International Journal of Innovative Research and Advanced Studies (IJIRAS)
Volume 5 Issue 9, September 2018

ISSN: 2394-4404

Assessment Of Interfractional Variation In Position Of Uterus During Radical Radiotherapy By Intensity Modulated Radiotherapy In Carcinoma Cervix

Chennareddy M

Owais A

Gurjar O P

Resident, Associate Professor, Sri Aurobindo Institute of Medical Science

Abstract: Carcinoma cervix is a common gynecological cancer occurring among women around the world. Worldwide. Radiotherapy (external beam and brachytherapy) has formed an integral component of treatment of this disease. IMRT can thus achieve much better dose conformity than conventional radiotherapy techniques like 3DCRT. Thus fulfilling the main aims of radiotherapy but normal tissue toxicity currently limits the total radiation dose that can safely be delivered. We want to assess the interfractional variation in position of uterus during radical radiotherapy by intensity modulated radiotherapy in carcinoma cervix patients. Interfraction movement of the target organs may lead to overdosing or under dosing of the target or the normal structures during IMRT, hence, CBCT at least once a week is necessary to minimize the geometrical miss of the tumor and get the planned doses to the target and normal structures for best local control with minimum toxicity which is the primary aim of IMRT treatment. This would also aid in the selection of appropriate and adequate planning target margins and may have an asymmetrical PTV conforming to the daily anatomical shift and contour of the patients. We also propose a tapered CTV to PTV margin especially around the fundus of the uterus as maximum uterine motion is known at the fundus. But for this further studies with larger number of patients and exact point localization of the uterus is required.

I. INTRODUCTION

Carcinoma cervix is a common gynecological cancer occurring among women around the world. Worldwide, Cervical cancer is, the second most common cancer in women and the most common cancer cause of cancer death in the developing countries. The worldwide incidence of cervical cancer is approximately 510,000 new cases annually, with approximately 288,000 deaths worldwide. 1Radiotherapy (external beam and brachytherapy) has formed an integral component of treatment the more advanced stages of this disease. Radical radiotherapy for cervical cancer comprises a combination of external beam radiotherapy (EBRT) to the pelvis followed by intracavitary brachytherapy to boost the central disease (Monk *et al*., 2007).

The introduction of three-dimensional radiotherapy techniques, including conformal radiotherapy and intensity modulated radiotherapy (IMRT), has enabled the production of dose distributions that fit more precisely to the target volume (Weiss *et al*.,2002). IMRT can thus achieve much better dose conformity than conventional radiotherapy techniques like 3DCRT·Thus fulfilling the main aims of radiotherapy i.e increase tumor control probability (TCP) and decrease the normal tissue complications probability (NTCP) There is a dose response relationship for local control and overall survival, but the risk of normal tissue toxicity currently limits the total radiation dose that can safely be delivered.

Hence we want to assess the interfractional variation in position of uterus during radical radiotherapy by intensity modulated radiotherapy in carcinoma cervix patients.

ISSN: 2394-4404

AIM AND OBJECTIVES

To study the effect of uterine motion and uterine margins on target and doses to normal organs in Intensity modulated radiotherapy of carcinoma cervix.

- ✓ To assess the interfractional motion of uterus in relation to volume of bladder.
- ✓ To assess the interfractional motion of uterus in relation to volume of rectum.
- ✓ To assess the effect of bladder and rectal filling and motion of uterus and cervix on dosimetric parameters.

II. MATERIALS AND METHODS

All carcinoma cervix patients attending the OPD of our department of Radiotherapy from September 2015 to March 2017 who opted for the IMRT technique were taken up for the study.

INCLUSION CRITERIA

- ✓ Age 18-65 yrs.
- ✓ Patients with performance status or KPS score of more than 60.
- ✓ All untreated Patient with histologically proven squamous cell carcinoma cervix FIGO stage IIB to stage IVA.
- ✓ Patients having no distant metastasis

EXCLUSION CRITERIA

- ✓ Patient not willing to give consent
- ✓ Patient who has already received radiotherapy
- ✓ Patients who have undergone hysterectomy
- ✓ Patients with other co-morbidities
- ✓ Patients with distant metastasis
- ✓ Stage-IVB disease
- ✓ Pregnant patients

Before starting radiotherapy a six clamp thermoplastic Orfit cast for immobilization was prepared for pelvic region of all the patients and then contrast enhanced CT scan pelvis was done. A radiation oncologist contoured the GTV, CTV, PTV and the normal organs of interest at risk on the CT images as well as on the PET-CT images. To facilitate the comparison of methods, the 3-D treatment plans and Dose Volume Histograms (DVH) was generated separately for all the patients. The patients will be registered on an IMRT system, for each patient the pre-treatment cone beam CT was taken and registered to the planning CT of the patient. From the registration the coordinate shift values were applied for table correction. The daily shift values in the X, Y and Z directions for each fraction were analysed and the mean variation along the X, Y and Z directions was calculated. From this standard deviation, systematic and random errors were determined. The average values along X, Y, Z directions are noted for all the patients. Standard Deviation (SD) of these average values along each direction respectively gives the systematic error. The root mean squares of these SD values taken along each direction respectively, gives random errors. High energy linear accelerator Clinac DMX (Varian Medical Systems Inc., Palo Alto, CA) with photon energies 6 MV and 15 MV and electron energies 6 MeV, 9 MeV, 12 MeV & 15 MeV and equipped with Millennium 80 MLC installed in our department is used. All the patients to defecate and urinate and then maintain a strict water intake of around 200 ml of water 20 minutes before the procedure. The position of the uterus was defined in the CTV during contouring on axial images of the disease for radical RT. The CTV included all the gross as well microscopic disease. The Organs at Risk (OAR) such as the bladder, rectum, intestines and the femoral heads were also contoured on axial images.(see images)

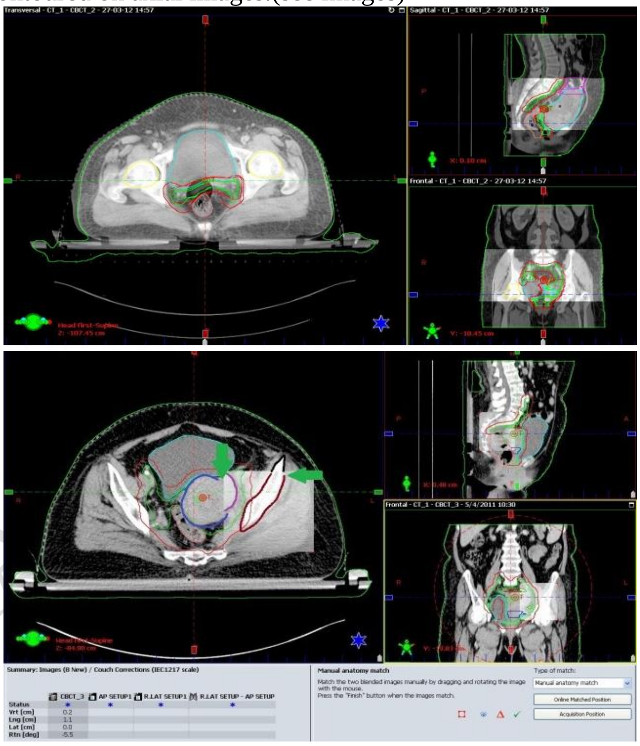

Figure 1

The position of the uterus was then compared in the following weekly scans on the axial images and with the help of the sagittal, coronal and 3D reconstructions. This was done by fusing the weekly CT images with the reference CT taken before the start of the treatment at the same level for every scan which was the lower level of the S1 vertebra. A preliminary bone to bone matching was done after the fusion of the images to negate the effect of patient setup errors and this was followed by soft tissue matching of the uterus in the two CT images. The change in CTV position during the bone to bone matching was subtracted from the A-P, S-I and lateral changes during the soft tissue matching. The position of the uterus was also correlated with the position and the filling of the bladder. This change in uterus position was measured separately in the A-P, S-I and Lateral Directions.

III. OBSERVATIONS AND RESULTS

The mean, median and the standard deviation of uterine motion in each plane were calculated to see the relation of the bladder filling and its influence on the displacement of the uterus.

As shown in the table, the displacement ranges were significant depending on the patient, though the mean value of the displacement was within 1 cm. In this the mean shift in anterio-posterior, lateral and superior-inferior direction was 0.30, 0.06 and 0.06 respectively for all the scans done for 20 patients over the period of EBRT.

COMBINED UTERINE MOTION (CM.)

S.No.		Lateral (X)	A-P (Y)	S-I (Z)
1.	Mean	0.06	0.30	0.06
2.	Median	0.15	0.5	0.07
3.	Standard Deviation	0.22	0.83	0.40
4.	Range of motion	-0.5 to +0.32	-1.8 to + 1.16	– 0.56 to + 0.72

Table 1

The mean extent of motion in the uterine position on a daily basis for individual patients in the antero-posterior direction ranged from-1.8 to + 1.16, lateral direction -0.5 to +0.32 and the superior inferior direction ranged from – 0.56 to + 0.72. The significance was calculated by an unpaired one sample student t-test. The p value is 0.0001 which is highly significant.

The mean movement in all the directions was also calculated for all the individual 20 patients over the course of the full treatment i.e. 4 scans per patient and their uterine motion [Figure] This shows more anterior and superior shift which may be due to bladder filling daily and the lateral deviation was minimum, although present. The posterior shift may be due to the rectal filling or presence or absence of gas in the rectum.

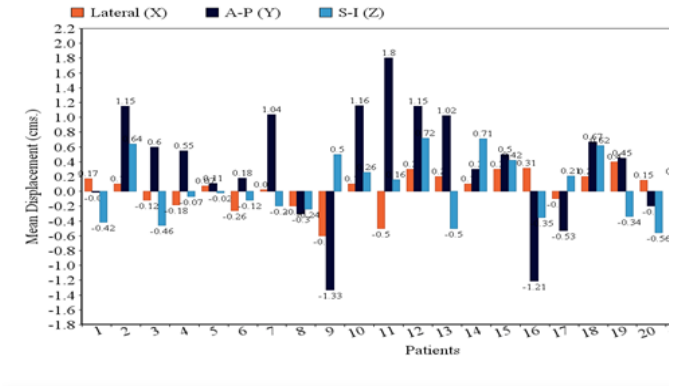

Figure 2

UTERINE MOTION IN RELATION TO BLADDER AND RECTAL VOLUME

Patient Number	LATERAL (X – cm)	A-P (Y – cm)	S-I (Z-cm)	Bladder Volume (Litres)	Rectal volume (mm)
1	0.16	-0.3	-0.06	0.031	0.012
2	0.1	-.133	0.1	0.111	0.021
3	0.2	1.32	-0.24	0.151	0.001
4	-0.6	-2.28	0.16	0.189	0.003
5	0.25	1.15	0.55	0.157	0.002
6	-0.08	1.04	-0.4	0.113	0.067
7	0.45	-0.75	- 0.225	0.062	0.061
8	0.3	1.15	-0.05	0.125	0.012
9	-0.06	0.6	-0.12	0.088	0.001
10	0.36	0.55	-0.2	0.067	0.080
11	0.4	0.3	-0.15	0.046	0.056
12	0.1	0.04	-0.36	0.064	0.078
13	-0.12	0.18	0.56	0.055	0.031
14	0.1	0.3	0.71	0.049	0.098
15	0.3	0.4	0.4	0.076	0.450
16	0.31	-1.21	-0.35	0.140	0.011
17	-0.1	-0.53	0.21	0.096	0.067
18	0.2	0.67	0.6	0.090	0.671
19	-0.45	0.45	-0.34	0.070	0.033
20	0.15	-0.22	-0.56	0.040	0.006

Table 2

IV. DISCUSSION

The efficacy of EBRT with radiation doses of 40-50 Gy followed by boost with brachytherapy has been proved efficacious in the local control of cervical and uterine cancer. However, one of the major concerns with this modality of treatment has been small bowel toxicities, either acute or chronic. With advancement in the treatment techniques of radiation therapy, it has been possible to reduce the toxicity to the bowel and bladder. However it is essential to see that the benefits are not achieved at the cost of decreased local control due to the target miss.

International Commission on Radiation Units and Measurement 62 (ICRU 62) states two margin volumes, CTV to create the planning target volume (PTV) should comprise two components: the internal margin (IM) to account for organ motion, and the set-up margin (SM) to account for variation in patient position Lee et al have previously reported about the changes in the uterus position by comparing two magnetic resonance (MR) images taken before and during the period of RT. They showed that uterus movement and its positional change was significant, and it suggested the importance of accurately determining the target mobility for the conformal treatment. However, in that study, two sets of MR images that were taken in the supine position without a small bowel displacement system (SBDS) while the patients were treated in prone position with a SBDS placed under the patient's abdomen. We studied the uterine motion once every week during the full course of radiotherapy and found a significant shift in uterine position in all directions every time.

In our study the bladder and rectum volumes have not been quantified as strict adherence to the bladder and bowel filling protocol was followed by all our patients. Thus we expected a standard maintenance of bladder volumes which was corroborated on the weekly CBCT scans. Our uterine shifts were derived despite maintaining a standard bladder volume.

A similar study has been done by Taylor et al where in addition to the uterus they also assessed the movement of the cervix to determine the internal margins for radiotherapy. They concluded that an asymmetrical margin with CTV–PTV expansion of the uterus and the cervix was needed during the treatment while also stressing the need for a strict bladder and rectum filling protocol during treatment. Very few studies have been done documenting the changes in uterine position during a course of radiotherapy. A relationship between bladder filling and uterine movement with no major A-P change in cervical position was reported by Buchali et al.

On comparison of the mean displacements of the uterus in A-P, S-I, Lat directions of our results with displacements observed by Taylor et al it was seen that there is maximum mean displacement in A-P direction but in Taylor et al study the mean displacement in S-I direction was also substantial [Table]. The difference may be due to strict adherence to the bladder-bowel filling protocol in our study and once weekly CBCT instead of two images on two consecutive days.

Table showing the comparison of the magnitude of displacements of the two studies.

Magnitude of Displacement (cm)	Present Study			Taylor et al		
	Lateral	A-P	S-I	Lateral	A-P	S-I
Mean	0.06	0.30	0.06	.08	0.7	0.71
Median	0.15	0.5	0.07	0.0	0.5	0.5
S.D.	0.22	0.83	0.40	0.13	0.9	0.68
Range	-0.5 to +0.32	-1.8 to + 1.16	– 0.56 to + 0.72	0-0.5	0-0.48	0-0.32

Table 3

A definite relationship with the filling of the bladder for the uterus and emptying of the rectum for the cervix movement exists. This has also been proven in the studies which have assessed the volumes of these organs and connecting them with the displacements of the uterus and the cervix respectively. Maximum uterine motion at the fundus is also proven emphasizing the need for a variable margin around it to account for its shift.

The interfraction movement in the uterine position during the course of radiotherapy despite maintaining a strict bladder and rectal protocol may lead to a miss in target or over treat the rectum leading to toxicity. We could not find any study in which uterine shift was observed during the whole course of Radiotherapy hence were unable to compare the results.

Recent cervix motion studies include the following: Van de Bunt et al (2008) investigated the merits of IMRT versus 3DCRT and traditional treatment, and looked at tumor regression during the treatment, concluding that the primary gross tumor on average shrinks 46% after 30 Gy, from 71 to 39 cc. Van de Bunt et al (2008) 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 whom a substantial change in bladder volume produced either no change, or a significant change, in CTV position.

Based on these observation we would like to recommend a margin of 1 cm in anterior direction, 1.5 cm posteriorly for fundus of uterus, 1 cm posterior direction for cervix, 0.5cm superiorly, 0.5cm inferiorly, 1 cm for right and left lateral directions.

The regression of CTV was also noted in the weekly CT scans, each CT was contoured to delineate the CTV and volume was noted. There was a stastically significant reduction in

CTV size each week of chemoradiation (p value<0.001) compared to pre treatment volume with volume falling from 153 cc to 82 cc, this was also contributing towards the shift in uterus but mostly in the posterior direction especially if rectal and bladder volume is maintained. The CTV showed a pattern in regression towards the posterior aspect becoming more retroverted towards each week of treatment. The pattern of regression of

CTV directly influenced the shift in CTV. A true estimate of regression of GTV would be quantified only with the help of MRI scan taken weekly. The shift in uterus could not be evaluated with respect to age as no clear pattern was determined with age. The sample size of 30 was not adequate to comment on this.

In literature few studies have evaluated the change in CTV dose due to interfractional variation in position of uterus. In this study the weekly mean CTV dose was maintained throughout the treatment (100.5%). This was in concurrence with the dosimetric study conducted by Han Y and Shin EH et al where they achieved mean CTV dose of 99.9% throughout IMRT treatment assessed weekly with CT scans.

Mundt et al 2002 studied the IMRT in gynecological malignancies. That study observed that whole pelvis IMRT plans provided excellent PTV coverage, with considerable sparing of the surrounding normal tissues. On average, 98.1% of the PTV received the prescription dose. The average percentage of the PTV receiving 110% and 115% of the prescription dose was 9.8% and 0.2%, respectively.

Karen Lim et al conducted a study using weekly MRI scans to delineate the motion of uterus and assess the dose variation due to this in IMRT for cancer cervix. That study concluded that individually, the planned dose was not the same as the simulated delivered dose; however, when taken as a group, this was not statistically significant for the four field box and large-margin IMRT plans. The small-margin IMRT plans yielded adequate target coverage in most patients; however, significant target under dosing occurred in 1 patient who displayed excessive, unpredictable internal target movement. The delivered doses to the organs at risk were significantly reduced with the small-margin plan, although substantial variability was present among the patients. They also advised that simulated dose accumulation might provide a more accurate depiction of the target and organ at risk coverage during fractionated whole pelvic IMRT for cervical cancer. The adequacy of primary tumor coverage using 5-mm planning target volume margins is contingent on the use of daily image-guided setup.

V. SUMMARY AND CONCLUSION

Interfraction movement of the target organs may lead to overdosing or under dosing of the target or the normal structures during IMRT, hence, CBCT at least once a week is necessary to minimize the geometrical miss of the tumor and get the planned doses to the target and normal structures for best local control with minimum toxicity which is the primary aim of IMRT treatment. This would also aid in the selection of appropriate and adequate planning target margins and may have an asymmetrical PTV conforming to the daily anatomical shift and contour of the patients. We also propose a tapered CTV to PTV margin especially around the fundus of the uterus as maximum uterine motion is known at the fundus., It has been shown that IMRT can be used to adequately cover the CTV with wide range of motion and setup error of postioning the patient if adequate margins are added to create PTV especially in anterior posterior direction. IMRT plans did not spare rectum as CTV was too close to it and was having high chances of retroversion of uterus after giving chemoradiation when there is regression of GTV. However the dose to bowels, bones and bladder was significantly reduced with IMRT. Hence IMRT for cervical cancer is feasible in a centre with on board Cone beam CT imager and if bladder, rectal filling can be maintained on daily basis. Further studies with larger number of patients is required and exact point localization of the uterus is also important.

REFERENCES

[1] Dr. Debjani Roy- Indian Journal of Spatial Science vol-3.0 No 2 winter Issue pp26-34 ISSN 2249-3921
[2] Shweta Shekhar- Term paper- Socio economic Issues of the indigenous people in Jharkhand
[3] Dr. N.N. Mahto- International Journal for exchange of Knowledge 4(1): 34-39 ISSN 2394-1669
[4] Jharkhand data Highlights
[5] KIundu M (1990) Tribal Education in India some problems. Pp246-254.
[6] Dr.N Minz- Indusrialization and Adivasi; Why The Latter Are Apprehensive
[7] www.Jharkhandgovt.in