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FULL PAPER

Internal target volume for post-hysterectomy vaginal recurrences of cervical cancers during image-guided radiotherapy

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Objective: The outcome of post-surgical recurrences of cervical cancer may be improved through radiation dose escalation, which hinges on accurate identification and treatment of the target. The present study quantifies target motion during course of image-guided radiotherapy (IGRT) for vault cancers.

Methods: All patients underwent planning CT simulation after bladder-filling protocol. A daily pre-treatment megavoltage CT was performed. All translations and rotations were recorded. Post-registration displacement of gross tumour volume (GTV) and centre of mass (COM) of GTV was independently recorded by two observers for fractions one to seven. Day 1 image sets served as reference images against which the displacements of COM were measured. We calculated the displacements of common volume (CV) and encompassing volume (EV) of GTV for both the observers.

Results: A total of 90 image data sets of 15 patients were available for evaluation. Individual patient GTV

and average GTV by both the observers were comparable. The average shifts for EV were 2.4 mm [standard deviation (SD) ± 1.2] in the mediolateral, 4.2 mm (SD ± 2.8) in the anteroposterior and 4.0 mm (SD ± 2.1) in superoinferior directions. Similarly, the average shifts for CV were 1.9 mm (SD ± 0.6) in the mediolateral, 3.7 mm (SD ± 2.7) in the anteroposterior and 4.4 mm (SD ± 2.7) in superoinferior directions. Using Stroom's/van Herk's formula, the minimum recommended margins would be 4.5/5.2, 8.2/9.4 and 7.3/8.3 mm, respectively, for lateral, anteroposterior and superoinferior directions.

Conclusion: Differential directional internal margin is recommended in patients undergoing IGRT for post-surgical recurrence of cervical cancers.

Advances in knowledge: Internal organ motion of vault cancers can be accounted for by a directional margin to the gross tumour.

INTRODUCTION

External beam radiation for uterine malignancies has rapidly evolved in the last two decades. The availability of high-precision treatment delivery techniques such as intensity-modulated radiotherapy (IMRT) allows highly conformal dose distributions. This translates into significant reduction in organ-at-risk dose and thereby acute and possibly late gastrointestinal and haematological toxicities along with high compliance to the treatment.^{1,2} Post-surgical recurrences of cervical cancer have the modest outcomes following the treatment with chemoradiation. The 5-year survival in various studies has ranged from 25% to 85%.^{3–5} We recently published our results.⁶ In this cohort, the 3-year actuarial survival was 64% with local recurrence in 39% of the patients. The integration of

advanced image guidance and ability to escalate the delivered dose-to-target volume has demonstrated improvement in local control for locally advanced cervical cancer.⁷ While in patients with intact uterus, dose escalation is essentially achieved by image-guided brachytherapy, for post-surgical recurrences, this could be achieved possibly both by image-guided external radiation and/or brachytherapy. However, any strategy for dose escalation through external radiation hinges on accurate identification and characterization of target displacement on verification images and subsequently minimizing target displacement. We published our data on performance of megavoltage CT (MVCT) images in target identification and demonstrated that MVCT images can be reliably used for identifying gross tumour volume (GTV) in vaginal vault after

hysterectomy for cervical cancer.⁸ The present study was designed to characterize patterns of GTV displacement and hence obtain internal target volume (ITV) for vault cancers during the course of pelvic radiation.

METHODS AND MATERIALS

MVCT data sets of patients undergoing image-guided radiotherapy (IGRT) on helical tomotherapy for post-hysterectomy recurrence of cervical cancer (www.clinicaltrials.gov NCT01117402) from November 2009 to August 2010 were included.

Treatment planning

All patients underwent CT simulation after bladder filling. The patients were instructed to empty bowel and bladder and then consume 500 ml of water over half an hour. All planning images were obtained after 30 minutes of water consumption. For treatment planning, all patients were positioned supine with knee rest and arms above the head. Contrast-enhanced CT (CECT) was obtained at an interslice interval of 3 mm, and all images were transferred to Focal Sim workstation v. 4.3.3 (CMS medical systems, St Louis, MO) for contouring. No oral contrast was used. GTV was delineated after using information from clinical examination and imaging [including diagnostic CT and T_2 weighted (T_2 -W) MRI]. Clinical target volume (CTV) for primary included cranial and anterior expansion of GTV by 1 cm and posterior expansion of 7 mm (extending up to mesorectal fascia). Laterally, the CTV expanded to medial extent of pelvic wall muscles. The CTV primary was expanded by 1 cm (7 mm posteriorly) to generate planning target volume (PTV) primary. Nodal CTV was delineated as per the guidelines for pelvic nodal contouring⁹ and expanded by another 5 mm to generate nodal PTV. No distensible organs were edited out of nodal CTV/PTV. All treatment planning was performed on TomoTherapy® Hi-ART® treatment planning system (TomoTherapy Inc., Madison, WI). All patients received 50 Gy for 25 fractions to the PTV over 5 weeks along with concomitant weekly cisplatin (40 mg m^{-2}). This was followed by pelvic interstitial brachytherapy to a total dose of 20 Gy for 5 fractions for 3 days.

Megavoltage CT imaging

The patients were instructed to repeat bladder regimen, as at the time of the planning scan. A daily pre-treatment MVCT was performed to correct for set-up errors and organ motion. The daily imaging volume was selected from vertebral level L4 to the lower extent of the pelvis such that the entire PTV was scanned, with some additional margin. The “normal” setting (4-mm slice thickness) was used for MVCT scanning. Automated registration of the planning kilovoltage beam CT (KVCT) and daily MVCT images was performed using bony anatomy. If the registration was not optimal, patient was repositioned and rescanned. All translations and rotations were recorded, but only translational shifts and roll were applied to the patient’s treatment position. The pitch and yaw in patient set-up were recorded but not applied. The treatment was delivered and a post-treatment MVCT scan was also performed. These post-treatment MVCT images were transferred to the Focal Sim (CMS medical systems) workstation for recording the displacements.

Contouring

To avoid the effect of tumour shrinkage on assessment of three-dimensional displacement, post-registration MVCT images from

fractions one to seven were used. Two radiation oncologists (MNU and SC) contoured GTV on MVCT image sets while blinded to their own and each other’s contours. Both observers were asked to select the most appropriate window and level for contouring.

GTV was recorded for each of the observers for fractions one to seven. In addition, centre of mass (COM) of GTV was determined for both observers. Day 1 image sets served as reference images against which the displacements of COM were measured.

As another parallel study from our group⁸ had demonstrated concordance between two observers in delineating GTV on MVCT images, displacements of either observer were considered to represent the “truth”. Paired *t*-test was performed to test the statistical validity of this assumption. However, as the concordance did not approach unity,⁸ we also calculated the displacements of common volume (CV) and encompassing volume (EV) of GTV separately for each of the observers. CV was defined as the “common volume contoured by both the observers: $CV = V_1 \cap V_2$ ”, and EV was the “combined volume by both the observers: $EV = V_1 \cup V_2$ ”. While the displacement of COM of CV represents minimum true displacement, the displacement of EV represents maximum displacement including component of localization uncertainty of the target volume as identified by the treating therapist or oncologist.

Statistics

Average displacements and standard deviation (SD) in COM in each direction were recorded for each of the image sets for each patient and observer. Similarly, the average displacements and SD in COM for EV and CV were also calculated. Margins for CTV to ITV expansion were calculated by first estimating the systematic and random displacements. In brief, the systematic component of the displacement was the displacement in gross tumour that was consistently present during all fractions. For an individual patient, the systematic displacement was assessed by mean values of all the displacements, and for the entire population, the systematic error was represented by SD from the mean values of all the patients. The random displacement of GTV for an individual patient is the dispersion around the systematic displacement. For the entire population, the random displacement was represented as root mean square of SD of all the patients. Systematic and random errors were calculated using the margin recipes using the Stroom’s ($2 \Sigma + 0.7 \sigma$)^{10,11} and van Herk’s formulae ($2.5 \Sigma + 0.7 \sigma$).¹²

RESULTS

GTV was delineated on a total of 90 image data sets of 15 patients by 2 observers. The GTV for each patient on T_2 -W MRI and on MVCT scan is depicted in Table 1. While MVCT contours were larger than that of T_2 -W MRI, there was a high agreement in the contoured volumes on MVCT between Observers 1 and 2 (Pearson’s correlation = 0.973). The shifts of the COM of GTV were averaged for each patient for Observers 1 and 2 and are depicted in Table 2. The average shifts for Observer 1 were 2.4 mm (SD ± 1.5) in the mediolateral, 3.7 mm (SD ± 2.6) in the anteroposterior and 3.7 mm (SD ± 2.1) in the

Table 1. Average gross tumour volume (GTV) of the target on T_2 weighted MRI and as contoured by each observer on megavoltage CT. Columns 5 and 6 depict average encompassing volume (EV) and common volume (CV) for each of the patients

Number	MR volume (cm ³)	Observer 1 GTV (cm ³)	Observer 2 GTV (cm ³)	EV (cm ³)	CV (cm ³)
1	4	17.83	15.23	22.75	13.13
2	32	27.30	32.37	41.33	22.30
3	26	51.63	43.93	62.72	37.15
4	24.5	39.37	40.54	51.74	30.47
5	37.5	50.91	52.23	65.54	41.3
6	NA	20.73	19.88	29.85	12.1
7	NA	25.40	35.50	44.43	20.0
8	8.4	16.63	22.33	26.8	14.8
9	49.2	33.23	40.23	51.63	26.67
10	8.4	18.67	18.57	24.26	16.43
11	42.8	84.23	84.61	103.56	72.13
12	NA	76.06	76.80	104	60.73
13	17	34.10	39.17	42.83	29.31
14	38.6	73.76	66.49	91.16	56.79
15	NA	65.93	57.11	79.10	46.73
Average	26.2	42.39	42.99	56.11	33.33
Median	26	34.10	40.23	51.63	29.31
Standard deviation	13.7	23.23	21.11	27.62	18.75

NA, not applicable.

craniocaudal directions. Similarly, the average shifts for Observer 2 were 2.5 mm (SD ± 1.2) in the mediolateral, 4.1 mm (SD ± 2.4) in the anteroposterior and 4.1 mm (SD ± 2.1) in the craniocaudal directions. The paired *t*-test was statistically non-significant for displacements in each of the directions ($p = 0.70$, 0.60 and 0.40, respectively).

To compensate for the interobserver variation in target delineation, we evaluated displacements of CV and EV. The average displacement of COM of the CV and EV for each of the patients is depicted in Table 2. The average shifts for EV were 2.4 mm (SD ± 1.2) in the mediolateral, 4.2 mm (SD ± 2.8) in the anteroposterior and 4.0 mm (SD ± 2.1) in superoinferior directions. Similarly, the average shifts for CV were 1.9 mm (SD ± 0.6) in the mediolateral, 3.7 mm (SD ± 2.7) in the anteroposterior and 4.4 mm (SD ± 2.7) in superoinferior directions. These results are tabulated in Table 2.

Margins calculated using the Stroom's, van Herk's and mean + 2 SD formulae is depicted in Table 3. With Stroom's formula, the

minimum recommended margins were 4.5, 8.2 and 7.3 mm, respectively, for mediolateral, anteroposterior and superoinferior directions. It increased to 5.2, 9.4 and 8.3 mm with van Herk's formula, respectively. The proposed ITV using directional mean + 2 SD (which would encompass 95% of the displacements) was 3.1, 8.4 and 9.2 mm in mediolateral, craniocaudal and anteroposterior directions, respectively.

DISCUSSION

The use of image-guided radiotherapy (IGRT) has led to refinement in treatment delivery. Online MVCT/KVCT imaging allows daily soft-tissue target localization.^{13–16} The information provided by daily scans can also be used for adaptive radiotherapy planning^{17,18} and most importantly for the ITV calculation for delivering IGRT.^{19,20} However, the generation of ITV necessitates careful identification of targets on MVCT/KVCT scans. For the conduct of the present study, we hypothesized that the displacement characteristics of central recurrences may be different than that of uterus^{21–23} and post-surgical vaginal remnant^{24–27} and

Table 2. Mean displacement of centre of mass and standard deviation of gross tumour volume (GTV) (Observers 1 and 2), encompassing volume (EV) and common volume (CV) for the study population

Direction	Observer 1 GTV (mm)	Observer 2 GTV (mm)	EV (mm)	CV (mm)
Mediolateral	1.82 $\pm$ 1.80	1.85 $\pm$ 1.5	2.44 $\pm$ 1.2	1.97 $\pm$ 0.6
Anteroposterior	3.01 $\pm$ 2.5	3.44 $\pm$ 2.9	4.18 $\pm$ 2.8	3.67 $\pm$ 2.7
Craniocaudal	2.72 $\pm$ 2.2	1.82 $\pm$ 1.8	4.01 $\pm$ 2.1	4.36 $\pm$ 2.7

Table 3. Internal target volume in mediolateral, craniocaudal and anteroposterior direction with different formulae

Reference volume	Mediolateral (mm)			Craniocaudal (mm)			Anteroposterior (mm)		
	Stroom	van Herk	Mean + 2 SD	Stroom	van Herk	Mean + 2 SD	Stroom	van Herk	Mean + 2 SD
Observer 1	4.88	5.62	5.40	8.24	9.52	7.12	7.06	8.09	8.1
Observer 2	4.19	4.77	4.85	8.07	9.26	5.42	7.46	8.52	9.2
Encompassing volume	4.24	4.82	4.84	9.12	10.52	8.01	7.35	8.40	8.21
Common volume	2.71	3.02	3.17	8.49	9.83	9.76	8.95	10.3	9.76

SD, standard deviation.

need prospective investigation. The methodology in the present study relied on evaluating COM displacement of recurrent tumour on daily MVCT images. The accuracy of our methodology hinged on robust identification of tumour on MVCT images. However, unlike T2-W MRI, MVCT/KVCT images do not allow accurate visualization of recurrent tumour. As seen in Table 1 and our earlier published series,⁸ there is an overestimation of tumour volume with MVCT and KVCT images owing to inferior soft-tissue resolution.⁸ Furthermore, there is a low spatial concordance in delineated targets on both MVCT (0.34) and CECT (0.36) images.⁸ While we demonstrated good concordance in overall volume, any estimation of COM displacement using MVCT images is bound to have a component of delineation inaccuracy contributing to the estimation of ITV margins. To overcome this limitation, we used displacements of CV and EV with an assumption that the actual displacement or “truth” will lie between the two extremes. To further minimize delineation inaccuracies, we restricted to image data sets acquired in the first week such that the volume changes due to tumour regression do not contribute to the displacement data.

While executing daily IGRT, only bony match was performed and residual soft-tissue errors were not matched. Hence, any displacement of the soft tissue from Day 1 scan provided us an estimate of displacements occurring despite strict bladder and bowel protocol. We choose to calculate ITV using Stroom and van Herk's method to account for systematic and random changes in bladder and bowel position. In addition, we also calculated ITV using mean + 2 SD method to estimate the

applicability of Stroom and van Herk's method to our data. Using these margin recipes, while a mediolateral margin of 5 mm may be enough to encompass tumour displacements, a larger anteroposterior (10.5 mm) and superoinferior (8.4 mm) expansion may be required. The margins required to cover 95% of treatment fractions were calculated to be 5.4, 9.7 and 9.7 mm, respectively, suggesting that the margins estimated by van Herk's formula may reasonably cover target position up to 95% of times. A set-up margin may further be added to the ITV for generating PTV.

Though we could propose margins for ITV, it must be noted that our study has certain flaws. Only the first seven fractions have been used to obtain the estimates of directional deviations. It is likely that the displacement characteristics may be different in subsequent fractions secondary to changes in bladder-filling capacity. Furthermore, as we did not account for all treatment fractions, we were unable to generate 95% confidence intervals for the directional internal organ motion. The proposed margins within our study have not been prospectively validated, and the data generated within our study require prospective validation in cohort undergoing IGRT.

CONCLUSION

The study results conclude that directional expansion can be used to obtain ITV for vault cancers while executing IGRT. The displacement of vault cancers is similar to post-operative vaginal vault. Additional ITV to PTV margins should be used as per institutional policy to account for set-up errors during IMRT.

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