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Impact of volumetric imaging (CBCT) in defining PTV margins in the treatment of carcinoma cervix

Abstract

Aim: To quantify the organ motion and set up errors in carcinoma cervix patients to individualized PTV margins.

Material and methods: Seven Carcinoma cervix patients who opted for treatment with Image Guided Radiotherapy were taken for quantification of interfraction set up errors and organ motion. 10 pre treatment Cone beams Computed Tomographic (CBCT) scans were evaluated per patient. Values for inter-fraction set up errors were registered for three principal axes in left-right (X-axis), supero-inferior (Y-axis) and antero posterior (Z-axis). Mid-rectum motion was evaluated in anterior, posterior, right and left directions. Antero-posterior (AP) and transverse diameter of mid-rectum in CBCT was compared with Planning CT scan (PCT). Interfraction bladder motion was assessed by comparing bladder volume and translation of the bladder wall in three dimensions in CBCT scans to the baseline PCT.

Results: Mean bone shifts noted were 0.32±0.24cm, 0.29±0.21cm and 0.13±0.12cm along X, Y and Z axis respectively. Mean mid-rectum movement was maximum in anterior direction. Mean PCT AP and transverse diameter of rectum were 2.49±0.72cm and 3.01±0.54cm and CBCT AP and transverse diameter were 2.61±0.83 cm and 3.10±0.42cm respectively. Maximum movements were seen along anterior followed by superior bladder wall and minimum movements were seen along right bladder wall. Mean PCT and CBCT (±standard deviation) bladder volume noted was 177.93±80.51cc and 183.33±25.14cc respectively.

Conclusion: Set up errors and organ motions were within our prescribed PTV margins. Close patient follow-up during treatment is mandatory to assess patients' dietary, bowel and bladder habits and weight loss.

Keywords: IGRT, CERVIX, cone beam CT, set-up errors, organ motion

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Abbreviations: PCT, planning CT scan; CBCT, cone beams computed tomographic; PTV, planning target volume; IGRT, image guided radiotherapy; EBRT, external beam radiotherapy; GTV, gross tumor volume; CTV, clinical target volume

Introduction

Carcinoma cervix presently poses a major burden on India's health care system. The incidence of these tumors is on an increasing trend worldwide. There will be 18.1 million new cases and 9.6 million cancer deaths worldwide in 2018. Globally, cervical cancer ranks fourth for both incidence and mortality. However, in India every year 96,922 new cases of cervical cancer are diagnosed and amongst them 60,078 die from the disease.[1]

Radiation is an integral part of multimodality management in these malignancies. There is always an issue of individual differences within the population and across radiotherapy centers regarding set up errors and to overcome these errors we give large Planning Target Volume (PTV) margins which in turn lead to more toxicity for normal organs in the treatment field. That emphasizes the need for individualized data in each radiotherapy centre considering patient variables along with technical issues.

There are few studies which show the effect of set up errors, rectal motion or bladder motion separately in pelvic malignancies on patient outcome.[2–4] In this study we have looked these parameters of set up errors in individual patient and evaluated that how they help decide patient specific PTV margin. Even after following strict bladder and rectal protocol, unpredictable and non isotropic errors do occur and are the major cause of giving wide PTV margins. Therefore, quantification of organ motion and set up errors will help us individualize PTV margins in a given patient.

Image Guided Radiotherapy (IGRT) is in fact a double edge sword, if not applied judiciously may adversely affect the outcome. We have looked into the frequency of volumetric imaging which is different in different radiotherapy centers.

Material and methods

Patient selection

It is single institution prospective evaluation study of patients for evaluation of interfraction set up errors and organ motion in patients of Carcinoma cervix. We analyzed 7 patients from 19 to 75years of age who were having confirmed histopathological diagnoses including all stages except metastatic disease from December, 2014 to June, 2015 and underwent External beam radiotherapy (EBRT) by IGRT technique.

Immobilization protocol

A custom immobilization cast (orfit industries, Belgium) was used for each patient in the supine position covering abdomen and pelvis

and indexed on the treatment couch. Knee rest and arm rest were used. Marks on the patients' skin and cast were made with lateral and anterior moving lasers installed in the CT simulator to assist in daily set up.

CT simulation

Planning CT (PCT) was acquired for all patients on dedicated CT simulator Machine (24 Slice Somatom Sensation Open with wide bore (82cm) with software version of Siemens CT 2007S). The scans were acquired from the top of L1 to 3cm below ischial tuberosity, with a slice thickness of 5mm.

Before scanning all patients were instructed to void urine and drink 300 ml of water for reproducible bladder filling 40-50 minutes before PCT and treatment. Patients having constipation or found to have a distended rectum at the time of planning were started on laxatives and subsequently planned. Similar bladder protocol was followed for daily radiation treatment as well.

Treatment planning, prescription, implementation and verification

The PCT data sets were transferred to Eclipse treatment planning system (Version 10.0 of Varian Medical System, Palo, Alto, CA). Gross tumor volume (GTV) and clinical target volume (CTV) were contoured as per guidelines.[5] PTV was the CTV expanded by margins as per our institutional protocol site wise, 0.5cm axially and 1cm in cranio-caudal direction. Radiation dose prescribed was 45Gy in 25 fractions over 5 weeks with boost to gross lymph node up to 54Gy followed by brachy therapy. VMAT plans were generated in the Eclipse Treatment Planning System (version 10) using 6MV photons. Anisotropic Analytical Algorithm (AAA v 10) was used. After plan evaluation, treatment commencement was done on Novalis Tx Linear Accelerator. For treatment verification CBCT were acquired on first 3 days of treatment and twice weekly thereafter, at least 10 pre treatment CBCT scans were taken for each patient.

Organ motion and set-up error quantification

The patients' setup error was calculated by registration of the planning CT and the current CBCT scan using the bony anatomy. They were matched by both bone auto fusion followed by manual bone and soft tissue matching (set up + organ motion) while documenting rectal filling and bladder filling simultaneously as indicated for each patient. Necessary couch correction (online correction) was applied.

Values for inter-fraction set up was registered for three principal axes, in left-right(x), supero-inferior (y) and antero posterior (z) axes. The axes used for these shifts define positive shifts from anterior to posterior, right to left, and superior to inferior.

Pelvic bone-match was rechecked for set up error followed by organ motion quantification for bladder and rectum. Bladder was outlined on PCT and CBCT image for each patient to calculate bladder volume and accuracy in superimposition of images. Interfraction motion was assessed by the differences in bladder volume and translation of the bladder wall in three dimensions in comparison to the baseline PCT. PCT mid-line sagittal imaging was used to assess cranio-caudal and antero-posterior displacements and a mid-bladder image in coronal plane was used to assess lateral displacements. The interfraction movement of rectum was recorded by documenting the antero-posterior and lateral diameter. Rectum length was measured and was equally divided into three parts. We have evaluated movement in mid-rectum in anterior, posterior, right and left direction and taken antero-posterior and transverse diameter and compared mean CBCT diameters with PCT diameters.

\The overall set up error was calculated based on CBCT imaging for individual patients. To illustrate the magnitude of set up error values, absolute values of position errors were considered for calculation. Statistical analysis was performed using Wilks'Lambda test for intra-patient variation while Huynh Feldt test was used for inter-patient variation among 7 subjects. Dunett T test was used for urinary bladder volume and rectal diameter variation. Discrete variables are reported as frequency, proportion and continuous variables as mean +/- standard deviation (SD). All statistical analysis was done using SPSS (version17) software.

Results and observations

Seven patients of carcinoma cervix of age 43 to 70 years were enrolled. Median age was 65 years. Patients were also segregated based on the International Classification of adult underweight, overweight and obesity according to body mass index (BMI) (Table 1).[6]

Table 1 Body Mass Index (BMI) wise distribution of cases

	BMI*(Kg/m^2)	Number of cases
Underweight	<18.5	0
Normal	18.5-24.99	3
Pre-obese	25-29.99	2
Obese class-I	30-34.99	2
Obese class-II	35-39.99	0
Obese class-III	≥40.00	0

*, body mass index

Bone match between CBCT and PCT images was first done in sagittal images for longitudinal and AP/PA correction with the help of sacro-coccygeal and pubic bones followed by coronal and axial images for lateral correction. Mean bone-shifts were calculated in total ten CBCTs of each patient and mentioned along with their range in x (right-left), y (supero-inferior) and z (antero-posterior) axes (Table 2, Figure 1 & 2). Maximum mean shift noted in both y axis and x axis was 0.52cm and along z axis was 0.16 cm although maximum shift was 1.1cm in x axis in patient number 6 (Figure 2), which was subsequently reduced in other CBCT with careful set up of patient.

Table 2 Mean bone shifts noted in carcinoma cervix (7) patients along X (right-left), Y(supero-inferior) and Z (antero-posterior)axes in each CBCT(total 70 CBCTs)

Patient No	Mean bone shifts and range					
	X axis		Y axis		Z axis	
	Mean ± SD(cm)	Range(cm)	Mean ± SD(cm)	Range(cm)	Mean ± SD(cm)	Range(cm)
1	0.42±0.31	0.1-1	0.52±0.34	0-1	0.16±0.22	0-0.6

Citation: Sehgal SA, Anand AK, Munjal RK, et al. Impact of volumetric imaging (CBCT) in defining PTV margins in the treatment of carcinoma cervix. *J Cancer Prev Curr Res.* 2019;10(4):74–80. DOI: 10.15406/jcpcr.2019.10.00396

Table Continues...

Patient No	Mean bone shifts and range					
	X axis		Y axis		Z axis	
	Mean ± SD(cm)	Range(cm)	Mean ± SD(cm)	Range(cm)	Mean ± SD(cm)	Range(cm)
2	0.38±0.20	0.2-0.7	0.25±0.10	0.1-0.4	0.15±0.11	0-0.4
3	0.52±0.31	0-0.9	0.24±0.22	0.1-0.8	0.12±0.10	0-0.3
4	0.16±0.16	0-0.4	0.19±0.26	0-0.7	0.16±0.18	0-0.5
5	0.24±0.19	0-0.6	0.19±0.21	0-0.6	0.12±0.06	0-0.2
6	0.32±0.33	0-1.1	0.4±0.18	0.1-0.6	0.1±0.08	0-0.2
7	0.17±0.16	0-0.4	0.26±0.18	0-0.5	0.08±0.10	0-0.3

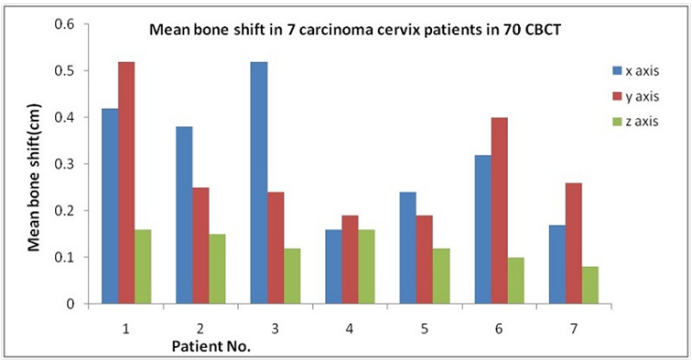

Figure 1 Mean bone shifts in 7 patients of carcinoma cervix along x (right-left), y (supero-inferior) and z (antero-posterior) axes in each CBCT (total 70 CBCTs).

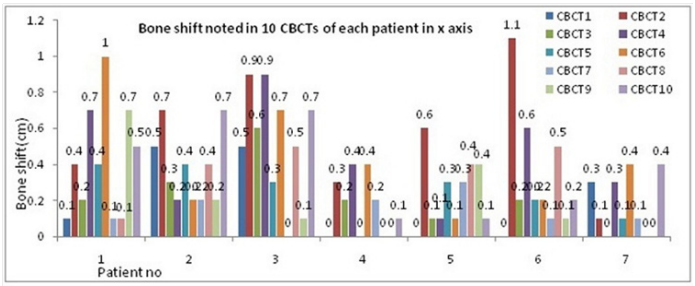

Figure 2 Bone shift noted along x axis in 7 carcinoma cervix patients from CBCT 1 to 10 in each patient.

Organ motion and organ filling in rectum

CBCT scan was overlaid on PCT scan where initial contour of rectum was visualized and compared at the level of mid-rectum. Mean movement was maximum in anterior direction i.e.0.53cm in patient 1 which just crossed the limits of our prescribed PTV margins i.e.0.5cm in axial sections. Mean movement was minimum in posterior direction.

In 5 cases (patient 2,4,5,6 and 7) mean CBCT AP diameter increased compared to PCT and again in 5 cases (patient 1,2,3,4 and 7) mean CBCT transverse diameter increased compared to PCT. Thus, increase in mean values of diameter was common. However the difference was 0.5cm in both mean AP and Transverse diameters which was again within our prescribed PTV margins. Maximum difference was noted in patient 4 i.e.0.47cm in antero-posterior diameter (Table 3, Figure 3).

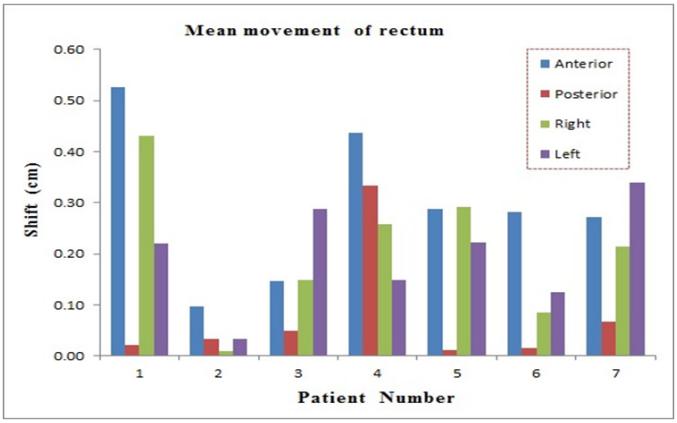

Figure 3 Mean movement of mid-rectum in anterior, posterior, right, and left direction in 7 carcinoma cervix patients.

Table 3 Mean movement of mid-rectum in anterior, posterior, right, and left direction and AP and transverse diameter in carcinoma cervix (7 patients) over 70 CBCT

Patient no	Mean rectum movement(cm)				AP diameter(cm)		Transverse diameter(cm)	
	Anterior	Posterior	Right	Left	CBCT(Mean)	PCT	CBCT(Mean)	PCT
1	0.53	0.02	0.43	0.22	2.34	2.53	3.31	3.29
2	0.10	0.03	0.01	0.03	2.21	1.87	2.69	2.68
3	0.15	0.05	0.15	0.29	2.41	2.45	2.97	2.7
4	0.44	0.33	0.26	0.15	4.23	3.76	3.08	2.85
5	0.29	0.01	0.29	0.22	3.09	3	3.62	3.76
6	0.28	0.02	0.09	0.12	1.69	1.63	3.55	3.57
7	0.27	0.07	0.21	0.34	2.29	2.19	2.51	2.24
Mean ± SD	0.29±0.15	0.08±0.11	0.21±0.14	0.20±0.10	2.61±0.83	2.49±0.72	3.10±0.42	3.01±0.54

Citation: Sehgal SA, Anand AK, Munjal RK, et al. Impact of volumetric imaging (CBCT) in defining PTV margins in the treatment of carcinoma cervix. *J Cancer Prev Curr Res.* 2019;10(4):74–80. DOI: 10.15406/jcpcr.2019.10.00396

Organ motion and organ filling in urinary bladder

Urinary bladder movement was measured in anterior, posterior, right, left, superior and inferior directions with respect to baseline PCT scan (Table 4). Maximum movements were seen along anterior bladder wall followed by superior bladder wall and minimum movements were seen along right bladder wall. These were within our limits of PTV margins i.e. 1cm in cranio- caudal and 0.5cm in axial direction. Urinary bladder volume was calculated after contouring on CBCT images and compared with PCT bladder volume. Mean bladder volume (and standard deviation) noted was 177.93±80.51cc in CBCT images and 183.33±25.14cc in PCT images. However the difference was statistically insignificant (p value 0.373) (Table 5).

Table 4 Mean movement of urinary bladder anterior, posterior, right, left, superior and inferior wall compared to PCT 7 patients of carcinoma cervix over 70 CBCTs

Patient no	Mean movement of urinary bladder (cm)					
	Anterior	Posterior	Right	Left	Superior	Inferior
1	0.78	0.4	0.06	0.09	0.73	0.22
2	0.12	0.05	0.06	0	0.38	0.04
3	0.13	0.33	0.03	0.1	0.46	0.25
4	0.39	0.17	0	0	0.19	0.12
5	0.02	0.24	0.03	0.17	0.06	0.03
6	0.3	0.14	0.04	0.02	0.15	0.2
7	0.07	0.06	0.17	0.19	0.41	0.29
Mean ±SD	0.26±0.27	0.20±0.13	0.05±0.05	0.08±0.07	0.34±0.23	0.16±0.10

Table 5 Urinary bladder volume change (cc) compared to PCT in 7 patients of carcinoma cervix over 70 CBCTs

	Bladder volume (cc)							
Patient No	1	2	3	4	5	6	7	
PCT	97.09	306.76	142.62	186.31	73.71	227.3	211.77	177.94 ± 80.51 (Mean PCT ± SD) versus
CBCT 1	101.16	328.66	322.64	206.47	81.37	239.51	220.17	188.33 ± 25.14 (Mean CBCT ± SD)
CBCT 2	98.55	360.33	280.16	289.38	54.79	276.97	185.46	p=0.373 (insignificant)
CBCT 3	147.41	368	122.95	126.89	59.69	288.56	227.02	
CBCT 4	155.21	372.52	143.34	134.18	220.93	151.81	211.21	
CBCT 5	133.67	209.47	89.92	119.02	52.83	298.1	201.56	
CBCT 6	98.79	218.85	121.85	132.27	94.19	201.46	296.08	
CBCT 7	159.08	300.57	78.02	150.27	73.7	180	210.87	
CBCT 8	115	321.37	132.65	84.91	76.21	222.58	193.46	
CBCT 9	113.7	381.14	154.88	296.89	75.21	217.82	184.14	
CBCT 10	130.49	241.99	88.34	132.02	74.51	189.02	211.13	
Mean CBCT ± SD	125.3 ±23.25	310.29 ±65.38	153.48 ±82.4	167.23 ±72.91	86.34 ±48.94	226.58 ±48.94	214.11 ±32.06	

Citation: Sehgal SA, Anand AK, Munjal RK, et al. Impact of volumetric imaging (CBCT) in defining PTV margins in the treatment of carcinoma cervix. *J Cancer Prev Curr Res.* 2019;10(4):74–80. DOI: 10.15406/jcpcr.2019.10.00396

Discussion

This study was aimed to quantify the set up errors, organ motion and organ filling in pelvic malignancies to confirm the adequacy of our institutional PTV margins. The patient set up at each radiotherapy treatment is affected by set up uncertainties such as variations in patient positioning, mechanical uncertainties of the equipment (e.g., sagging of gantry, collimators, and couch), transfer set-up errors from planning CT simulator to the treatment unit and human factors.

Multiple studies have reported on the setup errors for various treatment locations and different immobilization devices.[7,8] Among the various methods of estimation of set up errors and organ motion, kV CBCT has shown better acceptance with freedom of daily usage considering low dose delivered per fraction as compared with EPID and megavoltage CT (MVCT).[9,10] Multiple studies have reported reduced PTV margins with the use of CBCT image guidance.

Bone shifts

In our cases, mean (standard deviation) bone shifts noted were 0.32±0.24cm, 0.29±0.21cm and 0.13±0.12cm in x, y and z axis respectively (Table 1, Figure 2). Although mean value were<0.5cm but the maximum value reached 1.1cm x axis in first CBCT of sixth patient (Figure 1). This patient was obese category 1 with BMI of 30.38 and probably there was difficulty in aligning skin marks and lasers was tougher than normal. This emphasizes the need for frequent imaging in overweight patients.

Twenty patients of gynecologic malignancy were studied by Santanam L et al.[11] and found the average shifts per patient ranged from -1.3cm to 1.0cm in the lateral direction, -4.1cm to 2.2cm in the longitudinal direction, and -0.9 to 1.2cm in the vertical direction. A maximum shift of -4.1cm in the longitudinal direction was an outlier for the helical tomotherapy group.

The mean absolute values of the post-correction errors with CBCT were 0.045 cm medial-lateral (ML), 0.045 cm superior inferior (SI) and 0.03 cm anterior-posterior (AP) in study of thirteen patients with gynaecologic cancers by Yao et al.[12] Kim et al.[13] studied the set-up uncertainty using daily kilo voltage image guidance and found that the systematic and random errors were 0.11cm, 0.23cm, 0.23cm and 0.39cm, 0.50cm, 0.35cm in the AP, ML and SI directions, respectively, for the entire patient population. They also assessed the patient factors by evaluating BMI. The mean displacements in the AP, ML and SI directions for BMI 30 (28 patients) versus BMI <30 (24 patients) were 0.01 cm, 0.09 cm and 0.1 cm versus 0.01 cm, 0.01 cm and 0.04 cm, respectively(P=0.002). Ahmad et al.[14] reported setup errors in 15 cervical cancer patients with overall mean setup variations measured by CBCT imaging were −0.07cm ML, −0.11cm SI, 0.01cm AP.

Daily imaging has the disadvantage of prolonging a patient's time on the treatment table and exposure to greater doses of radiation.[13–15] Kim et al.[13] simulated different imaging frequency protocols to determine if the frequency of imaging could be reduced. They found that none of the simulated imaging protocols would ensure a set-up error <5mm for all fractions. But studies by Kupelian et al.[16] using IGRT for prostate cancer and Zeidan et al.[17] for head and neck cancer suggested that imaging should be carried out daily to reduce set-up error.

In the present study we found that there is reduction of shifts towards the end of treatment in all the subgroups in y and z axes. This emphasizes the need for more frequent CBCT in the beginning of treatment and may be reduced towards the last few fractions. However, patients with shifts >0.5cm should be noted earlier in the course of treatment, so that the error is corrected in the beginning of the treatment and is not carried forward. Subsequent CBCT should be analyzed meticulously for reduction of set-up errors.

Rectum motion and filling

Mean movement of mid-rectum was 0.29±0.15cm, 0.08±0.1cm, 0.21±0.14cm, 0.20±0.10cm in anterior, posterior, right and left wall respectively (Table 3). Similar findings are reported by Chong et al.[18] who quantified the interfraction changes in rectal movement and dimensions as well as rectal and bladder volume using CBCT. Mid-rectum movements observed were 0.70±0.29cm, 0.36±0.21cm, 0.51±0.24cm, 0.41±0.15cm in anterior, posterior, right and left wall respectively. Although higher values are noted in all the directions in comparison to the present study but maximum motion is observed in anterior direction and minimum in posterior direction which is in accordance to the present study.

Mean PCT AP and transverse diameter was 2.49±0.72cm and 3.01±0.54cm and mean CBCT AP and transverse diameter was 2.61±0.83cm and 3.10±0.42cm respectively. Silverman R et al.[19] measured rectal diameter (anterior/posterior and lateral) prospectively in 172 consecutive prostate cancer patients undergoing radical radiotherapy with three-dimensional conformal radiotherapy at the time of the radiotherapy planning. The median rectal AP diameter was 3.80 cm (range 2.00–7.50), and the median lateral diameter was 3.50cm (range 1.40–7.10). However they used MV portal imaging for image guidance and didn't measure distension during radiotherapy treatment. These values are in accordance with the values in present study but both PCT and CBCT images are used for assessing rectal distension. There is lot of variation across the world in measuring rectal distension. Many authors assessed rectal filling with more complex measurements such as the mean cross-sectional area. Kupelian et al.[16] measured rectal distension in terms of volume in a larger retrospective series of 488 patients undergoing regular image guidance and correlated with biochemical relapse-free survival rate at 5 years and found no differences in biochemical control in patients with and without rectal distension. Variability in studies pertaining to rectal motion and filling throughout the world, variable dietary habits and different protocols for bowel evacuation during planning is obscuring the way for definitive planning guidelines for pelvic malignancies.

This implies that at the time of planning itself detailed bowel history should be elicited and if there is history of chronic constipation patient should be given laxatives or enema (if constipated) and planning scan should be postponed. Patient with history of flatulence should be advised diet modification.

Urinary bladder motion and filling

Although strict bladder protocol was followed, wide variation was observed among patients. In the present study mean bladder volume (±SD) was 177.93±80.51cc in PCT and 183.3±25.14 cc in CBCT over 7 patients (Table 5). This was in contradiction to a study by Chong et al.[18] where the average planning CT bladder volume was 319cc (range, 93–663cc) which was larger than the mean CBCT bladder volume i.e. 210.93cc. We didn't find wide variation in mean CBCT and PCT volume and it was not statistically significant. However there was wide variation in the individual urinary bladder volume on different days acquired on CBCT with volume varying from 52.83cc to 368cc (Table 5).

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In order to improve bladder volume consistency, many studies have fixed the water drinking protocol as ours by specifying the volume of liquids to be consumed and timing of liquid consumption before treatment. However the bladder volume varies with such protocols also. O'' Doherty et al.[20] claimed that a fixed drinking protocol may not eliminate all variations in bladder volume, in part due to significant individual variations in velocity of bladder filling. These variations in bladder filling were perhaps due to pre-hydration status. If the patient is dehydrated, then bladder protocol would show reduced bladder volume. Also on the day of concurrent chemotherapy when the patient is hydrated with IV fluids, there is expected increase in volume of bladder. Patient should be well hydrated and preferably radiation should be given at the same time everyday to minimize volume variation. Thus, individualized adaptive approach is required to achieve better consistency in bladder filling.

In our study, the mean (standard deviation) movement of urinary bladder wall was 0.26±0.27, 0.20±0.13, 0.05±0.05, 0.08±0.07, 0.34±0.23, 0.16±0.10cm in anterior, posterior, right, left, superior and inferior wall respectively (Table 4).

The dominant direction of bladder expansion was primarily in the superior (cranial) and in the anterior (forward) directions studied by Mcbain et al.[21] This is in accordance with our study. Studies on bladder wall movements in pelvic malignancies except carcinoma bladder are scarce. Yee et al.[22] analyzed 262 CBCT images obtained from 10 bladder cancer patients. There was maximum magnitude of shift in anterior wall followed by left lateral wall but was statistically insignificant. But in the present study maximum movements were seen in superior and minimum movements were seen in inferior wall.

Conclusion

Imaging is important during radiotherapy treatment for monitoring of organ motion and set up errors. Our bone match results are within prescribed institutional PTV margins but exceptional errors need to be addressed on time. Organ motion i.e. rectum and bladder, mean movements are within our prescribed PTV margins, but protocol for these need to be individualized and adaptive strategies are needed based on first and second week CBCTs. Our study also emphasizes that close patient follow up during treatment is must and should assess patients' dietary, bowel and bladder habits and weight loss during treatment. More frequent CBCTs are required for patients with altered bowel and bladder habits. Further studies are warranted to quantify the effect of organ motion for PTV margin reduction in larger cohort of patients.

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Conflicts of interest

Authors declare that there is no conflict of interest.

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