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Inter-Fraction Analysis of One Week Hypo-Fractionation of Deep Inspiration Breath Hold (DIBH) Technique for Left Sided Breast Cancer Radiation Treatment

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Abstract

The aim of this study was to investigate the inter-fraction variations, patient comfort and knowledge at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). The differences in set-up that occurred between treatment sessions for the left sided breast patients were observed and recorded. Measurements of routine set-up variation for 24 patients were performed by matching the cone beam computed tomography (CBCT) and the planning computed tomography (CT). Scans of all five fractions per patient were used to quantify the setup variations with standard deviation (SD) in all the three directions (anterior posterior, left right, and superior inferior). The patients DIBH comfort and knowledge was also evaluated. The average translational errors for the anterior posterior (AP, z), left-right (LR, x), and Superior-inferior (SI, y) directions were 0.40 cm, 0.40 cm, and 0.40 cm, respectively. The translation variation of the three directions showed statistical significance ($P < 0.05$). On comfort and knowledge investigation, among all participants, 80% moderately agreed that the therapist's instructions for operating the deep inspiration breath hold (DIBH) technique were easy to understand, and 63.33% indicated that their comfort with the DIBH technique was neutral or average. The inter-fraction variations in patients with left-sided breast cancer were qualitatively analyzed. Significant shifts between CBCT and planning CT images were observed. The daily treatment verification could assist accurate dose delivery.

Keywords

Breast Cancer, Deep Inspiration Breath Hold, Hypo-Fractionation, Inter-Fraction

1. Introduction

Radiation therapy as a supplementary treatment is crucial in the curative aspect of breast cancer (BC) therapy [1]-[6]. However, variations between fractions can affect the overall effectiveness of radiotherapy treatment. Therefore, consistent positioning and breath holds techniques are crucial for delivering the planed radiation dose precisely. The deep inspiration breath hold (DIBH) method is recognized for its ability to lower the radiation dose to the heart by expanding the gap between the heart and the breast [7]-[12].

DIBH technique suspend patient breathing for computed Tomography (CT) simulation and treatment purposes. Breath hold techniques are typically used for tumour immobilization and margin reduction in most studies; however, in left-sided breast cancer radiotherapy, DIBH is utilized for its anatomical benefits in reducing cardiac and pulmonary toxicities.

The simplest way to account for respiratory motion uncertainty is to use motion-based margins method. However, this method results in a planned target volume (PTV) that includes all expected positional uncertainties such as setup errors. The PTV is based on an estimate of target motion and adds a margin around the clinical tumour volume (CTV). The CTV is always delineated inside the PTV. The dose is prescribed for the PTV on a static CT scan. PTV margin is made up of two parts: setup margin (SM) which takes into account patient setup differences and internal margin (IM) which compensates for internal physiological movement (e.g., respiratory motion) [13].

While motion-based approaches are the most effective at avoiding geometric miss, they also risk over-dosing neighboring normal tissues, and reducing the maximum dose that may be administered to the tumour. Margin calculation is the most common motion compensation technique used in breast radiotherapy during planning CT scans and radiation treatment [13]. Target volumes are increased by margin when breast contours are used to account for uncertainty in respiratory motion and to set up uncertainties.

Cancer patients who undergo radiotherapy procedures often experience stress and anxiety due to negative perceptions of the radiation, unease with the equipment and overall fear of the procedure. According to Eskelinen [14], 12% to 47% of patients with breast cancer reported baseline anxiety and 11% to 16% experienced anxiety and depression. According to Lewis [15], radiation therapy itself can cause anxiety and emotional distress. They also noted that up to 50% of patients experience persistent anxiety during their radiation therapy procedures.

Patients with breast cancer frequently experience additional difficulties due to the physical discomfort caused by previous surgeries, including ongoing pain and limited mobility. They also deal with side effects from chemotherapy, like exhaustion, and worry about how their bodies will look and the possibility of disfigurement [16]. This emotional distress can be extremely difficult for cancer patients to deal with or to tolerate their treatment. It is even more difficult especially for advanced radiation therapy procedures, where high-level, active, intricate and repetitive collaboration is often required of the patient.

The aim of this study was to investigate the inter-fraction variations, patient comfort and knowledge at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

2. Material and Methods

The Radiation Oncologist explained to the patients the DIBH treatment procedure and asked if they were willing to participate in the research study. The patients were having time to take a decision because they had to do the CT scanner, which takes 2 - 3 weeks before the treatment plan is ready, if they agree the Doctor gave them the informed consent form to sign. The patents were told that they have a right to withdraw her participation in the study anytime. The was no risk on the patient side since the researcher only interested on the patient data, but the patient was still having to go through the DIBH radiotherapy treatment as other patients who are not participating in the research study.

Between March 2020 and September 2022, a total number of 120 pre-treatment cone beam computed tomography (CBCTs) were analyzed, from 24 patients with a diagnosis of left-sided breast cancer, treated at Charlotte Maxeke Johannesburg Academic Hospital. Ethical approval was obtained from a Human sub-committee of North West University (NWU) Medical Research Ethics Committee MREC (NWU-00274-21-S1) and WITS MREC (M230852). The study was also evaluated and approved by CMJAH (GP_202310_020). The study was designed in a way that only one oncologist reviewed the images.

2.1. Dose Objectives and Constraints

The prescription dosage was 26 Gy divided into 5 parts. The main goal in designing the treatment was to ensure at least 95% of the dose was delivered to the target area, with a total dose of 24.7 Gy (V24.7) in the PTV. VMAT strategies were created and refined using Monaco® TPS.

2.2. Setup Error Inter-Fraction Data Collection

The CBCT monthly quality control was performed following the South African quality assurance standards. The monthly flex-map calibration and verification of the registration of 3D image (CBCT vs CT) was performed using the ball bearing phantom. All the quality control results were within the acceptable level.

The difference in variability between the fractions was calculated by aligning the CBCT scans with the planning CT scans. An experienced radiation oncologist examined the images on the computer to verify the accuracy of the alignment, paying special attention to bone formations, air spaces, and the soft tissues. For this research, a uniform method was employed to gather the necessary information. This was accomplished through the assistance of Elekta XVI version 5.1. The values of all three translational axes (x-lateral, y-longitudinal, and z-vertical) were documented from the initial CBCT scans to determine the daily setup errors (inter-fraction variation).

During treatment delivery of beams, CBCT images were acquired and compared with the original plan to assess reproducibility of patient setup in daily bases or inter-fractionally.

2.3. CBCT Image Acquisition and Registration

Prior to each treatment session, a CBCT scan was performed with the patient on the treatment position. The CBCT images were taken with the linear accelerator (LINAC) equipped with an onboard imaging system. The acquired CBCT images were registered (aligned) with the planning CT images. The registration process involves matching anatomical landmarks, such as bones or soft tissue structures, to assess any deviations from the planned position.

2.4. Error Analysis

The differences between the CBCT images and the planning CT images are quantified in terms of translational (shift). Translational errors were measured in millimeters along the X, Y, and Z axes.

2.5. Correction and Adjustment

Based on the quantified translational errors, adjustments were made to the patient's position to correct any deviations. Manual adjustments were performed by the radiotherapy team.

2.6. Verification

After making the necessary adjustments, another CBCT scan was performed to verify the corrected position. This step ensures that the patient was accurately aligned before the delivery of the therapeutic radiation dose. The CBCT images were taken daily for each treatment fraction, and lasers positions were considered after matching CBCT and planning images while using the CBCT matching software. Laser positions were checked for each fraction for reproducibility purposes. The chest wall displacement was recorded by Mosaiq verification system for all the fractionation treatments. The chest wall positions were verified for all five (5) fractions.

2.7. Patient Education and Comfort

Patient education is a very important component in DIBH technique, to reduce anxiety and increase their confidence about receiving radiation therapy. A qualitative research method such as face-to-face interview was chosen to assess patient's comfort and understanding on the first day of treatment. The primary objective of this standardised and open-ended interview was to determine the degree of understanding as well as patient's comfort. The areas of discussion were based on the patient's clinical experience with left-sided breast cancer treatment and their knowledge on DIBH. After the first treatment the radiotherapist interviewed the patients in order to collect information about education and comfort. This information was recorded in the prescribed form. Taking into considerations the criticality of DIBH procedure and the patient's cooperation needed, the patients need to be coached and be comfortable for radiotherapy treatment to be successful. During the treatment, CBCT acquisition was performed for a couple of times, each scan comprises a number of projection while the patient holding their breath. Hence, comfort and knowledge of the left sided breast cancer patients is important for their radiotherapy treatment tolerance. Halkett *et al.* [17] suggested that anxiety prior to RT is associated with the lack of information about treatment and side effects, and the unfamiliar procedures.

Radiotherapist had to ask six questions and had the possibility to tick three different options, 1) Relate to patients' knowledge and understanding of DIBH; a) Were the therapists' instructions easy to understand? b) Do you know the reason why you need to use the mouth device? c) Do you like having an active role in your treatment? 2) Relate to Patients comfort and experience with DIBH system. a) How comfortable could you hold your breath? b) Did you feel anxious while holding your breath? c) Did you feel you could easily recover after DIBH? The patients answered each question by rating it as "not at all", "Slightly", "Neutral", "Moderately", and "Very". The responses from the participants were recorded on the questioner. The overall goal of analyses was to reach some conclusions about the effectiveness of education method on DIBH and the treatment comfort as a whole.

3. Results

3.1. Patient Setup Reproducibility Analysis

The treatment setup variation was observed for left sided breast patients. Routine setup variation for 24 patients was measured by matching CBCT scans and planning CT of each patient. Scans of all five fractions per patient were used to quantify the setup variations with standard deviation (SD) in all the three directions (anterior posterior, left right, and superior inferior) (**Table 1**).

Table 1. Comparison of translational errors acquired by the CBCT.

Translation	Mean	95% Confidence Interval	Standard Deviation	p-value
AP	0.503	(0.445, 0.562)	0.334	<0.001
LR	0.477	(0.421, 0.534)	0.323	<0.001
SI	0.515	(0.459, 0.571)	0.321	<0.001

Figures 1-3 show the inter-fractional of the translational shift of the anterior-posterior, Left-right, and Superior inferior directions from the changes CBCT and planning CT in 120 fractions of 24 patients. The green represents the fraction 1, blue fraction 2, yellow fraction 3, orange fraction 4, and red fraction 5.

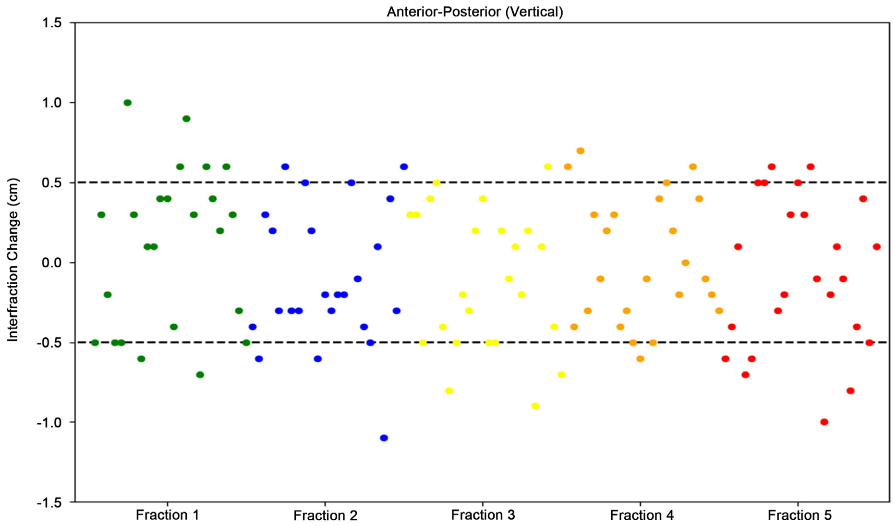

Figure 1. Comparison of Anterior-Posterior (AP) translational errors.

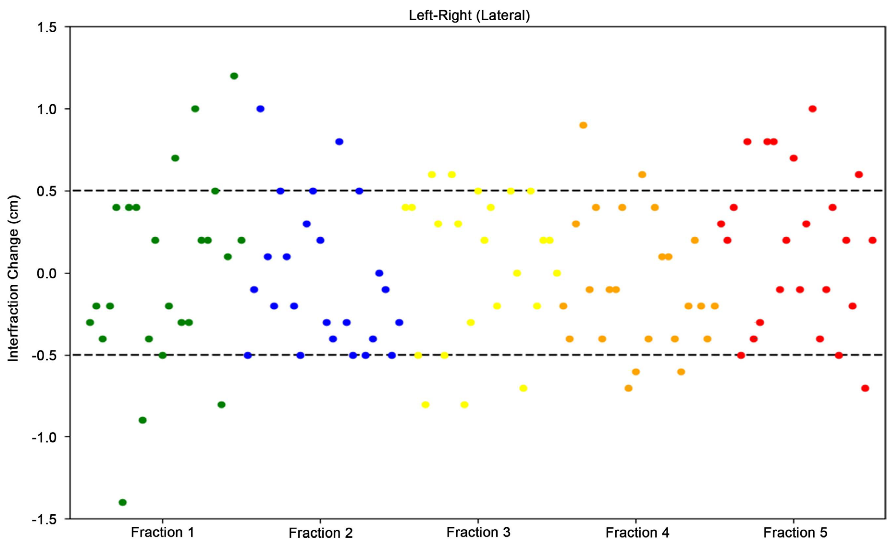

Figure 2. Comparison of Left-Right (LR) translational errors.

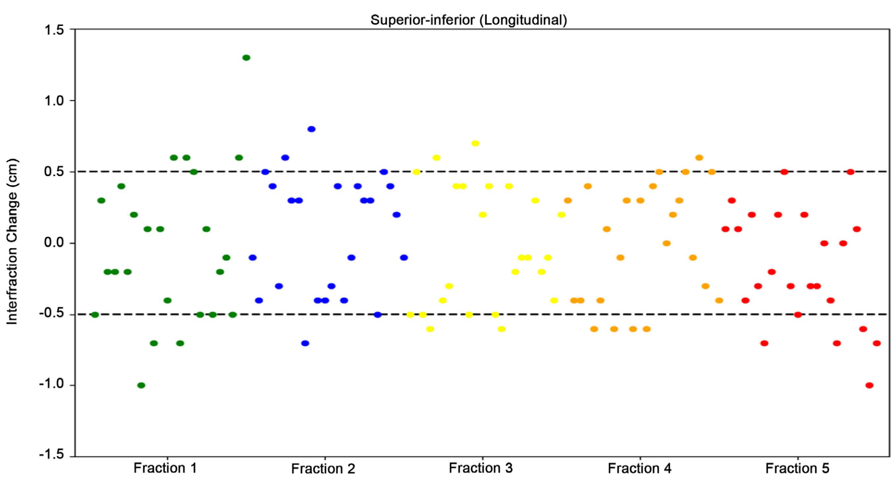

Figure 3. Comparison of Superior-Inferior (SI) translational errors.

3.2. Patients' Knowledge and Comfort Analyses

Table 2. Outline of the overall patients' knowledge and comfort with the deep inspiration breath hold technique.

Question	Classification	Frequency	Percentage
Knowledge and Understanding of the DIBH Technique			
Were the therapist's instructions easy to understand?	1: Not At All	0	0.00%
	2: Slightly	0	0.00%
	3: Neutral	1	3.33%
	4: Moderately	24	80.00%
	5: Very	5	16.67%
Do you know the reason why you need to use the mouth device?	1: Not At All	0	0.00%
	2: Slightly	0	0.00%
	3: Neutral	2	6.67%
	4: Moderately	22	73.33%
	5: Very	6	20.00%
Do you like having an active role in your treatment?	1: Not At All	0	0.00%
	2: Slightly	0	0.00%
	3: Neutral	0	0.00%
	4: Moderately	13	0.00%
	5: Very	17	43.33%
Patients' comfort of the DIBH technique			
How comfortable could you hold your breath?	1: Not At All	0	0.00%
	2: Slightly	0	0.00%
	3: Neutral	19	63.33%
	4: Moderately	9	30.00%
	5: Very	2	6.67%
Did you feel anxious while holding your breath?	1: Not At All	0	0.00%
	2: Slightly	0	0.00%
	3: Neutral	5	16.67%
	4: Moderately	23	76.67%
	5: Very	2	6.67%
Did you feel you could easily recover after DIBH?	1: Not At All	0	0.00%
	2: Slightly	0	0.00%
	3: Neutral	17	56.67%
	4: Moderately	9	30.00%
	5: Very	4	13.33%

4. Discussion

4.1. Patients' Knowledge and Comfort

The DIBH method was carried out using an active breathing control (ABC) device from Elekta, Sweden. Patients with breast cancer on the left side were taught to inhale and exhale through a mouthpiece linked to the ABC device. The ABC system incorporates a spirometer, which enables the tracking of air movement during the breathing cycle and halts the flow of air at a predetermined volume during the planning of imaging and treatment. This tool will help patients keep their breath and stay in place, but it needs to be used correctly, which required guidance from the patients. The amount of air the patient takes in while undergoing radiation treatment is crucial for keeping the position consistent, so they were asked about their comfort and understanding of the method (**Table 2**). Outline the classifications, frequency, and percentages according to the participant's response.

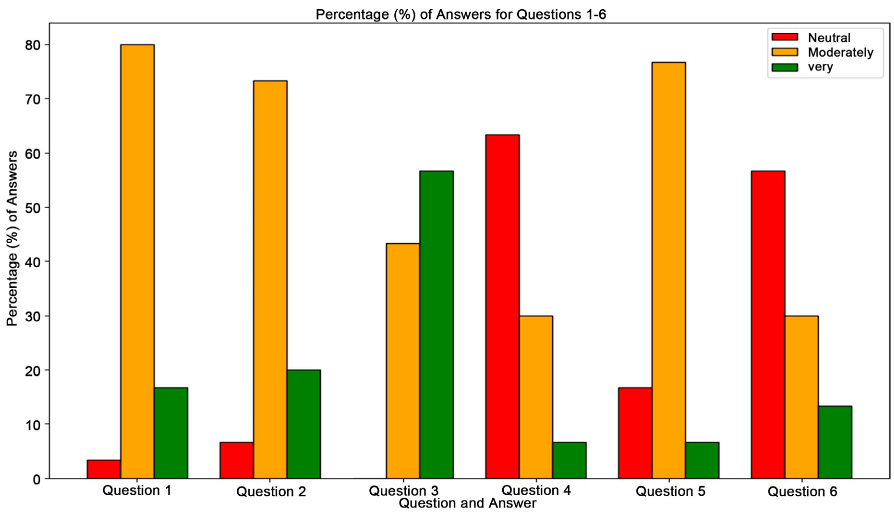

Figure 4. Graphical representation of the patients' comfort, knowledge, and understanding of the DIBH technique.

At the completion of the first fraction, the patients were administered a questionnaire asking about their comfort and knowledge on their DIBH treatment technique.

As seen in **Figure 4** in all participants, 80% reported moderately that they view the therapist's instructions as easy to understand on the operation of the DIBH technique, while 16.67% through the information was effective for them to start their treatment. About 3.33% was neutral about the effectiveness the education offered to them. When they were questioned about the importance of using the mount device, 73.33% of them rated moderately, 20.0% reported very knowledgeable, and 6.67% were neutral. 63.33% of the participants indicated that the DIBH comfort was neutral or average, and 6.67% reported that they were comfortable with the system. 30.0% reported moderately.

4.2. Patient Setup Reproducibility Analysis

Figure 4 presents a comparison of the maximum-minimum position within daily CBCT image sets with respect to planning CT. The maximum deviation of the position between planning CT and CBCT was mostly within 0.5 cm reproducible in a direction of anterior posterior, left right, and superior posterior. A comparison of the cone beam computed tomography and treatment planning computed tomography translational errors is presented in **Table 1**. The average translational errors for the anterior posterior (AP, z), left-right (LR, x), and superior-inferior (SI, y) directions were 0.40 cm, 0.40 cm, and 0.40 cm, respectively. The translation variation of LR, AP, and SI shifts of breast cancer patients treated was 0.503 ± 0.334 cm, 0.477 ± 0.323 cm, and 0.515 ± 0.321 cm respectively. The translation variation of the three directions showed statistical significance ($P < 0.05$). However, it was confirmed that the translational error significantly decreased longitudinally. The standard deviation from the mean variations of 24 patients presents the systematic error.

The results of P-value from the t-test were 0.01 in the anterior posterior, 0.01 in the left right direction, and 0.01 in the superior inferior direction. Our study shows significant positional deviations between CBCT and planning CT. Treatment protocols advice the justification of any radiation dose given to the patients, but justification of medical imaging is always debatable [18]. Planning target volume (PTV) is a term mentioned in the ICRU report, which refers to a specific volume considered in planning or administering treatments. PTV accounts for any uncertainties that may arise in the planning or delivery of treatments. A minimum geometric safety margin of 0.5 cm is set from the clinical target volume (CTV), as per PTV. This safety margin guarantees that the target area is not overlooked during radiotherapy. At the same time, it results in an additional 0.5 cm of normal tissue surrounding the CTV.

The challenge with the left sided breast is the heart dose. DIBH is used to create a distance between the heart and the chest wall. Applying a margin to accommodate the setup errors will results in the heart getting a bit closer to the target, which could result in more radiation dose to the heart. Therefore, even though the setup margin is permitted, for DIBH left-sided breast radiotherapy, considering the hypo-fractionated dose of 5.2 Gy per fraction there is no room for more errors on fractional dose. It is justifiable to do verification for all five fractions of 26 Gy, even though the average variations in all directions in this study were less, within or bit more than 0.5 cm as presentment in **Figures 1-3.** Inter-fraction breath hold variations may be relatively larger [19]. Hence, regular target and organs at risk (OAR) position verification with X-ray-based images is recommended [20], and reproducibility of DIBH should be within 0.2 - 0.5 cm regardless of the used technique [21] and [22].

Figures 1-3 demonstrate the variations of all five fraction for 24 patients in all directional translational shifts. Although most variations were within 0.5 cm, some movements were little more than 0.5 cm. Hence, we emphasize the importance of inter fractional CBCT treatment verification.

Our findings indicate that before-treatment DIBH and CBCT are capable of identifying the translational changes that necessitate modifications, and they can also enhance the precision of the treatment and guarantee consistent reproducibility, particularly with hypo-fractionated radiation dose. Nonetheless, there might still be a significant difference in heart position during DIBH, ranging from 0 to 1 cm.

4.3. Limitations to the Study

Even though our study showed good reproducibility between fractions, it has its drawbacks. The sample size of patients in our research was quite small because we had specific criteria for choosing the participants. Hypo-fractionation of 26 Gy, 5 Gy, 2 Gy per fraction was prescribed to patients with early breast cancer. But in our case few patents were diagnosed at the early stage. Most patients will come for treatment at their advanced stage. This small number of patients might have impacted the statistical strength of our findings. Additionally, we were unable to conduct intra-fraction analyses because the patients were not able to undergo additional DIBH scans following their treatments.

5. Conclusions and Recommendations

The differences among patients with left-sided breast cancer were qualitatively examined. There were notable changes observed between the CBCT and planning CT scans. The daily treatment verification could assist accurate dose delivery. The DIBH significantly reduces the radiation dose to the heart, and the CBCT, which ensures accurate daily positioning of the target volume. Additionally, the level of patient understanding and comfort with the DIBH system was successfully measured.

Future research could focus on studying the volumetric changes in the left breast during treatment. Our findings indicate that daily verification of treatment using CBCT is recommended, and the combination of DIBH and CBCT could be advantageous for patients with left-sided breast cancer receiving hypo-fractionated radiation therapy. The translational changes could not have been identified if the patients were aligned using only skin markings.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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