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Formation of Institutional Protocol for Planning Target Volume Margins in Carcinoma Cervix, Using Daily CBCT And Weekly KV Imaging: A Study From Central India

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Abstract

Introduction: Image guided brachytherapy and conformal external beam in the treatment of carcinoma cervix enables calculation and modulation of dose to OARs like the bladder and rectum. In highly conformal techniques, PTV margins are calculated according to the setup error windows of respective individual institutions and it is essential for every institute to evaluate and analyze their setup error. An effective way of producing geometrical margins is by statistical models, which allow for reduction in margin sizes and which are smaller but effective in tumor control. The current study aims to evaluate the various setup errors incurred during treatment and thus calculate the adequate CTV/PTV margins for irradiating cancer cervix patients

Objectives: Evaluate setup errors using available immobilization devices. Assess setup imaging and evaluation of interfractional movement. Analyze the total setup error (including setup and interfractional movement) and formation of guidelines for delineation of PTV margins.

Materials & Methods: 50 patients undergoing pelvic RT for cancer cervix, using either or IMRT or IGRT technique were included in the study. Immobilization using a four clamp orfit and pelvic base plate, was done. 10 patients were treated by daily image guidance by kVCBCT and 40 patients were treated by weekly kV portal imaging. Translational shift (difference between planned and new coordinates) in all three directions recorded for each patient, separately for IMRT and IGRT groups. Mean and median shift and standard deviation in each direction was calculated.

Results: Longitudinal shift was the greatest. Mean Isodisplacement vector calculated for IGRT treatment technique is 0.7 cm and for IMRT treatment technique is 0.96 cm. The difference between the two is statistically significant (p-value = 0.02). The standard deviation of shift in longitudinal direction was found to be 8 mm, 2.5 mm in the vertical direction and 3mm in the lateral direction. PTV margin calculated using the Van-Herk Margin formula for IGRT and IMRT treatments was found to be 0.21 cms and 0.39 cms respectively (Taking into account only random errors and assuming zero systematic errors). (p-value: 0.01).

Keywords: PTV Margin; Cancer Cervix; IGRT Planning.

Introduction

Depending upon the clinical FIGO stage of the disease, the management of Carcinoma Cervix may be either by surgery, or radiotherapy. Lesions up to FIGO stage IIa may be managed by surgery, most common of which is radical/ Wertheim's hysterectomy along with Pelvic lymph node dissection. Other surgical options include conization, radical trachelectomy and pelvic exenteration, in the extremes of locally advanced disease.[1] FIGO stages IIb and upwards, concurrent chemoradiation is the mainstay of treatment of cancer cervix. With the advent of modern radiotherapy techniques, dose escalation to the high risk areas, with minimum long term and acute toxicity, is possible with techniques such as IMRT, IGRT, VMAT, Tomotherapy.[2] This is followed by intracavitary image guided brachytherapy, in the patients having favorable anatomy). Brachytherapy allows for boosting of the high risk CTV, along with rapid dose fall off beyond the planning target volume, and high dose conformity to the high risk areas. Image guided brachytherapy and conformal external beam enables calculation and modulation of dose to OARs like the bladder and rectum. A reduction in setup uncertainties would allow for a reduction in treatment margins, leading to dose escalation and an improvement in local control at the tumor site.

With an increase in the dose conformity, the need for high setup accuracy has been observed. In highly conformal techniques, PTV margins are calculated according to the setup error windows of respective individual institutions, so that normal areas don't get over treated, and areas outside the CTV do not get irradiated. Wrong or unmatched PTV margins may also result in target miss. Hence, it is essential for every institute to evaluate and analyze their setup error. This will give more accurate margins and CTV to PTV ratios.[3,4]

An effective way of producing geometrical margins is by statistical models, which allow for reduction in margin sizes and which are smaller but effective in tumor control.

The current study aims to evaluate the various setup errors incurred during treatment and thus calculate the adequate CTV/PTV margins for irradiating cancer cervix patients.

Aim

To study different parameters for PTV margin formation in Carcinoma of Uterine cervix and draw up institutional guidelines.

Objective

Evaluate setup errors using available immobilization devices. Assess setup imaging and evaluation of interfractional movement. Analyze the total setup error (including setup and interfractional movement) and formation of guidelines for delineation of PTV margins.

Patient Population

Patients of biopsy proven Carcinoma cervix stage IIb to IVa with KPS score of more than 70 undergoing concurrent chemoradiation at our center were taken for the study.

Radiotherapy Treatment Workflow

Complete physical examination including per speculum, per vaginum and per rectal exams were done and stage of disease was established. Patients selected for pelvic radiotherapy were immobilized with 4 clamp orfit and pelvic base plate and taken for planning CECT. CT images were taken on the Siemens SOMATOM Definition AS Scanner (Siemens Medical Systems, Erlangen, Germany) and planning was doneon Eclipse vs. 13.8 (Varian Medical systems Inc. Palo Alto CA).

Gross tumor volume (GTV), Clinical Target Volume (CTV), Planning Target Volume (PTV) and OAR like bladder, rectum, bowel bag, femoral heads rectosigmoid etc. were delineated on the CT image of all the patients by same radiation oncologist to minimize systematic error and interpersonal variations. RTOG Guidelines were strictly followed for delineation of target volumes and OAR. While contouring GTV consisted gross visible tumor and its visible extension and CTV consists GTV, uterine cervix, uterine corpus, parametrium, vagina and ovaries includes involved nodes and relevant draining nodal groups (common iliac, internal iliac, external iliac, obturator and presacral Lymph Nodes. A PTV margin of 10 mm around the CTV was drawn.

IMRT plans for the same were generated by a physicist. Treatment delivery was done on the Varian Clinac DMXmedical Linear Accelerator.

Method of Study

Recording Random Errors: In our study of 50 patients of carcinoma cervix, a total of 520 portal images from IGRT and IMRT treatment plans, were taken and examined. Patients were positioned and immobilized on the couch of the medical linear accelerator with the thermoplastic sheet providing immobilization.

The shifts observed in patient position, i.e. the difference between planned coordinates and new coordinates were recorded for each patient.

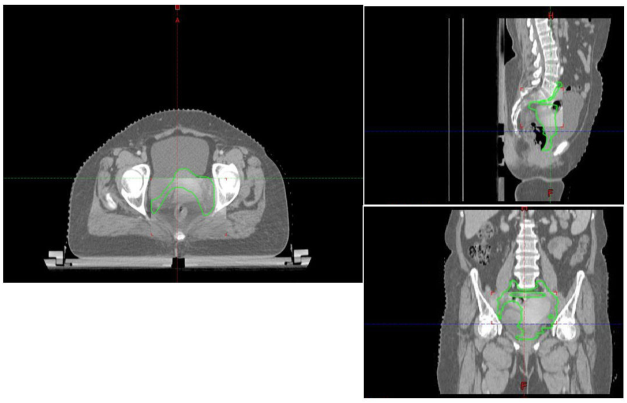

Fig. 1: CBCT matching

Data from matching of CBCT [Fig. 1] to planning CT of 10 patients treated with IGRT was recorded. Shift encountered during matching of kV images [Fig 2] from DRR in 40 patients being treated with IMRT was recorded.

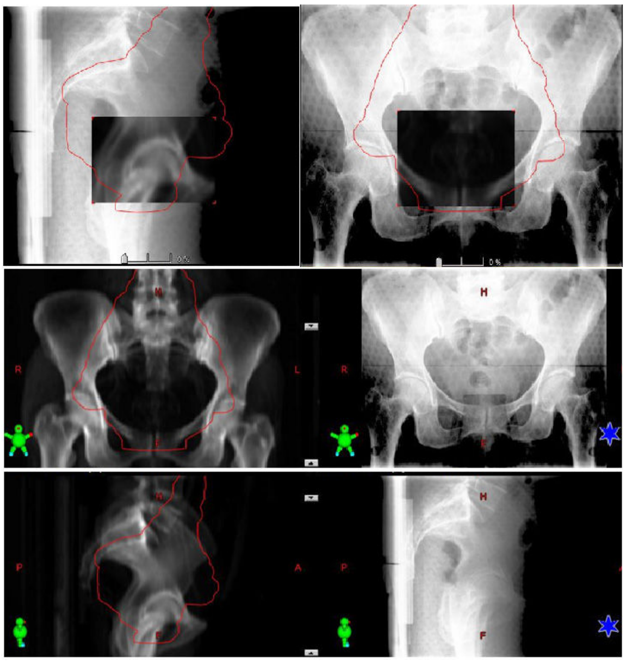

Fig. 2: KV matching

Mean shift, standard deviation and for each patient in all three directions i.e. Horizontal, Vertical and Latitudinal positions were calculated. This data was also used to calculate isodisplacement vector, defined as Isodisplacement vector (IDV)=(vert2+long2+lat2)1/2 Van Herk Margin formula was also used to calculate the PTV margins required for the treatment of cervical cancer radiotherapy at our institute.

Observations and Results

The mean, median and the standard deviation of geometrical shift in each plane were calculated as shown in Fig. 3 (Graph).

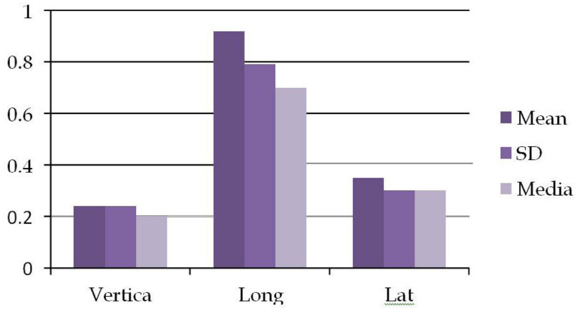

Fig. 3: Graph showing mean, median and standard deviation of the geometrical shift in each plane

The displacement ranges were significant depending on the patient, though the mean value of the displacement was within 1 cm. The mean movement in all the directions was calculated for all the patients over the course of the full treatment i.e. 25 scans per patient for IGRT and 6 OBI sessions per patient for IMRT (as shown in Table 1 &2).

Table 1: Mean displacement of 6 imaging sessions for 40 patients treated with IMRT

Pt. No.	Vert.	Long.	Lat.	IDV
1	0.138	1.15	0.12	1.16
2	0.6125	0.7	0.32	1.03
3	0.1375	1.12	0.51	1.25
4	0.56	0.9	0.52	1.32
5	0.1875	1.26	0.5	1.17
6	0.56	0.8	0.52	1.37
7	0.1875	0.82	0.34	1.10
8	0.56	1.11	0.21	0.93
9	0.26	0.66	0.42	1.14
10	0.15	1.34	0.52	0.8
11	0.12	0.94	0.33	1.44
12	0.15	0.4	0.4	1.03
13	0.24	0.41	0.27	0.85
14	0.65	0.64	0.4	0.51
15	0.12	0.7	0.6	0.79
16	0.23	0.9	0.24	0.7
17	0.24	0.49	0.2	1.55
18	0.15	1.05	0.216	0.94
19	0.15	1.42	0.4	0.55
20	0.16	0.71	0.1	1.08
21	0.12	1.02	0.25	1.48
22	0.15	0.5	0.3	0.73
23	0.27	0.66	0.33	1.03
24	0.15	0.61	0.25	1.10
25	0.21	0.56	0.26	0.59
26	0.12	0.4	0.165	0.77
27	0.36	0.8	0.3	0.82
28	0.15	0.92	0.4	0.67

29	0.325	0.285	0.15	0.71
30	0.15	1.075	0.15	0.46
31	0.225	1.03	0.28	0.82
32	0.2	0.3	0.3	0.38
33	0.128	0.15	0.2	1.09
34	0.07	0.814	0.78	1.1
35	0.23	0.74	0.32	0.46
36	0.12	0.69	0.41	1.2
37	0.15	0.82	0.53	1.4
38	0.42	0.9	0.51	0.83
39	0.16	0.75	0.42	1.67
40	0.52	0.72	0.6	0.45
Mean	0.24	0.78	0.35	0.96
Median	0.18	0.8	0.33	0.98
SD	0.15	0.28	0.15	0.32

Table 2: Shift noted in vertical, longitudinal and lateral directions by IGRT

Pt. No.	Shift noted by CBCT (Mean of 25 imaging sessions)			
	Vert.	**Long.**	**Lat.**	**IDV**
1	0.23	0.67	0.27	0.76
2	0.3	0.6	0.37	0.29
3	0.32	0.65	0.17	0.98
4	0.25	0.56	0.29	0.65
5	0.14	0.51	0.15	0.6
6	0.21	0.7	0.35	0.75
7	0.25	0.53	0.38	0.68
8	0.25	0.67	0.5	0.81
9	0.1	0.41	0.125	0.67
10	0.11	0.75	0.36	0.84
Mean	0.21	0.60	0.29	0.70
Median	0.24	0.62	0.32	0.71
SD	0.076	0.10	0.12	0.18

Longitudinal shift is the greatest. The posterior shift may be due to the rectal filling or presence or absence of gas in the rectum Bladder filling may also cause upward movement of the cervix. Isodisplacement VectorMean Isodisplacement calculated for IGRT treatment technique is 0.7 cm and for IMRT treatment technique is 0.96 cm. The difference between the two is statistically significant (p-value=0.02). PTV Margin calculation by Van Herk margin Formula PTV margin calculated for IGRT and IMRT treatments was found to be 0.21 cms and 0.39 cms respectively (Taking into account only random errors and assuming zero systematic errors). There is statistically significant difference in the PTV margins calculated for both the treatment techniques p-value (<0.01).

Discussion

Setup errors are created in radiotherapy treatment setup by a variety of causes. This depends upon the anatomical site receiving radiotherapy and the setup quality of the institute, including, but not limited to the accurate matching of laser markers, type of immobilization device used, poor patient setup, resolution of the kV imaging, plus accurate matching of the DRR to the kV images and CBCT to the planning CT before beginning of treatment. In addition to this, both inaccuracy in the position of the bony structures (patient setup) and unknown internal target motion relative to the bony anatomy contribute to the uncertainty in the target position during irradiation.

The maximum intended dose to the PTV in Ca cervix is 60 Gy by EBRT, followed by dose escalation via ICRT. Excess PTV margins may translate to extra dose to the sigmoid colon, small bowel, rectum and bladder. The toxicity of small bowel is the limiting factor in whole pelvic radiotherapy, leading to diarrhea, nausea, malabsorption and pain abdomen. Excess dose absorbed by small volume of bowel may cause radio-necrosis and its sequelae. Rabinowitz et al., have reported large setup variations in pelvis of up to 1.19 cm during pelvic RT.[5] Population based margins for PTV, can be as much as 40 mm and can result in large volumes of OARs getting irradiated. Since financial constraints play a major role in deciding quality of care in India, choosing a centre specific, and individualized PTV margins, which limits the bowel and bladder toxicity in patients where daily imaging is not available, are essential for ensuring quality care.

In our study, the noted mean shift in the vertical direction was 0.21 cms and 0.24 cms in IGRT and IMRT treatment techniques respectively. Similarly, mean shift in latitudinal direction was found to be 0.29 cms in IGRT and 0.35 cms in IMRT techniques. The shift in IGRT was lesser than that observed in IMRT treatment plans, but this is not statistically significant. This can be attributed to daily setup corrections in patients treated with IGRT technique. As noted in the study by Bujold et. al, efficient IGRT can bring positional uncertainties down to 1-2 mm if adequate immobilization and motion management is practiced[13] as graphically represented in [Figure 4&5].

In a study conducted by Taylor et al. the greatest displacement was observed in longitudinal direction (Mean = 7 mm). The standard deviation in the three directions were 3.4 mm in latitudinal, 5.2 mm in longitudinal and 5.2 mm in vertical directions

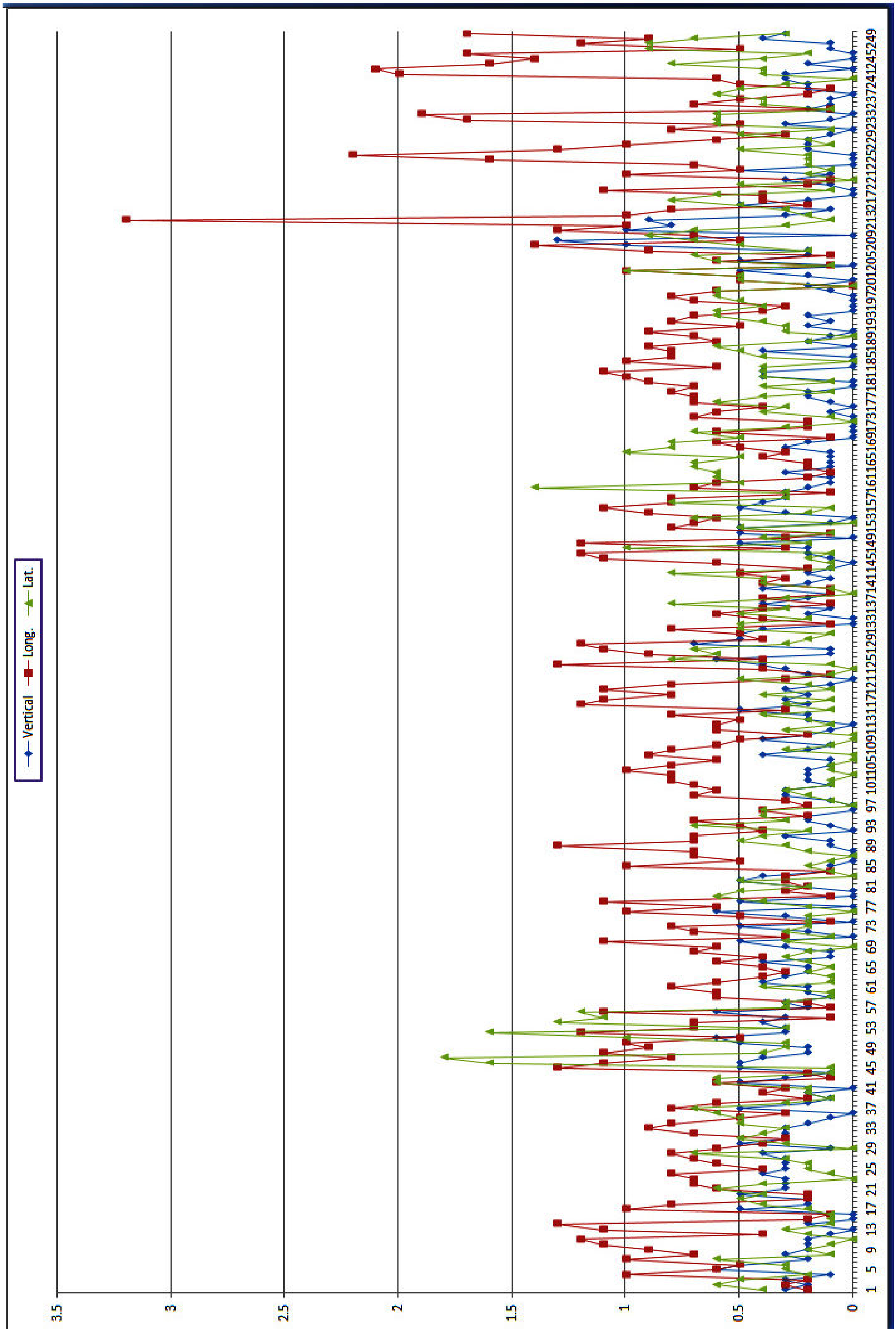

Fig. 4: Graphical representation of Shifts in CBCT Imaging

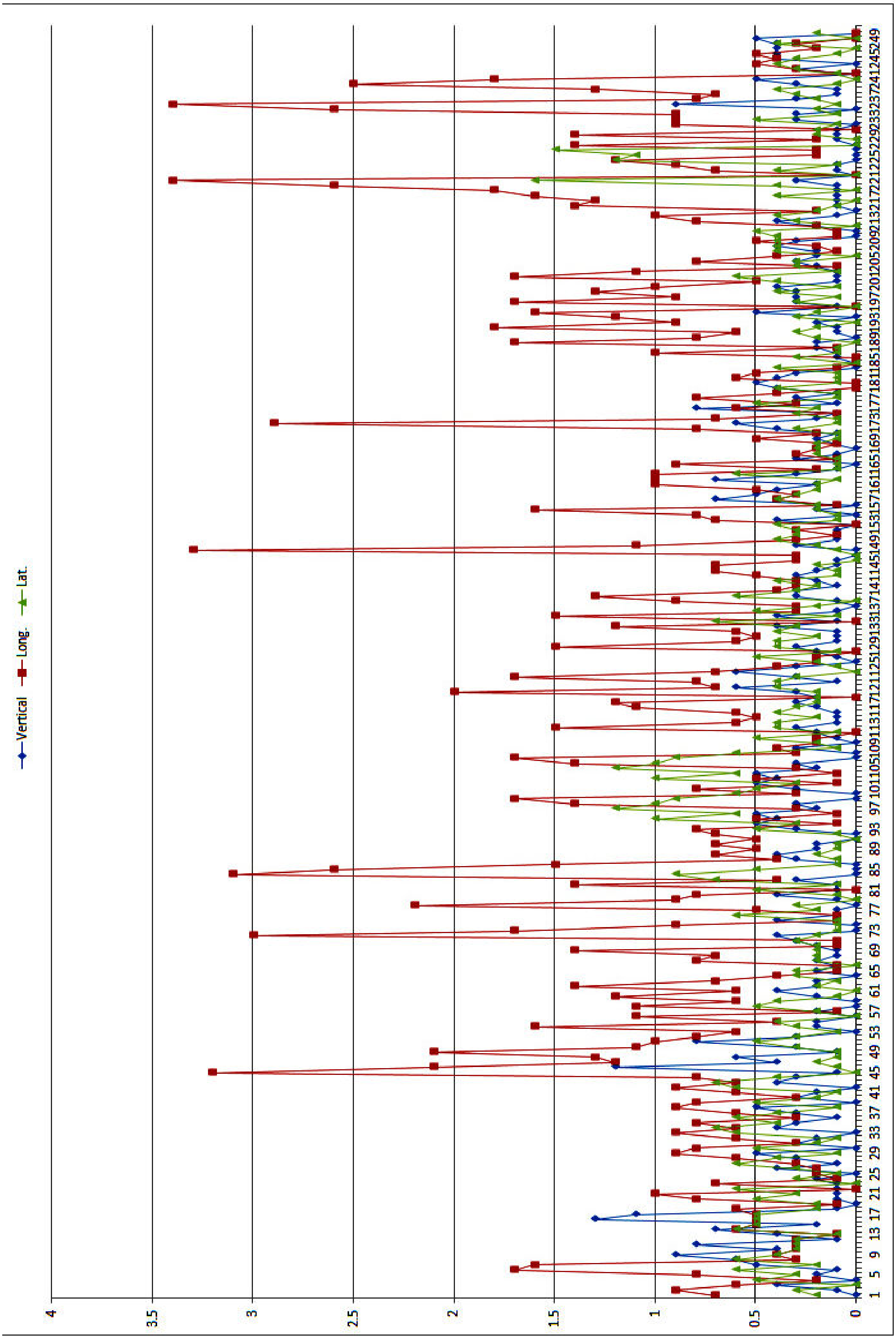

Fig. 5: Graphical representation of Shifts in KV Imaging

respectively. This can be attributed to daily variation in bladder and rectal volumes, which may differ on a day to day basis, even after having a strict bladder and bowel protocol in operation. A Study by Kaatee R et al demonstrated the greatest movement in cranio-caudal (longitudinal) direction. They also recommended lateral margins of 10mm, vertical margins of 12 mm and longitudinal margins of 12.1 mm.[6] In our study, the standard deviation of shift in longitudinal direction was found to be 8mm, 2.5 mm in the vertical direction and 3mm in the lateral direction

Better immobilization devices (such as vacuum cushions, leg-rest, six clamp orfit, etc) would ensure a greater reduction in shift in patients treated with IGRT techniques.In a study by Saini G, et. al, 6 clamp orfit improves reproducibility and reduces shift in longitudinal direction, while vacuum cushion reduces shift in vertical and lateral directions.[7] Nonetheless, the shifts noted with presently available immobilization devices generally concurred with the results of previous studies.

The PTV margins calculated by means of the Van Herk margin recipe (only accounting for the random errors) was found to be 0.21 cms for IGRT technique and 0.39 cms for IMRT treatment technique. However, the margin calculated by this formula cannot be taken as accurate, because even though systematic and random error and geometric uncertainties are taken into account, biological uncertainties remain unaccounted for.[9] In addition to this, the Van Herk formula assumes a perfectly conformal homogenous dose distribution to the CTV, which in practicality isn't achievable.

Similarly, as noted in the present study, translational shift in the longitudinal direction is much greater than in the other two directions. Since Van Herk calculates equal margins in all directions, a one size fits all approach cannot be applied when calculating PTV margins, especially for IGRT technique. The clinical status of the patient, stage of disease and treatment technique used should be kept in mind while deciding on appropriate margins for pelvic radiotherapy in cervical cancer.

A study conducted by Yilmaz et al. on the basis of analyzing 30 scans from 10 patients undergoing radiotherapy for cervical cancer, suggest a 15 mm margin in AP and SI directions, and 5 mm laterally.[10] Based on the data collected at our centre, when daily tumor to tumor matching protocol is not employed, the planning target margin volumes should be expanded around the CTV inhomogenously in the three dimensions with tighter margins in the lateral and AP directions, to at least 5 mm, and in the longitudinal direction to at least 8-10 mm, accounting for the uncertainty of bladder and rectal volume, and longitudinal motion due to four clamp orfit.[11]

Conversely, when protocol of daily CBCT for tumor to tumor matching is employed, we propose tighter planning target margin around the CTV which may be 4 mm in vertical and latitudinal directions, and 6-8 mm in longitudinal direction. Adaptive therapy is the ideal technique of choice, for pelvic RT, where a 'plan of the day' approach can be used to treat according to bladder and rectal volume status.

Conclusion

For patients of carcinoma cervix being treated without image guidance, non-homogenous PTV margins should be given, atleast 5 mm in Lateral and Vertical directions, and 10mm in longitudinal direction. In patients being treated with image guidance, tighter margins may be taken with 4mm in lateral and vertical directions, and 6-8 mm in longitudinal direction. A one size fits all method of selecting PTV margin should not be preferred. Ideal modality of treatment should be IGRT with daily CBCT, with a margin of the day approach.

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