

Set-up Errors and Determination of Planning Target Volume Margins Protocol for Different Anatomical Sites in a Newly Established Tertiary Radiotherapy Centre in India

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Abstract

Objective Our study aimed to assess the set-up errors for image-guided radiotherapy at a newly established tertiary radiation center in India and to establish the departmental protocol of clinical target volume–planning target volume (CTV–PTV) margins for different anatomical sites.

Materials and Methods This study enrolled the first 200 patients who were treated with curative intent at All India Institute of Medical Sciences, Patna, from February 2019 to September 2019. Number of patients were 53, 26, 53, 11, 6, 47, and 4 for head and neck, brain, breast, thorax, abdomen, pelvis, and craniospinal irradiation (CSI), respectively. The translational vectors for total 1,463 kV cone-beam computed tomography (CBCT) images were collected from the treatment record.

Results For the systematic error, the largest value is found for the thoracic subset on the X and Y directions, and for breast patients on Z axis, whereas the smallest values were found for CSI. For random error, the largest value was found for pelvic in the X, Y direction, and for breast subset on Z axis, whereas the smallest values on X and Z axes were found in the brain and for head and neck on the Y axis. Largest value for systemic error is smaller than 5 mm in all directions and for all anatomical subsets. The highest random error value is 5.07 mm in Y axis for pelvic subset. The largest values for CTV–PTV margin are found for thoracic subset and the smallest for CSI followed by the brain. Significant reduction of set-up error observed for the last hundred patients as compared to the first half of the patient population.

Conclusion Use of thermoplastic cast along with breast board and respiratory motion management should be recommended to reduce set-up error for breast and thoracic subset. Six degrees of freedom robotic couch system can also further rectify the set-up error in image-guided radiotherapy.

Keywords

- ▶ set-up error
- ▶ PTV margins
- ▶ Image-guided radiotherapy

Introduction

Image-guided radiation therapy (IGRT) is intended to deliver the therapeutic radiation after image-based target

relocalization ensuring precise delivery of beam and minimizing the volume of organ at risks (OARs) exposed to the ionizing radiation. Determination of the discrepancy between the intended and actual treatment position with the aid of

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cone-beam computed tomography (CBCT) is an integral part of IGRT.¹ This discrepancy is calculated as a shift in treatment field position comparing the CBCT images against its corresponding reference which is known as digitally reconstructed radiographs (DRRs). Set-up error comprises a systematic and random component² and is calculated over a horizontal axis or right-left (X), longitudinal axis or superior-inferior (Y), and depth or anterior-posterior (Z) axis. It also contains rotational changes which can be corrected if 6 degrees of freedom couch is available in the institute.

The systematic error is a reproducible consistent deviation that occurs in the same direction and magnitude throughout the treatment course. Systematic errors can enter into the treatment chain at any phases of localization, planning or beam delivery. Possible reasons for systematic errors^{2,3} are (1) target delineation error which represents the difference between the delineated and ideal clinical target volume (CTV); (2) target position and shape error which is due to the tumor regression or growth, bladder and rectum filling difference, hair loss, etc.; and (3) phantom transfer error⁴ which occurs during image transfer from initial localization through the treatment planning system (TPS) to the linear accelerator (LA). Several factors which might lead to such errors are differences in laser alignment between CT simulator and LA, minor changes in CT simulator couch longitudinal position, image resolution, isocenter location, source to surface distance (SSD) indication, margin growing algorithm, field edge and multileaf collimator (MLC) leaf position, gantry, and collimator angle accuracy. Many of these parameters are expected to be detected by the routine quality assurance program of the machines.⁵

The random component is a deviation that can vary in direction and magnitude for each delivered treatment fraction. It occurs at the treatment delivery or execution stage and possible reasons⁶ are (1) patient set-up error which is varying, unpredictable changes due to variation in patient's daily position, treatment equipment like immobilization devices, or set-up methodology between each delivered fraction; (2) change in target position and shape between fractions due to motion and breathing. These errors are influenced by the immobilization system, patient compliance, and department protocols. Only an off-line correction strategy cannot rectify the random error component in the subsequent fractions. Online correction⁷ of CBCT is necessary to rectify the random error component.

Set-up errors, CTV-planning target volume (PTV) geometric margins, beam delivery techniques, use of immobilization devices are interlinked. The daily online correction protocol, both for systematic and random error, may increase the treatment time significantly resulting in intrafractional variation. Longer treatment time also necessitates more skilled resources and caregivers which might be limited for high volume radiation centers in India. Volumetric arc therapy (VMAT) which is a single or multiple-arc treatment enables delivery of radiation with much shorter beam on time and lesser monitor units (MU) can reduce the intrafractional set-up errors.⁸

Our study aims to assess the three-dimensional set-up errors in image-guided fractionated radiotherapy at a newly established tertiary radiation center in India and to establish the departmental protocol of PTV margins for different anatomical sites.

Materials and Methods

Patient Selection

The first two hundred patients who were treated with curative intent in a newly established LA (Elekta Versa HD) at the department of radiation oncology, All India Institute of Medical Sciences, Patna, were enrolled retrospectively since February 2019 to September 2019. The patients were divided as per the following anatomical sites: (1) head and neck ($n = 53$), (2) brain ($n = 26$), (3) breast ($n = 53$), (4) thorax ($n = 11$), (5) abdomen ($n = 6$), (6) pelvis ($n = 47$), and (7) craniospinal irradiation (CSI; $n = 4$).

Immobilization and Simulation

Before the treatment, all the patients underwent CT scan in head first and supine position. Contrast dye was used as per clinician's discretion. Patients with squamous cell carcinoma head and neck region (HNSCC) and brain malignancy were immobilized with five clamps and three clamps thermoplastic cast, respectively. Suitable size of head rest (HR) was used for all patients with HNSCC and brain malignancy which were comfortable, reproducible, and fit for the patients. All the women with carcinoma of the breast were simulated with breast board (Micromedics) without a thermoplastic cast. Patients with carcinoma in the thoracic region were comprising with the various diagnosis of malignancy, namely, carcinoma lung, carcinoma oesophagus, soft tissue sarcoma, and lymphoma. Such patients were simulated with proper HR, four clamps thermoplastic casts or Vac-Lok cushion (Civco Medical Solutions trade mark, Iowa, United States). Patients with abdominal malignancy subset who had diagnosis of carcinoma stomach and carcinoma gall bladder were simulated with four clamps thermoplastic cast and HR.⁹ We followed the "bladder protocol"¹⁰ for the patients of the pelvic subsite, with the diagnosis of carcinoma in various pelvic organs namely cervix, endometrium, rectum, anal canal, and prostate. Such patients were asked to void their urinary bladder first and then to consume 500 mL of water 30 minutes before the simulation and to hold the urine till the simulation is complete. Knee rest was used for immobilization as per clinician's discretion. Children with the diagnosis of medulloblastoma, who were treated with CSI were immobilized with HR, three clamp thermoplastic cast for brain region, and Vac-Lok for the torso.

Fiducial Markers

The external markers for patients with brain tumor and HNSCC were placed on the surface of the fixation masks with the aid of CT simulation in-room laser in three directions (right, left, and roof).¹¹ Patients with breast

carcinoma were marked with skin tattoos in three positions (preferably on right and left midaxillary line and midline of the body) with the alignment of the room laser. Patients immobilized with Vac-Lok had three markers, one on the patient body and another two on the Vac-Lok. For patients treated with CSI, Three fiducial markers were kept for brain region and another three fiducial markers on Vac-Lok

Image Acquisition and Registration of Planning CT to CBCT

The CT simulation of all patients is undergone with GE Healthcare Optima full-rotation helical 16-slice CT scanner. Brain images are taken with 3-mm slice thickness while the rest of the sites underwent 5-mm slice images. These CT images were transferred to the Monaco 5.0 TPS. If available, magnetic resonance imaging (MRI), and positron emission tomography scan (PET) for any subsites were registered with CT simulation images for the better delineation of gross tumor volume (GTV).

For the first day treatment set-up, the patients were positioned according to the fiducial marker by using in-room set-up laser. Thereafter, kV-CBCT images were acquired using the gantry-mounted X-ray volume imaging (XVI).

The registration between the acquired CBCT images and planning CT images (DRR) was performed by bone and/or soft tissue grey value automatching followed by a manual correction if required. Rigid bony anatomy (vertebral column), visualized target volume within the PTV, adjacent landmarks, such as the carina or bronchus, bladder, and rectum filling difference, were taken into account during the process of manual matching. The translational position correction vectors were calculated after the whole matching procedure for lateral, longitudinal, and vertical axis.¹²

The clinical threshold level at our institution is 5 mm and 3 degrees for both translational and rotational directions. In cases of larger deviations, the patient was repositioned and online registration was performed again.

Methods of Data Analysis

The translational vectors for total 1,463 kV CBCTs images were collected from the treatment record. Individual average of shifts along the three-axis and standard deviation (SD) were calculated for each patient. Total average of the SD, minimum, and maximum value for each treatment sites were analyzed. Set-up errors are normally distributed and mean (M) and SD of errors most accurately describe them. M is defined as the mean of all individual means and ideally, it should be closer to zero. S corresponds to the SD of all individual means, and σ is determined through the root mean square of the individual SD of all patients.

According to the literature of The Royal College of Radiologist, Institute of Physics and Engineering in Medicine and Society and College of Radiographers are on target,

ensuring geometric accuracy in radiotherapy.³ The errors are categorized as follows.

Systematic Error

Individual Mean Set-up Error

Individual mean set-up error (m_{ind}) is the mean set-up error for an individual patient:

$$m_{ind} = \frac{\sum_{i=0}^n \Delta_i}{n}$$

where Δ_i is the set-up error for each imaged fraction and n is the number of imaged fractions.

Overall Population Mean Set-up Error

The overall mean set-up error (M_{pop}) is the overall mean for the analyzed patient group and should ideally be zero. Significant deviation from zero indicates an underlying error common to the patient group and requires corrective measurements. The equation to calculate the overall population mean set-up error is as follows:

$$M_{pop} = \frac{\sum_{i=0}^p (m_{ind})_p}{p}$$

where m_{ind} is the individual mean set-up error and p is the number of patients.

Population Systematic Error

The systematic error for the population (Σ_{set-up}) is defined as the SD of the individual mean set-up errors about the overall population mean (M_{pop}). It is calculated from the following equation:

$$\Sigma_{set-up} = \sqrt{\frac{\sum_{i=0}^p [(m_{ind})_i - M_{pop}]^2}{(p-1)}}$$

where m_{ind} and M_{pop} are individual and overall population systematic set-up error respectively and p is the number of patients.

Random Error

Individual Random Error

For each individual, the interfractional random (daily) set-up error (σ_{ind}) is the SD of set-up errors around the corresponding mean individual value (m_{ind}) derived from equation (01).

It is calculated from the following formula:

$$\sigma_{ind} = \sqrt{\frac{\sum_{i=0}^n (\Delta_i - m_{ind})^2}{(n-1)}}$$

where σ_{ind} and m_{ind} are the individual random error and individual mean set-up error. Δ_i is the set-up error for each imaged fraction and n is the number of imaged fraction.

Population Random Error

The population random error (σ_{set-up}) is the mean of all the individual random errors.

$$\sigma_{set-up} = \frac{\sum_{i=0}^p (\sigma_{ind})_i}{p}$$

where σ_{ind} is the individual random error, calculated from equation (04) and p is the number of patients.

Calculation of PTV Margin

There are several methods to calculate CTV to PTV margin like the International Commission on Radiation 62 (PTV margin = $\Sigma + 0.7\sigma$), Stroom’s method (PTV margin = $2\Sigma + 0.7\sigma$), and Van Herk’s (PTV margin = $2.5\Sigma + 0.7\sigma$) formula. Here Σ and σ are the population systematic error and population random error, respectively. For our institutional practices, the general margin is calculated from Van Herk’s equation. Analysis is carried out using the Microsoft Office Excel 2013 and graphs are made with OriginLab (OriginLab Corporation, Northampton, Massachusetts, United States)

Results

The average shifts for all the patients in our study including all the treatment sites in three directions are shown in

► **Fig. 1**, and the values of M, systematic error, and random error for each anatomical subset are shown in ► **Table 1**. For the systematic error, the largest value is found for the thoracic subset on the X and Y directions, and breast patients on Z axis, whereas the smallest values were found for CSI. Apart from CSI, lowest values are found on X and Y axes for head and neck subset and on Z axis, lowest value is for the brain. For random error, the largest value was found for pelvic in the X, Y direction, and for breast on Z axis, whereas the smallest values on X and Z axes were found in the brain and for head and neck on the Y axis.

In overall, the largest value for systematic error is smaller than 5 mm in all directions and for all anatomical subsets. For random error, the highest calculated value is 5.07 mm in Y axis for pelvic subset.

For the better evaluation of our continuous effort to reduce the set-up errors, we analyzed the systematic and random errors for first hundreds and second hundreds of patients irrespective of the anatomical sites. The results are calculated in ► **Tables 2 and 3**.

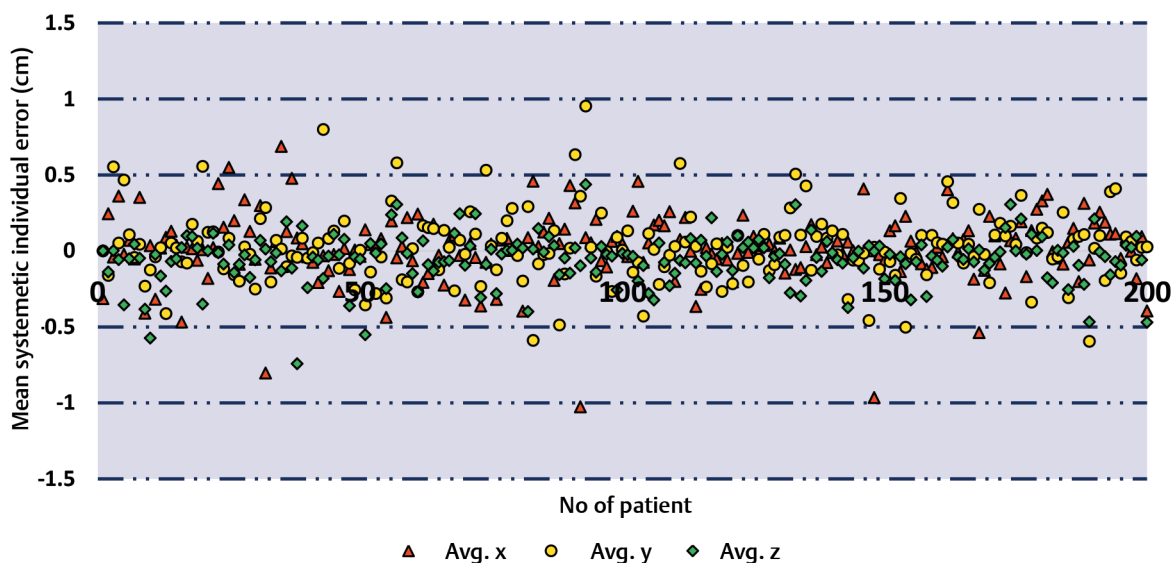


Fig. 1 Average shifts for all the patients in our study including all the treatment sites in three directions. Avg., average.

Table 1 Values of mean, systematic error, and random error for each anatomical subset

| Site | No. of patients | No. of kv-CBCT | Mean (mm) | | | Systematic error (Σ) in mm | | | Random error (σ) in mm | | |
|---------------|-----------------|----------------|-----------|-------|-------|-------------------------------------|-------|-------|---------------------------------|-------|-------|
| | | | X | Y | Z | X | Y | Z | X | Y | Z |
| Brain | 26 | 202 | 0.264 | 0.476 | 0.419 | 1.106 | 1.347 | 1.001 | 1.658 | 2.020 | 1.328 |
| Head and neck | 53 | 436 | 0.203 | 0.253 | 0.035 | 1.091 | 0.767 | 1.924 | 2.205 | 1.490 | 1.928 |
| Thorax | 11 | 83 | 0.055 | 0.319 | 0.348 | 3.347 | 3.670 | 1.346 | 2.425 | 3.053 | 2.350 |
| Breast | 53 | 309 | 0.198 | 0.211 | 1.441 | 2.771 | 3.344 | 2.986 | 4.423 | 3.903 | 3.879 |
| Abdomen | 6 | 46 | 0.068 | 2.592 | 0.116 | 1.274 | 2.254 | 1.799 | 1.997 | 2.721 | 2.818 |
| Pelvic | 47 | 347 | 0.031 | 0.064 | 0.684 | 2.753 | 2.323 | 1.419 | 4.554 | 5.077 | 3.130 |
| CSI | 4 | 40 | 0.025 | 1.730 | 0.200 | 0.588 | 0.751 | 0.651 | 2.291 | 2.263 | 1.374 |

Abbreviation: CBCT, cone-beam computed tomography; CSI, craniospinal irradiation.

Table 2 Systematic and random errors for first hundred and second hundred of patient population irrespective of the anatomical sites and technique of planning

| No. | Systematic error (Σ) (mm) | | | Random error (σ) (mm) | | |
|------------------|------------------------------------|-------|-------|--------------------------------|-------|-------|
| | X | Y | Z | X | Y | Z |
| 1st 100 patients | 2.506 | 2.507 | 2.169 | 3.300 | 3.152 | 2.520 |
| 2nd 100 patients | 1.910 | 2.040 | 1.403 | 3.263 | 2.992 | 2.565 |

Table 3 Systematic and random errors for first hundred and second hundred of patient population treated by two different techniques

| No. | Technique | Systematic error (Σ) in mm | | | Random error (σ) in mm | | |
|------------------|-----------|-------------------------------------|-------|-------|---------------------------------|-------|-------|
| | | X | Y | Z | X | Y | Z |
| 1st 100 patients | 3DCRT | 3.141 | 2.891 | 1.991 | 4.057 | 3.979 | 2.744 |
| 2nd 100 patients | | 1.225 | 1.903 | 2.254 | 2.336 | 2.099 | 2.234 |
| 1st 100 patients | VMAT/IMRT | 2.067 | 2.475 | 1.721 | 4.077 | 3.713 | 3.273 |
| 2nd 100 patients | | 1.743 | 1.432 | 0.928 | 2.480 | 2.299 | 1.885 |

Abbreviations: 3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; VMAT, volumetric arc therapy.

Table 4 Calculated CTV-to-PTV expansion values for the overall sessions for each treatment sites

| Site | No. of patients | X (lateral) in mm | Y (longitudinal) in mm | Z (vertical) in mm | Margin (mm) |
|---------------|-----------------|-------------------------------|-------------------------------|-------------------------------|-------------|
| | | $2.5 * \Sigma + 0.7 * \sigma$ | $2.5 * \Sigma + 0.7 * \sigma$ | $2.5 * \Sigma + 0.7 * \sigma$ | |
| Brain | 26 | 3.9 | 4.8 | 3.4 | 4.8 |
| Head and neck | 53 | 4.3 | 3.0 | 6.2 | 6.2 |
| Thorax | 11 | 10.1 | 11.3 | 5.0 | 11.3 |
| Breast | 53 | 10.0 | 11.1 | 10.2 | 11.1 |
| Abdomen | 6 | 4.6 | 7.5 | 6.5 | 7.5 |
| Pelvic | 47 | 10.1 | 9.4 | 5.7 | 10.1 |
| CSI | 4 | 3.1 | 3.5 | 2.6 | 3.5 |

Abbreviations: CSI, craniospinal irradiation; CTV, clinical target volume; PTV, planning target volume.

CTV-to-PTV Margin

For each treatment site, the calculated CTV-to-PTV expansion values for the overall sessions are presented in the ► **Table 4**. The largest values are found for thoracic subset and the smallest for CSI followed by the brain. These results are in expected range because of the values of systematic and random errors computed in our study.

Discussion

Interfraction set-up errors for seven different treatment sites of the first two hundred treated patients at our institute were analyzed retrospectively using 1,463 CBCT studies. The mean error and the SD on three axes are shown in the ► **Figs. 2–4**.

For intrafraction variation, several studies¹³ showed that intrafraction tumor deviation is significantly greater if the interval between target localization and repeat CBCT imaging is more than 34 minutes. The average time from localization to treatment in our institution is approximately 15 minutes.

The results of our study showed that the variation was large for breast and thoracic subset and small for CSI and brain treatments. The large values for the thoracic region are probably due to the free breathing motion. The use of only breast board without immobilization cast and improper localization of skin tattoos might have resulted in a larger shift for breast cancer subset. Several factors like curved external anatomy, loosening, or tightening of the fixation mask due to changing body contours, tumor shrinkage can also contribute to significant set-up errors. Keeping such changes in mind, rescanning and replanning with new fixation mask were done in our institution if considerable discrepancies occurred.^{14–16}

Multiple studies^{17,18} have recommended the reduction of PTV margins with the use of CBCT image guidance. PTV margin without image-guided radiation therapy should be ≥ 5 mm, whereas, with daily CBCT image guidance, it could be reduced to approximately 2 to 3 mm. The calculated PTV margins of approximately 3.5 to 4.8 mm in all translational directions for the brain and CSI treatment sites in our institution were in tune to available published studies.

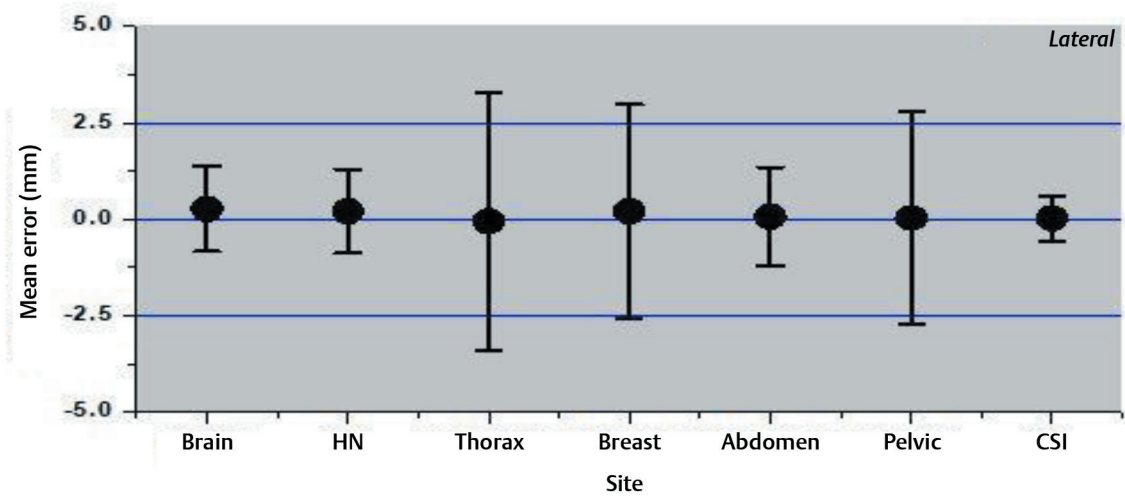


Fig. 2 Mean errors and the standard deviation for lateral axis for different treatment sites.

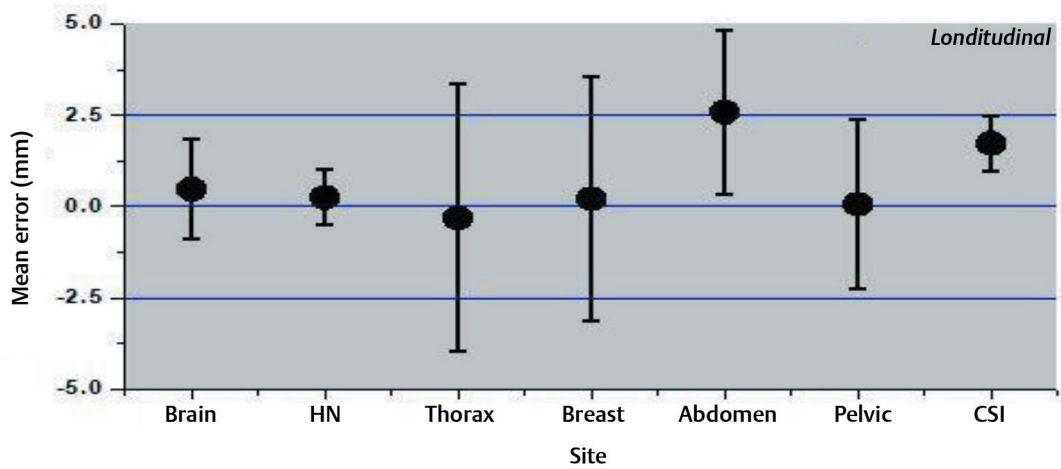


Fig. 3 Mean errors and the standard deviation for longitudinal axis for different treatment sites.

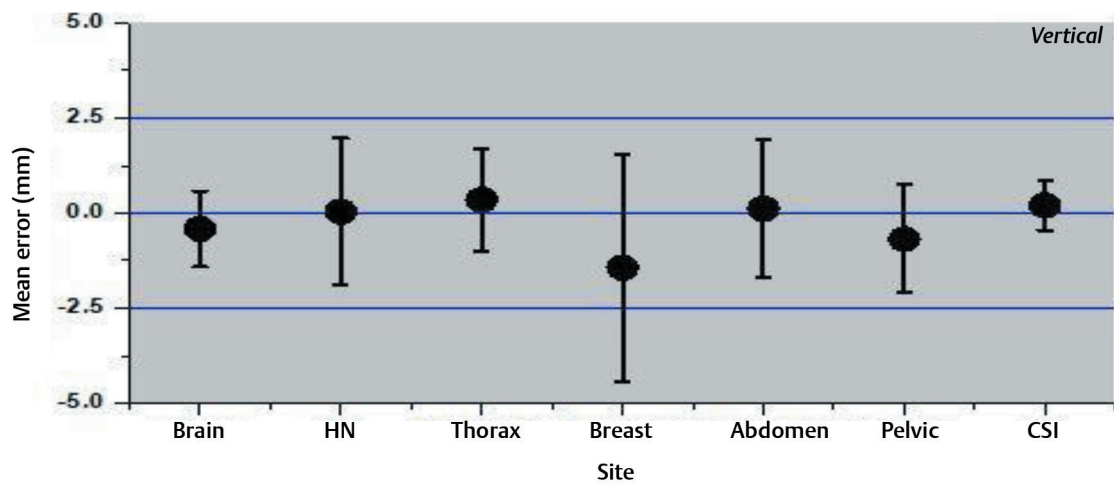


Fig. 4 Mean errors and the standard deviation for vertical axis for different treatment sites.

Therefore, reduced PTV margins for the brain and CSI should be applied under daily CBCT imaging guidance. For thoracic and pelvic subsites, the PTV margins were mainly affected by set-up errors due to respiratory motion, tumor shrinkage, nonuniform protocol for the use of thermoplastic casts.

With our analysis of the second half of the patient population, we found a significant improvement in terms of set-up errors for both systematic and random component which was consistent with three-dimensional conformal radiation therapy, intensity-modulated radiation therapy, and VMAT techniques. Gaining more expertise and efficiency by the radiation technologists for patient simulation, molding of thermoplastic casts, patient positioning, and localization in treatment couch and more uniform use of thermoplastic devices and skin markings with ink tattoos can explain this significant improvement.

Limitations

One of the limitations which need to be addressed for this study is the unavailability of 6 degrees of freedom robotic couch system in our institute and hence not accounting the rotational changes in the analysis. Not taking a second or verification CBCT scan after the repositioning and not accounting the residual errors after matching is another drawback of our CBCT protocol. Second CBCT will also lead to a higher dose of exposure to the patient and longer treatment time. But the assessment of the residual errors might help to calculate CTV-to-PTV expansion margins more accurately when IGRT is followed.

Conclusion

Based on the result and observations of this study, we recommend the following four points to be addressed for our future treatment:

1. To use thermoplastic immobilization masks along with breast board for all patients with carcinoma breast.
2. The patients who follow bladder protocol are to consume uniform volume of water with a uniform time gap between water intake and simulation and water intake and treatment.
3. Six degrees of freedom robotic couch system for correction of rotational errors is to be installed.
4. Respiratory motion management devices should be considered especially for breast carcinoma and thoracic malignancy subsets.

Conflict of Interest

None declared.

Acknowledgement

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