. While the target was outside the ITV_study in two, one and one fraction in three patients, respectively, for another patient, the target was outside the ITV study in eight treatment fractions.

The mean of the PTV_study and PTV_EBFB was 814 and 881 cm³ ($p < 0.0001$), respectively. The median doses to the urinary bladder, rectum, sigmoid, large bowel and small bowel are detailed in Table 4. Of these, median doses to the urinary bladder were significantly different from those of PTV_EBFB leading to higher median doses (Table 4). Furthermore, planning on PTV_study contours demonstrated a statistical trend towards reduction of volume of small bowel receiving 40 Gy and non-statistical reduction in 15 Gy, a metric correlated with reduction of acute and late bowel toxicity.⁷

DISCUSSION

IMRT has a favourable therapeutic ratio for radical and adjuvant treatment of gynaecological malignancies.^{12–18} However, small-bowel sparing achieved with the use of IMRT is markedly reduced by relatively small expansions of the target volume. Therefore, accurate target delineation, highly reproducible patient immobilization and a clear understanding of internal-organ motion are needed to achieve optimal advantage in the use of IMRT over conventional methods of post-hysterectomy pelvic radiation therapy.¹² Dosimetric and prospective clinical studies demonstrate that decreased bowel and bladder doses translate into decreased incidence of acute and possibly late grade $\geq$ II GI and urinary toxicity.^{7,19,20} IMRT is also associated with steeper dose gradients around target volumes, increasing the risk of underdosing or overdosing of a target as well as OAR, if either the patient set-up or organ motion is not properly addressed. There is paucity of data evaluating the extent of vaginal movement during the course of adjuvant radiation.^{19–22} The post-operative surgical bed and bowel/bladder filling patterns in post-hysterectomy patients are distinct from those of an intact

Figure 1. (a) Scatterplot for displacements in the mediolateral direction. (b) Scatterplot for displacements in the anteroposterior direction. (c) Scatterplot for displacements in the craniocaudal direction.

patient. Even after a uniform bladder filling protocol, the bladder filling patterns may not be uniform over a 5- to 6-week period of external radiation leading to unpredictable vaginal displacements.^{4,21}

Therefore, the RTOG recommends generation of ITV through target volume delineation in EBFB pelvic scans in an attempt to capture the maximum excursion of the vagina, at least related to

Table 3. Internal target volume margins as per various formulae

Direction	Component of error (mm)		Margin generation with various formulae (mm)		
	Systematic (Σ)	Random (σ)	von Herk's ($2.5\Sigma + 0.7\sigma$)	Stroom's ($2\Sigma + 0.7\sigma$)	95% confidence interval (mean + 2 standard deviations)
Mediolateral	0.84	1.11	2.88	2.46	4.1
Craniocaudal	1.91	3.06	6.92	5.96	10.3
Anteroposterior	1.69	2.89	6.25	5.40	10.6

bladder filling.⁸ But data are lacking to demonstrate that the vaginal excursion, as defined by one set of EBFB CT images, truly defines the maximal possible excursion of the vagina throughout a 5- to 6-week course of treatment. There are only a few studies evaluating vaginal displacement during the course of adjuvant pelvic radiation.

Ma et al¹⁹ evaluated vaginal displacement for 11 patients during adjuvant radiation through displacement of vaginal cuff markers placed prior to CT simulation. Authors used vaginal dilator during simulation; however, none during treatment was used. No explicit bowel or bladder instructions were given to the patients. The displacement of the vaginal apex during the course of adjuvant radiation was compared for daily images with Day 1 MVCT (without dilator). The average vaginal cuff displacement was 16.2 mm when referenced to simulator position (with dilator). In the axial plane, the mean and maximum cuff displacement was 12.9 and 30.7 mm, respectively. In CC axis, the mean and maximum displacement were 10.3 and 27.0 mm, respectively. The probability of vaginal cuff outside the planned CTV (not PTV) decreased to <5% with a margin of 2.5 cm, however at the cost of OAR doses.²² In another small study on five patients, Rash et al²⁰ observed mean displacement of 7.0, 3.0

and 2.9 mm in the AP, ML and CC directions, respectively. While authors reported significant interfraction displacement, they did not provide any recommendation for ITV expansion.

In a study on patients undergoing tomotherapy-based IG-IMRT, Harris et al²² recommended that 3.1, 9.5 and 12.1 mm of ML, CC and AP expansions, respectively, can encompass 95% of vaginal displacements during adjuvant radiation. The mean COM displacement of 15.7 and 19.8 mm could encompass 95% and 99% of all displacements, respectively, and directional displacement data should be used. This is very similar to our study wherein 4.1, 10.6 and 10.3 mm of ML, CC and AP margins, respectively, could encompass 95% of the observed displacements. We also analysed the systematic and random component of error in vaginal displacement and observed that the random errors in localizing the vaginal apex exceeded the systematic component thereby making the published expansion margin formulae ineffective in describing the margin for expansion. As seen in our results, van Herk's and Stroom's expansion formulae^{10,11} led to a coverage of the target only in 67–86% of the cases.

In another study, in patients undergoing adjuvant radiation, Jhingran et al²¹ obtained twice weekly CT scans during treatment

Figure 2. Figure depicting internal target volume (ITV) for each patient using empty and full bladder (EBFB) scans and 95% confidence interval along directional displacements.

Table 4. Table depicting doses received by adjacent organs with internal target volume (ITV) generation using empty and full bladder (EBFB) scan fusion and with margins derived using population data

Variable	EBFB ITV method	Population-based ITV method	p-value
Bladder dose (Gy) (median)	46.2	43.2	0.001
Rectum dose (Gy) (median)	46.4	45.0	0.215
Sigmoid dose (Gy) (median)	45.5	45.2	0.756
Large bowel dose (Gy) (median)	24.5	25.5	0.121
Small bowel dose (Gy) (median)	27.5	27.6	0.776
Small bowel V15 Gy (absolute vol cm ³)	174.0	159.7	0.438
Small bowel V40 Gy (absolute vol cm ³)	68.2	60.1	0.098
Large bowel V15 Gy (absolute vol cm ³)	213.2	204.6	0.679
Large bowel V40 Gy (absolute vol cm ³)	68.0	70.3	0.733

Vol, volume.

of 16 patients and reported a median of maximum vaginal displacements of 5.9 mm (0–9 mm), 14.6 mm (8.0–27.9 mm) and 12 mm (6.0–21.1 mm) in the ML, AP and CC directions, respectively. However, as they observed large displacements as a result of rectal and bladder filling instead of recommending an average expansion in each direction on the basis of 95% or 99% CI, the authors recommended that the ITV be generated by fusing empty and bladder CT simulation data sets. This method although generously encompassing excursions due to bladder changes, may not necessarily encompass rectal excursions. Furthermore, owing to generous ITV expansions (which do not necessarily represent day-to-day variation), this method may lead to increased OAR doses. In an attempt to compare the RTOG approach with our study approach, we generated ITV and PTV using EBFB scans and study (95% CI) expansion method. As seen in the results, the ITV expansion using EBFB scans leads to statistically significant increase in the bladder dose (which may possibly contribute towards post-surgical and post-radiation bladder complications) and a trend towards increasing the volume of small bowel receiving doses >40 Gy and a non-significant difference in the volume receiving 15 Gy. Although the clinical significance of these minor changes in volumes and bladder and small bowel doses can be questioned, an individualized margin (as generated from reviewing image data sets of patient population) ensures that all displacements (bladder or rectal) are encompassed.

Our study demonstrates that there may be some merit in considering individualized margins, however, the limitations include generating PTVs using population rather than individual data. This was considered appropriate by us, as the individual data for a given patient will never be available before the

initiation of radiation. Secondly, although the overall measured displacement did account for both vaginal and rectal excursions, we did not specifically investigate whether it arose from the bladder or rectal volume changes. Thirdly, although we recommend using individualized directional margins, this may not be applicable to patients with post-surgical bladder atony or post-surgical bladder complications. In such a scenario, obtaining EBFB scans may be more appropriate for ITV generation. We did not specifically investigate the probability of geographical misses using the EBFB ITV generation method; however, using the 95% CI method in 21/348 fractions, the target could possibly be outside the ITV_study. In a vast majority of fractions wherein the target is missed, the vaginal vault markers would lie outside the ITV by 0.5–2 mm. Considering that a separate PTV margin of 7 mm and daily image guidance is used to minimize set-up errors, these minimal variations may be fully or partially compensated by the PTV margin. We therefore hypothesize that an individualized method may possibly be marginally superior to the EBFB method of ITV generation in terms of target volume coverage, as it contains displacements owing to the rectal and bladder movement and may also facilitate OAR dose reduction.

CONCLUSIONS

Adopting patient population-based ITV leads to high probability of target volume coverage and reduction in dose received by the bladder and small bowel as compared with ITV generation using EBFB scans in patients undergoing post-hysterectomy radiation.

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