LEVEL OF ANXIETY IN BREAST CANCER PATIENTS RECEIVING LOCOREGIONAL RADIATION THERAPY AND ITS CORRELATION WITH INTER-FRACTION VARIATIONS OBSERVED DURING DELIVERY OF TREATMENT

DEPARTMENT OF RADIOTHERAPY
CHRISTIAN MEDICAL COLLEGE
VELLORE 632004

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF

MD BRANCH IX RADIOTHERAPY

EXAMINATION APRIL 2017

TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY

CHENNAI - 600032

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I Shina Goyal, PG Registrar ,Department of Radiation therapy ,Christian Medical College Vellore hereby declare that the dissertation titled **"Level of anxiety in breast cancer patients receiving locoregional radiation therapy and its correlation with inter-fraction variations observed during delivery of treatment."** is a bonafide work done by me for partial fulfillment towards MD Radiotherapy (Branch IX) Degree examination of the Tamil Nadu Dr M G R Medical University to be held in April 2017.

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I enclose the following documents:-
1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

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The Committee reviewed the following documents:

1. IRB Application format
2. Patient Information Sheet and Informed Consent Form (English, Tamil, Hindi
3. Beck Anxiety Inventory Questionnaire
4. Proforma
5. Cvs of Drs. Shina Goyal , Antonisamy, Rabi Raja Singh, Patricia S, Rajesh B, Subhashini John, Ms. SherlyChristy
6. No. of documents 1 - 5

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We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "Level of anxiety in breast cancer patients receiving loco-regional radiation therapy and its correlation with inter fraction variations observed during delivery of treatment" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in)

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A sum of Rs.28,700/- INR (Rupees Twenty eight thousand seven hundred Only) will be granted for 8 months.

Yours sincerely

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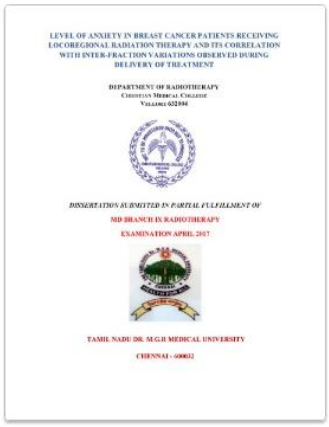
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CONTENTS

AIMS AND OBJECTIVES

AIM

To study the level of anxiety in breast cancer patients receiving loco-regional radiation therapy and to study its correlation with inter fraction variations observed during delivery of treatment.

OBJECTIVES

Primary:

- To assess the level of anxiety of breast cancer patients during planning and treatment of radiation therapy.

Secondary:

- To measure the inter fraction variations during the course of radiation therapy.
- To correlate the anxiety levels with inter fraction variations recorded during the treatment.
- To determine the need of counseling for anxious patients to reduce the inter fraction variations.

INTRODUCTION

Breast cancer is the most frequent cancer among women according to the GLOBOCON 2012 report. In India, breast cancer is the most common cancer contributing to 27% of all new cancers in women.

Breast cancer requires multi-modality treatment including surgery, chemotherapy, radiation therapy and hormonal therapy. Many patients undergo radiation therapy as part of their treatment for breast cancer and the number is rising with increase in breast conservation surgeries. Various studies have looked into the psychological distress of patients undergoing radiation therapy. Studies have shown that the patients experience anxiety particularly prior to planning and at the start of radiotherapy treatment, likely due to the fear of unknown. This study aimed to estimate the level of anxiety of non metastatic breast cancer patients undergoing radiation therapy using the Beck anxiety inventory. The questionnaire was administered at the time of simulation, on the first three days of treatment and weekly once.

Radiation therapy treatment consists of continuous treatment of five days a week for 3-5 weeks. It involves radiation of the chest wall or whole breast with or without regional nodal irradiation. Tangential fields have been used conventionally to ensure minimum dose to the underlying normal tissue including the lung and heart. 3DCRT and IMRT has made it possible to achieve better dose distribution with high dose to the target and

sparing of the surrounding normal structures. However, with these conformal techniques, it is important to ensure accurate delivery of beams as per the treatment plan. Studies have shown there are daily variations which contribute to changes in irradiated volumes during treatment. On board electronic images are taken for verification of position and treatment volume. We can measure the inter-fraction variations by comparing the on board images with reference images and this helps to decide the appropriate setup margin for our planning.

For treatment of breast cancer patients, other than setup uncertainties, organ motion due to breathing need to be taken into account during treatment planning and delivery. It was hypothesized that the change in breathing pattern may be correlated with the level of anxiety and altered breathing pattern during treatment would affect our planned treatment volumes. This study was a step to understand that whether anxiety causes a significant change in breathing pattern and hence significant increase in inter fraction variations.

A positive correlation of anxiety with inter-fraction variability may provide a new insight into the need for improving communication with patients regarding the radiation therapy to alleviate their symptoms of anxiety.

REVIEW OF LITERATURE

3.1 INCIDENCE - GLOBAL AND INDIAN EPDEMIOLOGY

Breast cancer is the most common malignancy diagnosed in females throughout the world. According to WHO GLOBOCON 2012 report, breast cancer is the second most common cancer in the world and the most common cancer among women. An estimated 1.67 million new cases were diagnosed in 2012 (i.e. 25% of all diagnosed cancers). It is the most common cancer in women both in the developed and less developed regions of the world. Breast cancer is the fifth most common cause of cancer death overall. It is however the most common cause of cancer related death in women in less developed regions and second most common cause of cancer related death in the developed regions, first being lung cancer.

In India, as per WHO GLOBOCON report 2012, number of new cases of breast cancer diagnosed in 2012 was 1,45,000 and number of deaths related to breast cancer was 70,000. Based on review of population based cancer registry in India 2009-2011 data and Hospital based cancer registry 2007-2011, breast cancer accounts for 25% to 32% of all female cancers. Therefore, one fourth of all female cancer cases can be attributed to breast cancer.(1)

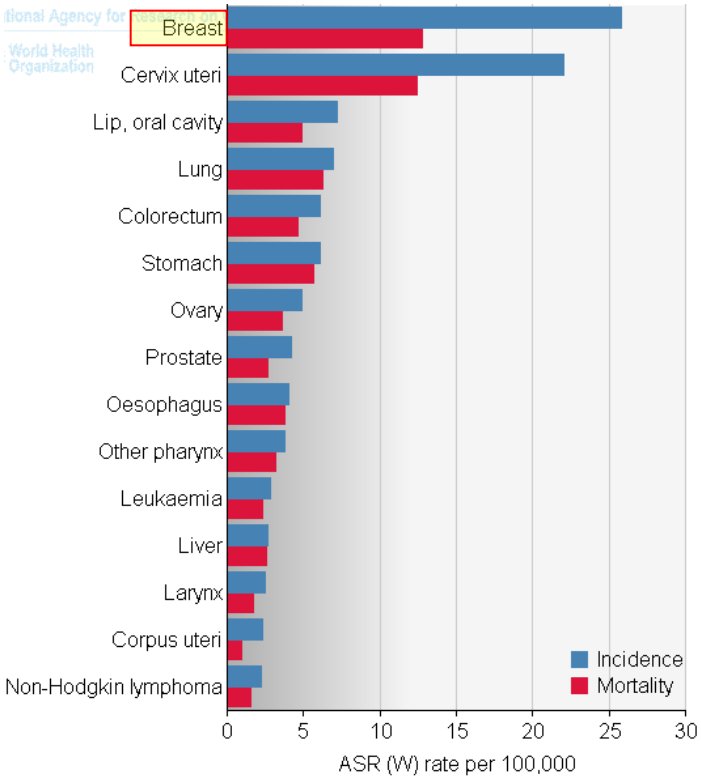
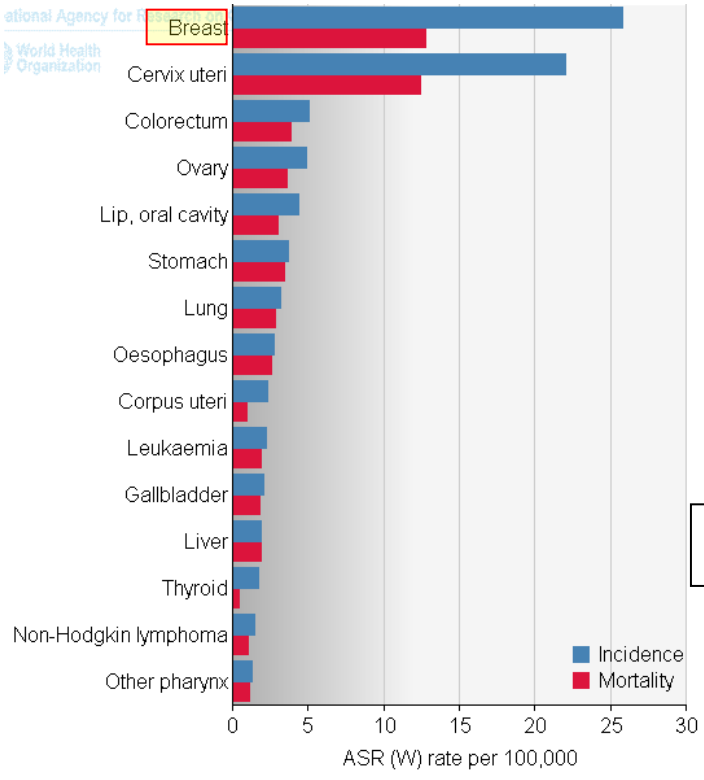


Figure 1. GLOBOCON 2012 - Incidence and Mortality in India for both sexes



GLOBOCON 2012 - India (females)

Figure 2. GLOBOCON 2012 - Incidence and Mortality in India for women

The mortality from breast cancer is showing a declining trend as a result of earlier diagnosis through screening, improved surgical and radiotherapy techniques and more adjuvant therapies. Mortality rates are higher in younger women i.e. less than 35 years and very old i.e. more than 75 years. This is because young females have a more aggressive tumor and for very old women, aggressive treatment may not be feasible or there other co-morbidities may cause death.

3.2 ETIOLOGY OF BREAST CANCERS

Breast cancer is a heterogeneous disease caused by progressive accumulation of genetic aberrations, including point mutations, deletions, chromosomal amplifications, rearrangements, translocations, and duplications (2,3). Germ line mutations account for only about 10% of all breast cancers, while the vast majority of breast cancers appear to occur sporadically and are attributed to somatic genetic alterations.

Breast cancer has many etiological factors including genetic and family history, estrogen exposure (based on menarche and menopause age, use of estrogen containing medictaions like oral contraceptive pills etc, nulliparity and lack of breast-feeding. It is also associated with history of certain breast conditions like papilloma or prior history of radiation therapy to the chest region (4).

3.3 ANATOMY OF BREAST (5)

The female breast lies on the anterior chest wall superficial to the pectoralis major muscle. It extends from the midline to near the mid axillary line and cranial caudally from the second rib to the sixth rib. The upper-outer quadrant of the breast that extends into the region of the low axilla is frequently referred to as the axillary tail of Spence. This area contains a greater percentage of total breast tissue compared with the other quadrants, and, therefore, a greater percentage of breast cancers occur in this anatomical location.

The breast is made up of mammary glands, fat tissue, blood vessels, nerves, and lymphatics. The surface of the breast is anchored to deeper tissue by fibrous septa called Cooper's ligament, which run between the superficial fascia (attached to the skin) and the deep fascia (covers the pectoralis major and other muscles of the chest wall). The chest wall includes the ribs, intercostal muscles, and the serratus anterior muscle, but not the pectoral muscles.

The predominant lymphatic drainage of the breast is to axillary lymph nodes, which is commonly described in three levels, based on the relation to the pectoralis minor muscle.

- Level I axilla is caudal and lateral to the pectoralis minor muscle
- Level II is beneath the pectoralis minor muscle,
- Level III (also known as the infraclavicular region) is cranial and medial to the pectoralis minor muscle.

The axillary lymph nodes continue underneath the clavicle to become the supraclavicular lymph nodes, which can be involved in locally advanced breast cancers. Lymphatics can also drain directly into the internal mammary lymph node chain (IMC), which are intrathoracic structures located in the parasternal space. When breast cancer involves the IMC, the majority of patients will have disease that is limited to lymph nodes in the first three interspaces. Regardless of location in the breast, the axilla is the most common site of lymphatic involvement. However, breast cancers that develop in the medial, central, or lower breast more commonly drain to the IMC (in addition to the axilla) than those occurring in the lateral and upper quadrants.

3.4 STAGING OF BREAST CANCER

Breast cancer has been staged as per the AJCC 2010 (6) (Appendix 1) . Early breast cancer (EBC) comprises of Stages I, IIA, IIB and IIIA. Locally advanced breast cancer (LABC) comprises of Stage IIIB onwards.

3.5 HISTORICAL PERSPECTIVE

Ancient Egyptians first noted the disease more than 3,500 years ago. Over the years, many theories came up to explain its occurrence and spread. It was understood that it spreads to lymph nodes and hence different surgical approaches aiming at removing the breast along with lymph glands were tried.

3.6 SURGERY

Mastectomy, or removal of the entire breast tissue with the muscles of the chest wall including the pectoralis major muscle, is one of the surgical procedures used in breast cancer treatment. There are various types of mastectomy that have evolved over time. In the 1900s, Radical Mastectomy (Halsted mastectomy) was the standard of care for breast cancer (7). It reduced local recurrences, but caused significant side effects, functional and psychological morbidity and diminished quality of life. It resulted in gross deformity and problems of lymphedema and sensory abnormalities over the arm and chest. Hence over the next few years, more conservative surgeries evolved.

The recent practice of surgery involves a more conservative approach which is known as the Modified Radical Mastectomy (MRM). It is a surgical procedure in which the entire breast is removed, including skin, areola, nipple, and most of the axillary lymph nodes, however, the pectoralis major muscle is spared.

Long term follow up data of breast cancer patients treated by radical mastectomy showed that 30 year survival rate was about 38% (8). It is rarely used now days. Modified radical mastectomy has been shown to have an equivalent survival outcome and lesser morbidity (9). Simple mastectomy is another new surgical technique that involves removal of entire breast while preserving the pectoral muscles and the axillary contents. With the emergence of data of use of sentinel node biopsy, simple mastectomy is being performed more frequently. Skin-sparing mastectomy (SSM)

involves preserving the natural breast skin envelope that provides the reconstructed breast with a more natural shape and contour and thus give a superior cosmetic result(10,11). It is considered to be an oncologically safe surgery.

In cases of early breast cancer, nowadays a breast conservation approach is being used in which instead of the entire breast tissue, only the lump is removed with adequate margins. The EORTC 10801 trial on breast conservation surgery (BCS) versus MRM showed no significant difference in twenty year overall survival rate among women who underwent breast conservation surgery and radiotherapy and those who were treated with modified radical mastectomy, for early breast cancer (Stage I and II). Overall survival at 20 years was 44% in the BCS group and 39% in the MRM group. Time to distant metastasis also did not differ significantly between the two groups, however the study found that the 10-year locoregional recurrence of cancer was higher in the breast-conserving group than in the patients who underwent mastectomy (20% vs 12%, respectively) (12).

There has been a paradigm shift in the understanding of the natural history of breast cancer from local disease theory to systemic disease theory. Surgical procedures have become less aggressive and less invasive and surgical treatment is just one part of the multidisciplinary treatment required in breast cancer (13).

Today, the treatment of breast cancer is always a multimodality approach. Surgery forms the mainstay of management with radiation therapy and chemotherapy taking a major adjunct role (14).

3.7 CHEMOTHERAPY

Role in adjuvant setting

Chemotherapy was introduced in the fifth and sixth decades of the twentieth century and resulted in the development of curative therapeutic intervention in management of various cancers. In breast cancer, initially single-agent chemotherapy was used - cyclophosphamide, phenylalanine mustard, vincristine, vinblastine, methotrexate and 5-fluorouracil. Bonadonna et al., in 1976 showed for the first time the efficacy of adding various chemotherapy agents together in the management of breast cancer. CMF (cyclophosphamide, methotrexate and fluorouracil) was used as an adjuvant treatment to radical mastectomy for breast cancer with lymph nodes positive disease and provided better local control of disease, better disease free and overall survival (15). Role of Adriamycin based chemotherapy in adjuvant setting was shown with further studies. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) studied recurrence and 15-year survival for different chemotherapy and hormonal therapy for early breast cancer. It showed that anthracycline based chemotherapy for 4–6 months (FAC or FEC) reduced annual breast cancer mortality rates by 38% in women less than 50 years and by 20% in women aged 50–69 years. This was found to be more effective than the CMF regimen (16). This resulted in the change of chemotherapy regimens from CMF to anthracycline based regimens which till date form the mainstay of chemotherapeutic management of breast cancer.

Role in neoadjuvant setting

Chemotherapy is used in neoadjuvant setting in locally advanced breast cancer to downstage the disease. Response to chemotherapy in terms of complete pathological response (pCR) has been shown to be the strongest predictor of disease-free survival and overall survival (17). Cochrane meta-analysis in 2007 included 5500 women and showed neoadjuvant chemotherapy was associated with fewer adverse effects. It further confirmed that pathological complete response to neoadjuvant chemotherapy was associated with better survival than residual disease after chemotherapy (18). It also has a role in early breast cancer before considering breast conservation surgery.

3.8 RADIATION THERAPY FOR BREAST CANCER

Radiation Therapy forms an integral part in the management of breast cancer. It is beneficial in reducing the local recurrence and improving the overall survival after surgery in both early and locally advanced breast cancer patients. It is also beneficial in palliation of symptoms in cases of metastatic breast cancer.

Indications for radiation therapy in breast cancer are;

1. As an adjuvant treatment after breast conservation surgery in cases of early breast cancer
2. As an adjuvant treatment after modified radical mastectomy in locally advanced breast cancer

3. For palliation of symptoms (bone pains, impending fracture, spinal cord compression and brain metastasis etc.) in cases of metastatic breast cancer

In cases of early breast cancer, after a breast conservation surgery, the addition of adjuvant radiation therapy has shown to improve both local control and overall survival. The Early Breast cancer Trialists Collaborative Group (EBCTCG) conducted a meta-analysis from 17 randomized controlled trials which had 10871 patients of early breast cancer post breast conservation surgery. It showed a reduction in the 10-year risk of any (ie, locoregional or distant) first recurrence from 35·0% to 19·3% (absolute reduction 15·7%) and reduced the 15-year risk of breast cancer related death from 25·2% to 21·4% (absolute reduction 3·8%) with the addition of adjuvant radiation therapy (19). They concluded that after breast-conserving surgery, radiotherapy to the conserved breast reduces the rate at which the disease recurs by half and reduces the breast cancer death rate by about a sixth. Based on the results of this meta-analysis and other randomized controlled trials, adjuvant radiation therapy is presently the standard of care after any breast conservation surgery.

In cases of locally advanced breast cancers, or in patients who have undergone modified radical mastectomy, adjuvant radiation therapy has been found to be beneficial in cases where high risk factors are present. Randomized controlled trials from the Danish group and British Columbia studies first demonstrated the benefit of adjuvant post mastectomy radiation therapy in selected patients with high risk features (20,21). Later a meta-analysis published by the EBCTCG in 2014 showed that post mastectomy radiation therapy reduced both recurrence and breast cancer mortality in

the women with one to three positive lymph nodes. For women with axillary dissection and four or more positive nodes, radiotherapy reduced overall recurrence by 21% and breast cancer mortality by 13% (22).

As per the ASTRO consensus guidelines, ASCO guidelines and American College of Radiology criteria (23–25), post mastectomy adjuvant radiation therapy is indicated in:

1. Patients With Four or More Positive Axillary Lymph Nodes
2. Patients with 1-3 positive axillary lymph nodes and presence of high risk features
3. Patients With T3/T4, or Stage III disease
4. Patients Undergoing Preoperative Systemic Therapy

3.9 EVOLUTION OF RADIOTHERAPY

Radiation therapy has evolved a lot in the past few decades. From the initial era of 2D conventional radiation therapy to 3D Conformal Radiation Therapy (3D CRT) and the present day era of Intensity Modulated Radiation Therapy (IMRT), Image Guided Radiation Therapy (IGRT), Volumetric Arc Therapy (VMAT), Tomotherapy and Intensity Modulated Proton Therapy (IMPT). This evolution has led to more precision based treatment with better dose distribution to the area of interest and less radiation dose delivery to the normal tissues. Hence, a higher therapeutic ratio can be achieved with better results.

3.10 TARGET VOLUMES FOR RADIATION THERAPY IN BREAST CANCER

When radiation therapy is planned in any case of breast cancer, the area which is targeted depends upon the surgery which has been performed and the presence or absence of high risk factors for the inclusion of the nodal drainage areas. In a case of early breast cancer in which a conservative surgery has been performed, the target area comprises of the entire remaining breast tissue (excluding the chest wall) and the lumpectomy cavity (defined by the pre-surgical clinical and mammographic findings and surgical clips) which is given added dose of radiation therapy by a lumpectomy cavity boost. Inclusion of regional nodes depend on axillary approach during surgery (axillary clearnce versus sentinel lymph node biopsy), presence of other risk factors and administration of neoadjuvant chemotherapy.

In cases where a more radical surgery has been performed and the entire breast tissue has already been removed, the target area comprises of the chest wall including the muscles and the ribs underneath. If high risk features are present which warrant the nodal areas also to be irradiated, then the axilla, supraclavicular area and the internal mammary areas are included in the target areas as required.

3.11 ORGANS AT RISK

The most critical organs in breast planning include lung, heart and contralateral breast tissue. Studies have shown that the risk of contralateral breast cancer after radiation

therapy for breast cancer is estimated to be a function of the radiation dose delivered to the contralateral breast. Most of the older studies showed no significant association with radiotherapy (26,27). However, in a relatively recent study (28), less than 3 percent of second breast cancers were attributed to previous radiation treatment. The risk was higher among women who underwent irradiation at a relatively younger age (<45 years) (28). Thus, there is an emphasis on the need of reduction of dose to contralateral breast tissue.

Volume of lung tissue irradiated during loco-regional irradiation of breast cancer patients correlates with the risk of lung toxicity. There is irreversible reduction in lung function parameters accompanied by radiological evidence of persistent lung injury suggestive of radiation pneumonitis (29,30). Hence, there is a need to minimize the lung dose during radiation therapy to prevent the long term complication of pneumotoxicity in breast cancer survivors.

Morbidity due to irradiation of heart tissue, especially in left sided breast cancer patients has also been reported in various studies(31,32). Radiation related heart disease can be broadly classified into following conditions - pericarditis, pericardial fibrosis, valvular disease, diffuse myocardial fibrosis, and coronary artery disease. A meta-analyses by EBCTCG had shown that death due to heart disease was increased by 27% in breast cancer women who received RT after surgery compared with women who underwent surgery alone (33). The updated EBCTCG report related the cardiac mortality to estimated cardiac doses in 30,000 women followed up to 20 years and showed that there was radiation-related increase in cardiac events with larger mean cardiac doses. It

concluded that the risk of death from any heart disease increased by 3% per Gy of radiation therapy received to the heart (34). With recent data, there is substantial evidence that has shown that mean heart doses of less than and equal to 20 Gy, and even less than 5 Gy can increase the risk of cardiac morbidities (35)

Therefore, various beam modifying techniques are being used to reduce dose to these critical structures like use of half beam blocks, asymmetric jaws, heart blocks and wedges and some form of radiation beam fluence modulation

3.12 CONFORMAL RADIATION TECHNIQUES

The evolution in Radiation Therapy led to development of newer techniques of delivering radiation therapy which not only helped in achieving a good dose distribution in the target area, but also helped in reducing the doses to the adjacent critical normal structures.

3D Conformal Radiation Therapy (3DCRT)

3D CRT planning is done with the patients planning CT scan done in the position in which the everyday treatment will be delivered and then the target areas and the adjacent at risk organs are contoured cut by cut on the CT scan.

In case of a breast cancer treatment, the beams in 3DCRT consist of two opposing tangential field portals which allow optimum coverage of the breast tissue and

minimizes the dose to the adjacent normal structures. Wedges (physical or dynamic) are added to these tangential beams to compensate for the changes in body contour and hence, this improves the dose uniformity in the desired target volume. The obtained dosimetry is then confirmed based on the target coverage and the doses received by the organs at risk, which is plotted on a dose-volume histogram (DVH). ICRU 50 and 62 are used for selecting an appropriate plan for the delivery of radiation therapy (36,37).

Intensity Modulated Radiation Therapy (IMRT)

In IMRT, the first steps of planning are similar to that followed in 3D CRT. The patient is positioned in the intended daily treatment position following which a planning CT scan is taken and a cut by cut contouring of the target areas and the organs at risk is done. After this, the dose constraints to the target area and the organs at risk is defined and an "Inverse Planning" technique is used for planning purpose.

Multiple beams are used for inverse planning IMRT. The optimizer uses inverse planning objectives and anatomy contours to produce beamlets which give the desired dose fluence maps and dose distribution. ICRU Report 83 is used as a tool for plan evaluation in selecting the appropriate plan for IMRT technique (38). The American Society of Radiation Oncologists (ASTRO) has issued series of quality assurance and safety guidelines called as white papers to investigate and develop focused quality assurance methods for radiation therapy treatment. These white papers consolidate the abundant available knowledge to focus on preventing failures and complications (39).

IMRT has superior dosimetric advantages over 3-dimensional conformal radiotherapy (3DCRT) treatments. By using an inverse planning technique with predefined dose constraints and optimization, it improves conformity of the target dose facilitating escalation of dose that can improve local control. It also reduces irradiation of nearby normal tissue which minimizes the degree of morbidity associated with the treatment (40). However, as IMRT used more number of radiation beams for delivering the radiation therapy, the low dose radiation area is increased in IMRT when compared to the conventional means of delivering radiation therapy.

Harsolia et al. compared the acute and chronic toxicity of whole breast irradiation with IMRT versus conventional radiation treatment. They found that use of IMRT resulted in a significant decrease in acute dermatitis, edema and hyperpigmentation and also reduced the development of chronic breast edema(41).

Field in field technique (FIF)

Field in Field (FIF) technique is a newer modality of delivering IMRT for breast cancer. It is also referred to as "Forward Planning" IMRT. In this field in field technique, an open beam is first planned and evaluated without any wedges, looking at the hot regions over critical structures. After this, subfields per gantry angle are planned in which MLCs can be moved manually to cover the hot regions. Also the monitor unit change iteration in these sub fields is done till an optimal dose coverage is achieved. Usually, a lung block field and three additional subfields per gantry angle are

used. The open beam contributes about 80% of the delivered dose while the additional subfields contribute the remaining 20%.

Several studies have shown Field in Field IMRT facilitates a better control of dose homogeneity and reduces hot regions as well as cold regions (42–47). Woo-Lee et al showed that there was an improved performance using the field in field technique compared with the conventional wedge and dynamic wedge system in terms of improved PTV conformity, while protecting the normal structures (48). Another study showed that with FIF technique, the heart volumes receiving 2 Gy, 30 Gy and 40 Gy were significantly reduced. Also, the ipsilateral lung volumes getting irradiated were significantly reduced.

Other than these dosimetric advantages, FIF requires less planning time and is less skill dependent. An inverse planning IMRT plan for breast consumes longer planning time, requires advanced planner skills and need for more MUs (49). Field in field technique being a simple and more efficient form is widely preferred in many centers for administering tangential radiotherapy to whole breast or chest wall.

3.13 BREATHING PATTERN

Normal respiration is an automatic, effortless inspiratory expansion and expiratory contraction of the chest. It has a relatively constant rate and inspiratory volume, both of

which together form the normal respiratory rhythm. Breathing pattern characteristics include

1. Posture - upright, supine, prone, lateral decubitus

2. Breathing type - chest or abdominal

3. Depth of respiration - shallow, normal, deep

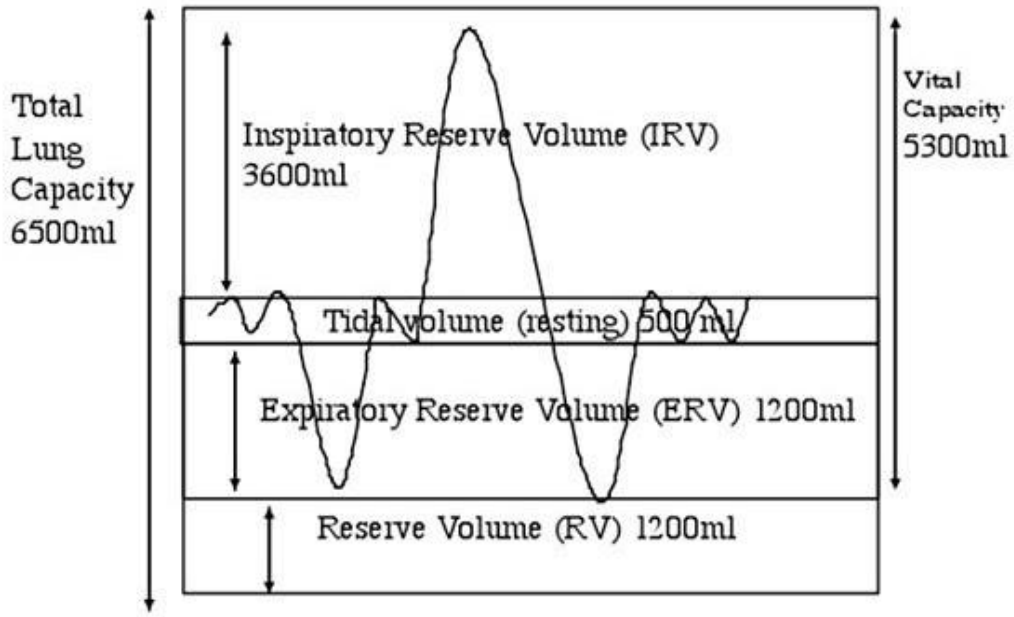


Figure 3. Normal breathing curve

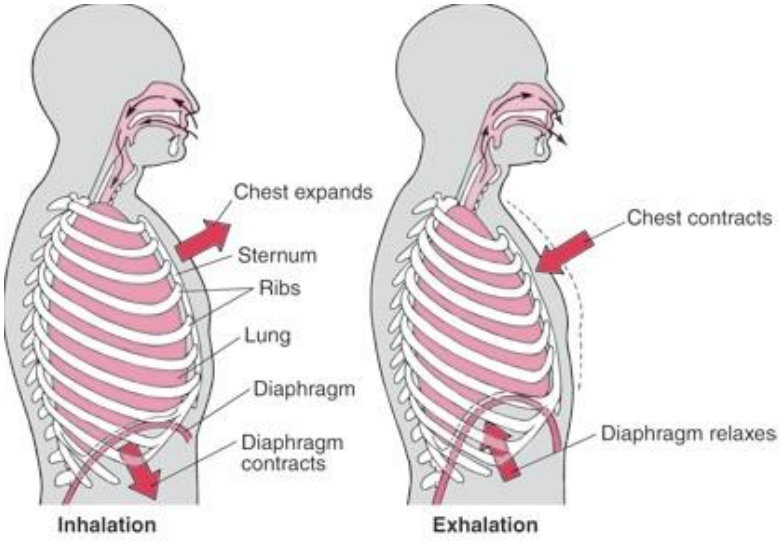


Figure 4. Chest wall movements in normal breathing.

Accurate control of breathing is under the central respiratory pacemaker which is located within the brainstem. This medullary respiratory center receives three kinds of feedback which alters its output and leads to changes in the number of breaths per minute and the volume of each inspiration (50). One of the feedback input comes from the higher cortical centers. It includes the state of being awake which is associated with significant neural inputs to the respiratory center and when an individual falls asleep, this cortical input decreases thus altering the respiratory center output. The change in output from the respiratory center lead to alteration of the rate and tidal volume which affects the chest cage contraction and expansion. The higher center input can be increased with anxiety which may lead to hyperventilation.

3.14 DOSIMETRIC IMPACT OF RESPIRATORY MOTION AND DAILY SETUP ERROR

The planned dose on planning CT scans differs from the actual patient dose during treatment due to respiratory motion and daily setup errors. Prabhakar et al. have reported the dosimetric impact of setup error and showed that isocentric shifts along a particular direction has a significant effect on the dose to PTV and critical structures. They concluded that the isocentre shifts should be checked prior to treatment and the setup error in the isocenter should be kept strictly below 3mm (51).

As per a study conducted by Furuya et al. (52), with FIF technique, significant differences in the mean dose and dose homogeneity index were noted even with a 0.5-cm isocenter shift. Volume received 20 Gy radiation (V20) of the entire lung showed a change of 4% from the original plan if there was a shift in the isocenter in the antero-posterior (AP) direction. They concluded that the FIF irradiation technique for breast cancer radiotherapy, was more sensitive to respiratory motion and setup error than the conventional techniques. However, they also found that the dosimetric impacts of this during the entire course of treatment was relatively small and might be clinically acceptable.

Another study from Chicago by J. Cao et al. showed that for patients who had a large respiratory motion of >0.6 cm (measured in their study with the marker movement) , the difference in coverage of Volume receiving 100% dose (V100) for the target volume was >10% and upto 18% (53).

However, a study by Robert Frazier on early-stage breast cancer patients who received whole breast irradiation had shown that the dose delivery to breast using step and shoot IMRT technique was relatively insensitive to the effects of breast movement due to normal breathing (54).

During a phase of normal respiration, the lung volume changes by around 20% (3.3 liters to 4.1 liters on average) (55). At end of deep inhalation, the increase in the lung volume is approximately three to four times that of normal breathing. The AAPM task report 76 on management of respiratory motion during delivery of radiation therapy, (56) has recommended that if the magnitude of the motion observed in any direction during treatment is greater than 5 mm or if there is chance of significant normal tissue sparing, dosimetric effect of motion should be considered and a respiratory management technique should be used.

3.15 REDUCING EFFECT OF BREATHING ON RADIATION THERAPY

Considering the impact of breathing pattern on homogeneity of radiation dose delivered to target volume and nearby critical structures, various methods have been described and under evolution for controlling the effect of breathing and respiratory motion during radiation therapy. These techniques may work by reducing the effect of respiration on treatment planning and delivery or by reducing the effect of inter fraction motion by daily or continuous verification of patient and simultaneous online correction of errors prior to treatment.

There are four main strategies which are commonly used to reduce the effects of respiratory motion (57) :

1. Integrating respiratory movements into treatment planning

2. Breath-hold techniques

3. Respiratory gating techniques

4. Tracking techniques.

Integrating respiratory movements into planning (Motion encompassing techniques)

In this technique of management of respiratory motion, the range of motion of the target and other structures due to breathing is estimated and their mean position is calculated. It can be based either on measurements done in a representative sample of general population, or measurements done directly on the patient before planning and delivering radiation therapy. The imaging which can be used for determining the desired range of respiratory motion are slow CT scans, inhale and exhale breath hold CT scan or 4D CT scan (58) .

The measured amplitude is then added as a geometrical margin to get the internal target volume (ITV) which is then used in place of the Clinical Target Volume (CTV) for radiation therapy planning. The drawback of this technique is that it would result in larger irradiated volumes thus increasing the chances of increased dose delivered to the normal tissues.

Respiratory Gating

It denotes the delivery of radiation during a specific phase of the respiratory cycle, often referred to as ‘Gate’. The patient's respiratory cycle is monitored using either external or internal signals like the infrared camera or fiducial markers and radiation delivery is allowed only during certain time intervals that is synchronous with the patient's respiratory cycle. This is particularly useful in reducing the effect of respiratory motion during the radiation therapy delivery (intra-fraction motion) (59,60). The Varian Real-time Position Management (RPM) system is the only commercially available software used for respiratory gated therapy.

Breath holding techniques

There are three types of breath hold methods which are used for managing the respiratory motion during delivery of radiation therapy.

1. Active Breathing Control (ABC)
2. Self-held breath-hold and Self-held breath-hold using an External Marker
3. Deep inspirational breath hold (DIBH).

In active techniques, an ABC apparatus which has a valve is used to temporarily block airflow of the patient and the radiation therapy is delivered in that particular time, thus nullifying the effect of respiratory motion.

Active breathing control (ABC) has been tried by various institutions. Its feasibility and practicality in terms of patient's tolerance is under investigation. With ABC, the

patient's breathing is temporarily immobilized and treatment planning and delivery is performed at identical ABC condition. This allows for safe margin reduction for target volumes with minimal margin for breathing motion (61). The results have been encouraging, ABC may possibly provide a simple mean of minimizing breathing motion in thoracic irradiation.

The self-holding techniques are voluntarily breath-hold techniques also called as passive techniques.

In DIBH which is a controlled breathing technique, patient performs a supervised breath hold during the treatment. It thus reduces the respiratory motion (60). It requires more patient effort than respiratory gating. Korreman et al. studied the cardiopulmonary dose sparing effect of respiratory gating (named as breathing adapted radiotherapy - BART) using free breathing gating and compared this with voluntary breath-hold techniques - deep inspiration breath-hold (DIBH) and end-expiration breath-hold (EBH). The Varian RPM was used to monitor the respiratory movements and for gating the scanner. They found that there is a significant chest wall motion during treatment. The mean anterior-posterior chest wall excursion during free breathing was 2.5 mm whereas for DIBH and EBH, it was 4.1 and 2.6 mm respectively. Thus, both respiratory gating or DIBH technique, were comparable in their results and were found to substantially reduce the cardiac dose and lung dose in adjuvant radiotherapy after breast-conserving surgery for breast cancer patients (62).

Tracking techniques

Tumour tracking consists of two major aspects - a real-time localization of the constantly moving tumor and real-time beam adaptation to this moving tumor. Thus, it dynamically accommodates with the respiratory motion of the patient by shifting or sweeping the beam in space (63). This technique is less practiced due to limited experience, increased costs for tracking devices and limited technical expertise.

3.16 ANXIETY

Anxiety is defined as the apprehensive anticipation of future danger or misfortune accompanied by feelings of dysphoria or somatic symptoms of tension (64). Pathological anxiety is defined under World Health Organization's International Classification of Disorders (ICD–10) (65) and the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-IV) (64). It requires symptoms out of proportion to the level of threat which persists or deteriorates with no intervention and the intensity of symptoms is disproportionate to the intensity of the threat. There is disruption of the usual functioning of the patients.

In the standardized diagnostic systems, four main types of anxiety disorders are defined.

1. Anxious adjustment disorder - represents quantitatively excessive response to a stressful event

2. Generalized anxiety disorder - can be due to severe negative life-event and requires more symptoms

3. Anxiety in panic disorder - builds up in a rapid crescendo and has a rapid exit with exit from the situation in which it occurs

4. Phobic anxiety - only occurs in specific situations in the presence of provoking stimuli. In this type of anxiety, anticipatory avoidance is possible.

The pathological anxiety criteria is difficult to apply to cancer patients as they have a constant threat of loss, death, body functions, roles, body image, etc (66). The natural history of anxiety in oncology is also uncertain.

3.17 ANXIETY IN CANCER PATIENTS

Anxiety in cancer patients can be categorized into three groups (67):

1. Reactive anxiety - It is the most common form of anxiety in cancer patients. It corresponds to the adjustment disorder. However, it varies in duration, intensity and functional impairment. It can be due to waiting for starting of new treatment, uncertainty of future and treatment effectiveness.

2. Pre-existing anxiety disorders - Patient may have underlying panic disorders, phobias, generalized anxiety disorders or post-traumatic stress disorder. These can be

differentiated from anxiety due to cancer in terms of duration and would usually be diagnosed preceding to the diagnosis of cancer.

Phobias like fear of witnessing blood or tissue injury or claustrophobia may interfere with the administration of cancer treatment and may lead to anticipatory anxiety.

3. Anxiety related to medical illness - This can be due to underlying causes like uncontrolled pain, metabolic causes, and medications like steroids, withdrawal states from alcohol, narcotic analgesics or due to a hormone secreting tumors.

Anxiety is a major symptom seen in cancer patients. It produces a number of symptoms and signs like symptoms due to autonomic over-activity which include palpitation and sweating. Behaviors such as restlessness and changes in thinking like apprehension, worry and poor concentration. Physical symptoms may also be seen such as muscle tension or fatigue.

Anticipatory anxiety has been defined as the appearance of anxious symptoms and feelings in days or hours before a feared event, and a rapid decline in these symptoms after the event has occurred (68). It leads to autonomic arousal. It can be experienced by a person with or without an underlying anxiety disorder. It is thus usually a normal reaction that may be experienced by any person, however, it may lead to emotional distress or may be a sign of clinically relevant anxiety (69). Anxiety has been described to be either a relatively stable personality characteristic i.e. trait, or anxiety generated as a result of the situation or state. Some patients have high levels of trait anxiety which will be noticeable throughout the disease course.

Stark et al. reported a prevalence of anxiety in cancer patients in the United Kingdom to be 10-30% (70). Jenkins et al. reported that in a general population, younger women were more prone to anxiety(71). However, Noyes et al. (72) showed that in cancer patients- age, gender, social class and education level were not consistently associated with anxiety.

A study by Andersen and Tewifik (73) which looked into the psychological responses of patients receiving external radiation therapy found that there was a significant change in state anxiety from pre-treatment to post-treatment. However, the trait anxiety scores showed no significant difference across the treatment course. These findings were consistent with the Janis model, which showed that in case of a threatening situation, the level of fear and anxiety can potentially determine the adequacy of adaptation of a person (74).

3.18 ANXIETY IN BREAST CANCER PATIENTS

Amongst the breast cancer patients, there is a high proportion of patients who have anxiety disorders. A study from Thailand which looked into anxiety and depression in 300 women diagnosed with breast cancer showed that the prevalence of anxiety disorder was 16 % while that of anxiety symptoms was 19%. They suggested that being alert on emotional reactions and potential psychiatric disorders among patients is essential during treatment (75).

A systematic review (76) of studies published between 1990-2010 looked into anxiety levels in breast cancer patients during treatment. It included stage 0 to stage IIIA patients who had had undergone chemotherapy, radiotherapy and surgery. Anxiety level in women was upto 91% before the first chemotherapy infusion and reduced in subsequent infusions. Different radiotherapy regimen were compared and it was found that no significant difference existed in the level of anxiety between patients who received the short regimen and long regimen treatment. This study also concluded a higher level of anxiety among women who underwent mastectomy compared to those women who underwent breast conservation surgery.

Various studies have reported anxiety in cancer patients who receive radiotherapy for different sites of malignancy (77). Lewis et al. reported 5-16% clinically relevant anxiety in patients during radiotherapy based on visual analogue scale scoring (68). They also found significant differences in pre-treatment and post-treatment scores at the time of simulation and first session of RT. Thus, they concluded that before starting treatment and during treatment, it is important to check patient's understanding and identify those patients who would require appropriate support throughout the treatment. They further extended their study assessing the communication provided to the patients during RT simulation. Clinically relevant anxiety during first session of RT was related to less efficient communication with the radiotherapy team, the perception of lower support from the radiotherapy team and lower knowledge of side effects (78).

A study by Bidstrup et al. looked into the trajectory of anxiety and other distress in breast cancer patients and showed that women moved from severe anxiety at diagnosis

to a moderate level after four and eight months. Association on anxiety with radiotherapy showed an odds ratio of 1.16 [CI 0.57–2.36]. A younger age, poor family support and shorter education were associated with more risk of chronic distress. Patients who received chemotherapy but not radiotherapy showed severe psychological symptoms eight months after diagnosis. There was no subgroup of women with chronically severe anxiety, only one subgroup showed chronically severe distress in 8% women (79).

3.19 REASONS FOR ANXIETY

The anxiety can be due to the diagnosis of the disease, the treatment or due to the fear of uncertainty. Diagnosis of cancer generates various forms of psychosocial distress among patients and anxiety forms one of this type of distress.

The prolonged cancer treatment further adds to the anxiety as there can be positive or negative implications of treatment and unpleasantness of side effects. The patients feel a threat from these processes while having a hope of relief from the illness.

The women who are advised radiotherapy know little about this treatment and experience treatment related anxiety. Studies have shown that their main concern is about the impact of treatment on their health in the future. Thus, there are high information needs among patients prior to treatment planning and commencing treatment and their anxiety persists until after the commencement of the treatment (80).

Substantial correlation has been found between anxiety and poor communication with the medical team (81).

3.20 MANAGEMENT OF CANCER ASSOCIATED ANXIETY

There is a need of an effective communication with patients to help reduce the cancer related anxiety. It is important for the health professionals to discuss about radiotherapy with patients and this opportunity should be taken up at the planning appointment, prior to the starting of treatment. There is a need to assess patients' understanding and concerns about radiotherapy and listen to their fears and provide reassurance about radiotherapy and the management of its side effects (82).

Workshops encouraging open questioning with patients and discussions on psychological issues and empathy while discouraging ‘advice mode’ were shown to achieve enduring change and more awareness on patients' psychological distress (83).

3.21 SCALES FOR MEASURING ANXIETY

Various scales have been describe to assess the level of anxiety.

- Beck anxiety inventory (BAI)
- Hospital anxiety and depression scale (HADS) : 14-item scale measuring symptoms of clinical depression and anxiety (84)

- Brief symptom inventory (BSI) : 18-item scale measuring somatization, depression, anxiety and general distress (85)
- Profile of mood states (POMS) : 65-item scale measuring six mood states: anxiety, depression, fatigue, confusion, anger, vigor (86)
- State-trait anxiety inventory (STAI): 40-item measure that indicates the intensity of feelings of anxiety. It differentiates between state anxiety (a temporary condition experienced in specific situations) and trait anxiety (a general tendency to perceive situations as threatening) (87)
- Visual analogue scale

3.22 BECKS ANXIETY INVENTORY

The Becks Anxiety Inventory (BAI) was developed by Dr. Aaron T. Beck (88). It includes total of 21 items, each is rated on Likert scale from 0 (not at all) to 3 (severely) based on patient's response. The items on the BAI are simple descriptions of symptoms of anxiety in one of the four expressed aspects:

(1) Subjective component (e.g., "unable to relax")

(2) Neurophysiologic component (e.g., "numbness or tingling")

(3) Autonomic component (e.g., "feeling hot")

(4) Panic-related symptoms (e.g., "fear of losing control").

As per the Beck anxiety inventory (BAI) usage guidelines, this questionnaire can be administered via self-report or via a trained administrator. It is simple and can be

completed in 5-10 minutes. The BAI items describe the subjective, somatic and panic related symptoms of anxiety but not of depression and hence it can fairly discriminate anxiety from depression. It has focus on many somatic symptoms of anxiety and assess symptoms like nervousness, inability to relax, dizziness etc. Compared to various other available scales, it obtains a purer measure of anxiety which is relatively independent of depression.

The interpretation of the score is done as follows:

Summing the scores for 21 items gives the total score, this may range from 0-63.

0–7 = Minimal anxiety

8–15 = Mild anxiety

16-25 = Moderate anxiety

26–63 = Severe anxiety

Validity : Construct validity studies have shown a good convergence of the BAI with other anxiety scales like the HADS (r = 0.51), the STAI (r =0.47–0.58), and the anxiety scale of the Symptom Checklist-90 (r = 0.81)(89) . Also BAI has been assessed and found to be useful self-report scale in assessing anxiety symptomatology among the older adults (90).Netherlands Study of Depression and Anxiety (NESDA) had shown that BAI scores in patients with an underlying anxiety disorder or an underlying depressive disorder were significantly higher. Thus it may be used as a severity indicator of anxiety in patients with different anxiety disorders(91).

Reliability : A meta-analysis was conducted by University of Nebraska–Lincoln for coefficient alpha and test-retest reliability estimates which showed that the diagnostic classification of participants and the within-study BAI score variability were well related to the magnitude of the reliability estimates (92). Internal consistency presented by cronbach's alpha of 0.94 was high with BAI. It also fared better than Trait Anxiety on tests of convergent and discriminant validity and it was found to be significantly less confounded with depression as measured by the Beck Depression Inventory. However, the scores for STAI were highly confounded with depression (93).

As the breast cancer patient undergoing various modalities of treatment suffer from distress both due to anxiety and depression, BAI was the preferred scoring used in our study taking into consideration the above factors. It is a brief, validated, easily administered and easily scored measure of anxiety.

3.23 EFFECT OF ANXIETY ON BREATHING PATTERN

Anxiety in breast cancer patients during radiation therapy may lead to changes in breathing pattern. The respiratory rate is noted by observing the frequency of the inspiratory phase and recording the number of breaths per minute. During normal breathing, the expansion of the chest cage which is dependent on the respiratory rate and depth of respiration should be the same for each cycle. In anxious patients, there is increase input from higher center to the respiratory pacemaker in the medulla which alters:

1. Number of breaths per minute i.e. the respiratory rate and

2. Tidal volume i.e. the depth of respiration

Thus, the inspiratory expansion of the chest cage varies.

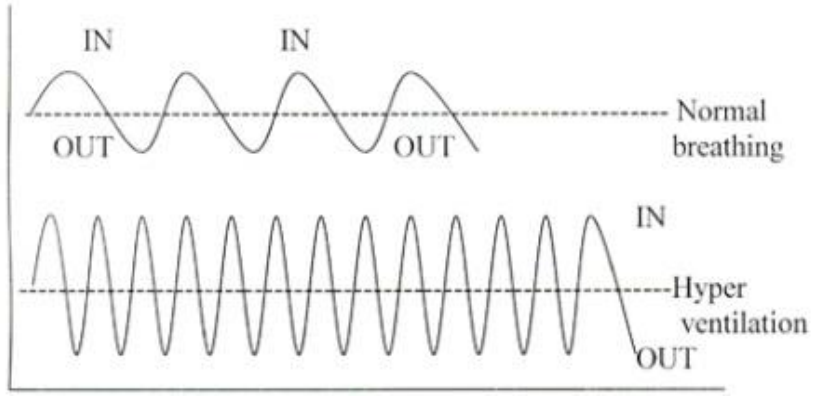


Figure 5. Change in breathing curve with hyperventilation

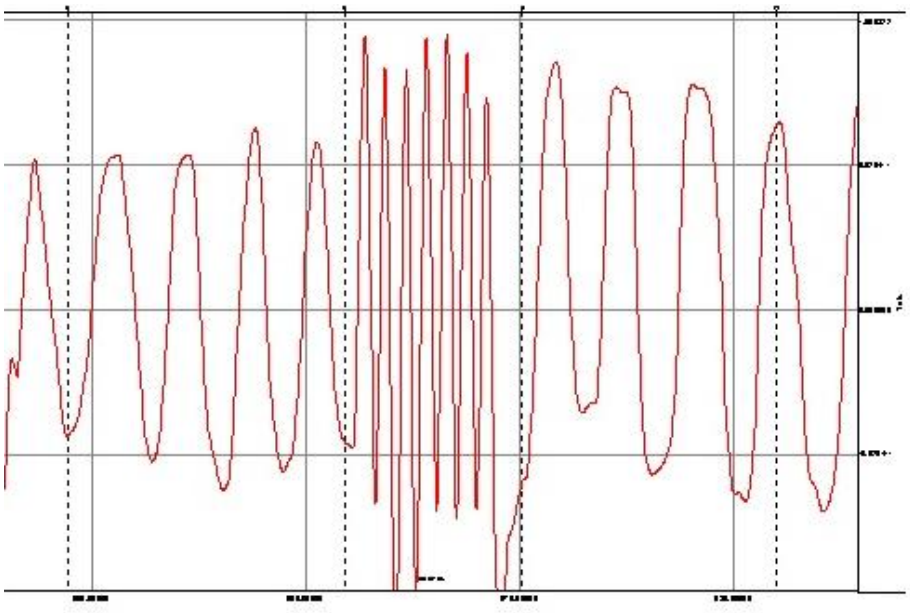


Figure 6. Changes in breathing movement may occur during the course of treatment.

Minute ventilation is the amount of air that a person breaths per minute and is a product of the respiratory rate and tidal volume. An increase in the minute ventilation is seen in subjects with high anxiety. The increase in respiratory rate is more than tidal volume in anxious patients resulting in a positive correlation between the anxiety score and respiratory rate (94). Anxiety creates a situation of hyperventilation in which there is an increase in the rate of respiration and the depth of respiration becomes shallow. This means that the chest wall expands less than the normal expansion during a full inspiration. This variation in the chest wall movement leads to inter fraction variations during the delivery of radiation therapy.

The radiation therapy planning, defining target volumes and measurement of irradiated lung tissue assumes a normal breathing pattern with constant chest expansion in each cycle. In anxious patients with the above changes, the irradiated target volume and lung volumes would vary and they can lead to a variation from the originally planned radiation therapy plan

3.24 INTERFRACTION AND INTRAFRACTION VARIATIONS DURING RADIATION THERAPY

With the newer techniques in use like IMRT, FIF, VMAT etc., highly conformal dose distribution can be achieved around the planning target volume (PTV) with reduction in the radiation dose to the normal tissues. There is increased accuracy of radiation delivery which is based on the initial planning CT scan done for the patient and any deviation in the anatomy of the patient from this CT scan can lead to wide variations in

the radiation therapy dosimetry. Thus, any amount of motion observed during these newer techniques is of greater consequence than in the traditional conventional plans. Immobilization is necessary to ensure reproducibility of position and accurate localization of the treatment volume.

Inter-fraction variations

Inter-fraction motion is the variation seen in position during different treatment fractions. It has both systematic and random components. Systematic error is the average variation in treatment position during the course of radiation therapy compared with the planning CT reference images which is constant. . It may be due to error in immobilization or positioning, error in target delineation, error in planning or error in reproduction of the initial planning position. Any mistake made at any of these levels can lead to a systematic error. Random error is the variation in treatment position seen in daily fractions which is difficult to avoid and is taken care of by the margins given during the planning procedure

Intra-fraction variations

Intra-fraction motion is seen during delivery of a radiation treatment beam on a particular day. It is due to patient movement or internal organ motion while treatment is ongoing. It is a random error.

Systematic error is more important for designating margins in radiotherapy treatment as a small error occurring repeatedly may have a more cumulative effect on dosimetry than a large error occurring once. Lawson et al. found the random errors were greater

than the systematic errors and position verification prior to treatment delivery with an on-board imaging (OBI) may help reduce the random component (95).

3.25 METHODS OF RADIATION DELIVERY VERIFICATIONS

Various on-board imaging (OBI) techniques are available to measure the variation with reference to the digitally reconstructed images of the planning CT scan. These include

- Port films
- Electronic portal imaging device (EPID)
- Cone beam computed tomography (CBCT)

These modalities allow to verify the treatment position, minimize the effect of motion by analyzing the images and simultaneous correction of the errors prior to treatment.

Portal imaging

It involves the acquisition of images with radiotherapy beam which are then used to verify the treatment position prior to the treatment delivery. Geometrical verification requires the portal image to be registered with a reference image obtained at the time planning (96).

It was initially film based with subsequent development into film-less electronic portal imaging devices (EPID). Megavoltage (MV) radiation was used to acquire these images which were then compared to the kV images of a simulator. Nowadays, most

linear accelerators have kilovoltage (kV) imaging for acquisition of these images. This provides a better image contrast and quality than MV imaging and reduces the radiation dose due to verification images.

EPID

It is a very useful tool in measuring the inter-fraction variations during radiation therapy. Electronic images are taken which can be viewed instantaneously and matched to the planning digitally reconstructed radiographs (DRRs) before initiating the treatment. The measured deviation from the intended isocenter will thus give the magnitude of the error. Various studies have proven the advantage of kV imaging unit mounted on traditional LINAC for quantification of setup variability and its correction prior to treatment in comparison to the earlier mounted MV imaging (95,97)**.**

Orthogonal images can be acquired and isocenter shift can be measured by the use of on-board imaging techniques (95). Some studies have taken tangential field EPIDs to assess the inter-fraction variation. Acquisition of these images was found to be a quick and easy way to establish the amount of patient movement during breast radiotherapy.

EPID can be used to measure variations from treatment to simulation (systematic error) and from treatment to treatment (random error).

CONE BEAM CT

It quantifies the inter-fraction motion in three dimensions. Daily cone-beam CT (CBCT) imaging can be used to measure the inter-fraction motion during breast IMRT. Studies have quantified the daily PTV volume variation to be upto 23%. This reveals

high inadequacies of patient positioning and need of stringent verification during IMRT delivery (98).

A systematic review (99) to evaluate the inter-fraction and intra-fraction variation during radiotherapy to the whole breast showed inter-fraction variation was larger but on an average within a tolerance of 5mm. Thus, for breast cancers a PTV margin of 5mm may be considered adequate. However, there were large maximum variation observed for some patients which define the need of daily imaging for position verification, more so for highly conformal treatment techniques.

3.26 MEASUREMENTS TO DETERMINE MAGNITUDE OF ERRORS

Central lung distance (CLD)

It is the perpendicular distance from the posterior tangential field edge to the posterior part of the anterior chest wall at the center of the field. Bornstein et al. (100) conducted a study to determine the relation between CLD and percentage of irradiated ipsilateral lung volume in the tangential fields. It showed the following correlation between the two parameters.

CLD	Percentage of ipsilateral lung volume
1.5cm	6%
2.5cm	16%

3.5cm 26%

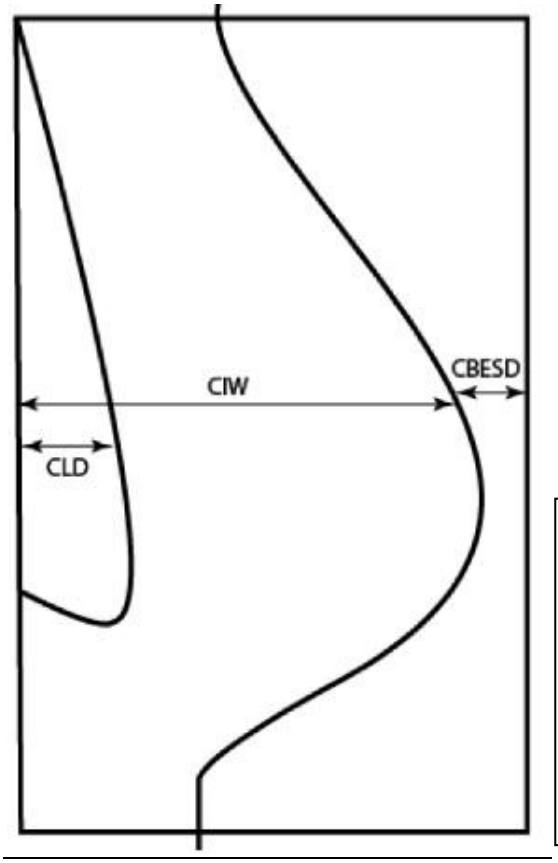
Thus, they concluded that the CLD measured at the time of simulation gives an estimate of the percentage of the lung volume irradiated and thus CLD should be kept to the minimum at the time of simulation. An increase in the CLD signifies an increase in the irradiated lung volume which in turn increases the incidence of radiation induced radiation pneumonitis.

Central irradiated width (CIW)

It is the distance between the posterior field border and the anterior breast outline at the level of central axis.

Central beam edge to skin distance (CBESD)

It is the distance from the anterior breast outline to the anterior field edge at the level of central axis.



CLD : Central Lung Distance

CIW : Central irradiated width

CBESD : Central beam edge to skin distance

Figure 7. Measurements taken to determine the inter-fraction error.

Another method of measuring the magnitude of motion is by using the anatomical landmarks to match the images, following which it gives the computer calculated shift of the isocentre. It calculates the following parameters :

- Anterior-posterior shift / Vertical shift
- Medio-lateral shift / Lateral shift
- Cranio-caudal shift / Longitudinal shift

MATERIALS AND METHODS

Study Design

A total of 27 patients with early-stage or locally advanced breast cancer who received whole breast or chest wall irradiation with or without regional nodal irradiation using the conformal technique were chosen for this study.

Inclusion criteria:

- Females more than >18 years
- Diagnosed to have biopsy proven breast cancer
- Patients who have undergone surgery for breast cancer (either lumpectomy or modified radical mastectomy)
- Patients who require adjuvant radiation therapy for breast cancer
- Patients willing for radiation therapy treatment with conformal techniques
- Patients willing to sign the consent form and be a part of the study

Exclusion criteria:

- Patients with diagnosis of male breast cancer
- Patients not willing for treatment with conformal techniques
- Patients not willing to be a part of the study

RT planning

All the patients included in the study underwent a planning CT scan under free-breathing conditions in Biograph true point high definition CT scan (Siemens, Germany) with 5.0 mm slices to encompass the entire thorax.

A breast board was used to immobilize patients in the supine position with arms above head. All patient underwent simulation for marking of three external fiducial markers in the simulator which were then tattooed. Radio-opaque markers were placed on these tattooed sites during the planning CT scan. Approximate field borders were also marked during the simulation. While taking the planning CT scan, the field borders and surgical scar site was marked using lead wires.

Dose, target volume and critical structure delineation

Two fractionation schemes were used for the treatment of the patients (administered five days a week):

- Hypofractionation: 4005 cGy in 15 fractions, 2.67cGy per fraction over 3 weeks
- Conventional fractionation: 5000 cGy in 25 fractions, 200 cGy per fraction over 5 weeks

The sites of radiation therapy were individualized based on the stage of breast cancer, neoadjuvant treatment received or not, receptor status and histopathological factors in the surgical specimen. The axilla was treated only if there was gross extranodal extension, inadequate axillary dissection or positive sentinel lymph node biopsy with no subsequent axillary dissection. Patients for whom axillary lymph node irradiation was planned, they were not considered for the hypofractionated regimen.

CT image sets were imported to the Eclipse treatment planning system (Version 10.0) for contouring and treatment planning. The body, clinical target volume (CTV) and organs at risk (OAR) including lungs, heart, esophagus, contra lateral breast, spinal cord were contoured on each CT slice. RTOG breast contouring guidelines were used for contouring (Appendix II).

Boost to lumpectomy cavity was planned for all patients who underwent breast conservation surgery. It was delineated based on the surgical clips and pre-operative clinical and radiological findings. Dose prescribed to the lumpectomy cavity was 10 Gy in 5 fractions (2 Gy per fraction for 5 days). Gel bolus was used for all patients during the course of treatment and they were assessed weekly once while on RT for any radiation induced dermatitis or other complications.

Treatment planning

Field in field (FIF) conformal technique with a single isocentre was used for all patients. The isocenter was set at the junction between the supraclavicular field and breast

tangential fields. All open tangential fields included a 2.0 cm flash beyond the patient skin surface to take into account the patient's breathing movement and setup error. A 6 MV photon beam was used for all tangential fields.

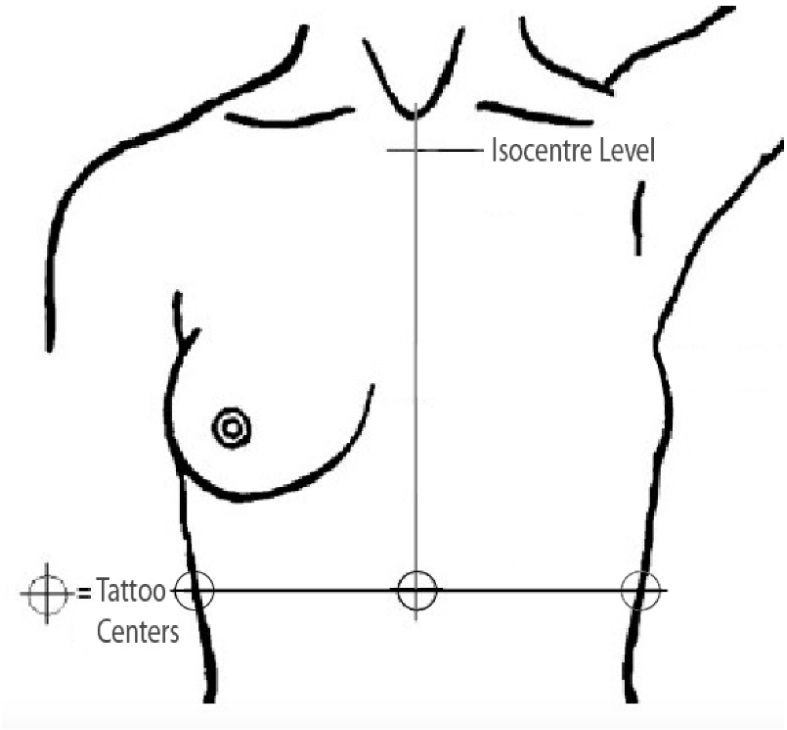


Figure 8. Single isocentre technique with isocentre at the junction between the supraclavicular field and breast tangential fields. CT centers were tattooed on patients' body to help in setup during treatment.

The breast has a complex external shape. It requires dynamic wedges to achieve a homogenous dose distribution. In the field in field (FIF) technique planned for our patients, firstly two main open photon tangents were set and dose distribution was calculated. For medial tangent, 7-8 subfields were created with MLC changes to remove the hot spots. Subfields in lateral tangent were used only in few patients to

achieve better dose homogeneity. The monitor unit (MU) weightage was subsequently adjusted for the main radiation field and sub-fields so that the dose distribution was uniform at all levels in the planned target volume as per the ICRU recommendation (95% to 107%). The supraclavicular field was included in the medial tangent field and dose deficit to the region was calculated which was then prescribed with an additional direct anterior field. Bolus was added to the tangential fields. Anisotropic Analytical Algorithm (AAA) (Version. 10.0) with inhomogeneity correction was used to calculate the dose for each plan.

A dose–volume histogram (DVH) analysis was performed for all generated plans. The dose indices used to evaluate the plan quality were as follows:

Table 1. DVH constraints for PTV evaluation.

		Conventional	Hypofractionated
PTV	Ideal	V95> 95% At least 95% of PTV receives 47.5 Gy	V95> 95% At least 95% of PTV receives 38 Gy
	Acceptable	At least 90% of PTV receives 45 Gy	At least 90% of PTV receives 36 Gy
PTV Dmax	Ideal	Dmax < 115% Maximum dose does not exceed 57.5 Gy	Dmax < 115% Maximum dose does not exceed 46 Gy

	Acceptable	Dmax < 120% Maximum dose does not exceed 60 Gy	Dmax < 120% Maximum dose does not exceed 48 Gy

Table 2. Dose constraints for organs at risk. Dose (C) - dose constraint for conventional fractionation. Dose (H) - dose constraint for hypofractionated RT.

		Volume	**Dose (C)**	**Dose (H)**
IPSILATERAL LUNG	Ideal	No more than 15% exceeds	20 Gy	16 Gy
	Acceptable	No more than 20% exceeds	20 Gy	16 Gy
	Ideal	No more than 35% exceeds	10 Gy	8 Gy
	Acceptable	No more than 40% exceeds	10 Gy	8 Gy
	Ideal	No more than 50% exceeds	5 Gy	4 Gy
	Acceptable	No more than 55% exceeds	5 Gy	4 Gy
CONTRALETRAL LUNG	Ideal	No more than 10% exceeds	5 Gy	4 Gy
	Acceptable	No more than 10% exceeds	5 Gy	4 Gy
HEART	Ideal	No more than 5% for left-sided and 0% for right-sided exceeds	20 Gy	16 Gy
	Acceptable	No more than 5% for left-sided and 0% for right-sided exceeds	25 Gy	20 Gy
	Ideal	No more than 30% for left-sided and no more than 10% for right-sided exceeds	10 Gy	8 Gy
	Acceptable	No more than 35% for left-sided and no more than 15% for right-sided	10 Gy	8 Gy

		exceeds		
	Ideal	Mean heart dose does not exceed	400 cGy	320 cGy
	Acceptable	Mean dose does not exceed	500 cGy	400 cGy
CONTRALTERAL BREAST	Ideal	Dmax does not exceed	310 cGy	240 cGy
	Acceptable	Dmax does not exceed	496 cGy	384 cGy
	Ideal	No more than 5% exceeds	186 cGy	144 cGy
	Acceptable	No more than 5% exceeds	310cGy	240 cGy

Measurement of Anxiety level

All the patients who consented to be a part of the study underwent anxiety scoring using Beck Anxiety Inventory (BAI) at the following time during the course of planning and treatment of radiotherapy:

1. Before the simulation
2. Day 1, Day 2 and Day 3 of radiotherapy treatment
3. Weekly once during the treatment

The patients' anxiety scoring was taken 6-8 times based on the duration of their treatment which varied from 3-5 weeks. It was interpreted as follows:

0–7 = Minimal anxiety

8–15 = Mild anxiety

16-25 = Moderate anxiety

26–63 = Severe anxiety

An attempt was made to find a correlation between the baseline anxiety level of the patients and other patient related parameters like age, occupation, type of surgery, duration of treatment.

Digitally reconstructed images (DRR)

From the planning CT scan, digitally reconstructed images (DRR) were obtained for antero-posterior and lateral setup (AP and Lateral DRR). Similarly digitally reconstructed images were obtained for main tangential fields for the medial and lateral gantry angles.

Measurement of Inter- fraction variation

On board imaging (OBI) was used for all patients on specified days prior to the delivery of radiation therapy. It can be remotely extended or retracted by the treating radiographer using the control console station. There is a dedicated OBI console and a software system for the same.

Four electronic portal images (EPI) were taken for each patient on any particular day:

- Anterio-posterior (AP)

- Lateral
- Medial field EPID
- Lateral field EPID

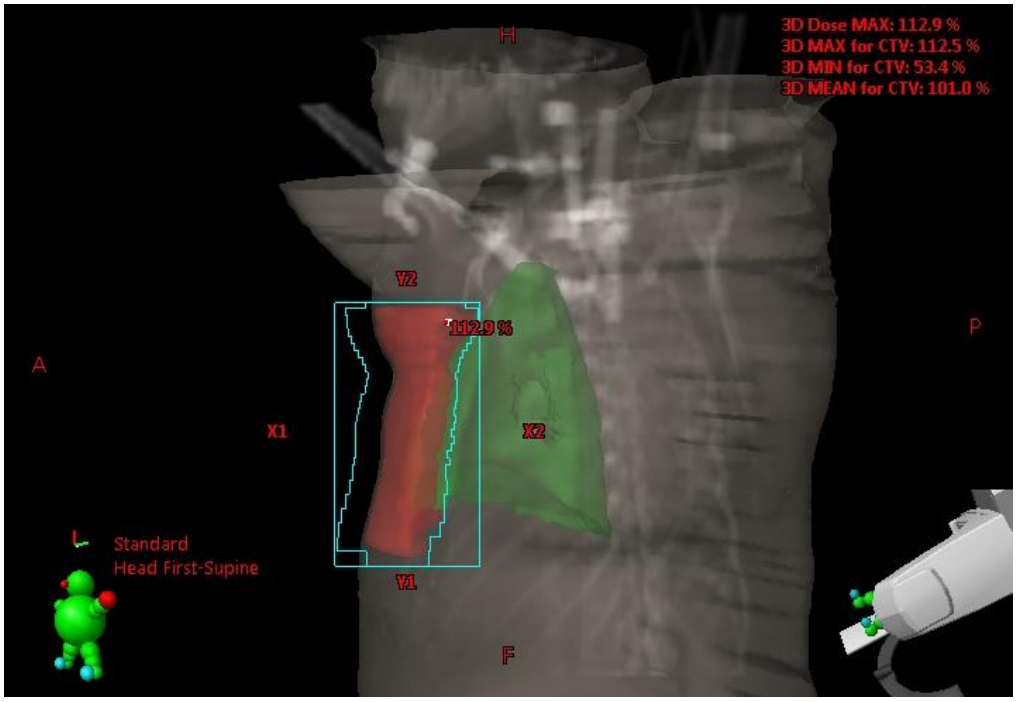


Figure 9. Planning System showing beams eye view of a tangential field for a patient.

After positioning the patient on the breast board in the treatment position, first 2 orthogonal EPIs were taken. DRRs obtained from the planning CT scan were used as reference images for position verification of the patient. The treatment console system allows matching of the images to be performed either manually or automatically. The OBI was first automatically superimposed with the reference image and then this was verified manually and adjusted as per required to get the positioning errors. As the PTV margin used for our plans was 5mm, any shift within 5 mm from the initial planning position was considered to be acceptable, while a shift of more than 5mm was corrected before delivering the treatment. After the above positional verification, for the purpose

of this study, medial and lateral tangential field EPIs were taken and the positional differences were recorded. The patient was subsequently treated.

The dose delivered during an EPID is 1cGy and as we have taken two extra field EPIs per day for the patients for 5 to 7 days depending on the duration of treatment, it can be assumed that there was an exposure of extra 10cGy to 14cGy of radiation due to these extra images. This is a very small dose and it was delivered to the treatment field with no extra radiation dose delivered to the normal surrounding tissues.

As a routine protocol for all conformal treatments at our institute, image verification is done is done on first three days of treatment and then subsequently weekly once. In this study, same protocol of image verification was used and along with the AP and lateral images, medial and lateral field EPIs were also taken during these sessions.

The following shifts were noted from the AP and lateral images:

1. Vertical shift
2. Lateral shift
3. Longitudinal shift

The following measurements were done on the medial and lateral tangential field images:

1. Central lung distance (CLD) - perpendicular distance from the posterior tangential field edge to the posterior part of the anterior chest wall at the center of the field

2. Central irradiated width (CIW) - perpendicular distance between the posterior field border and the anterior breast outline at the centre of the field

3. Central beam edge to skin distance (CBESD) - perpendicular distance from the anterior breast outline to the anterior field edge at the center of the field.

These shifts were recorded from Day1- Day 3 of radiotherapy and then subsequently weekly once.

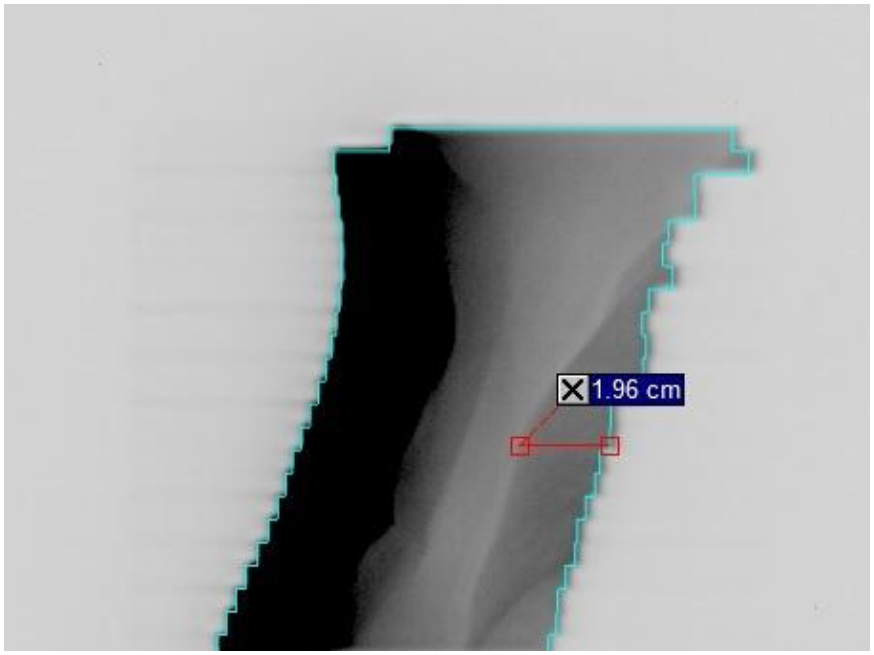


Figure 10. CLD measurements on a tangential field electronic portal image

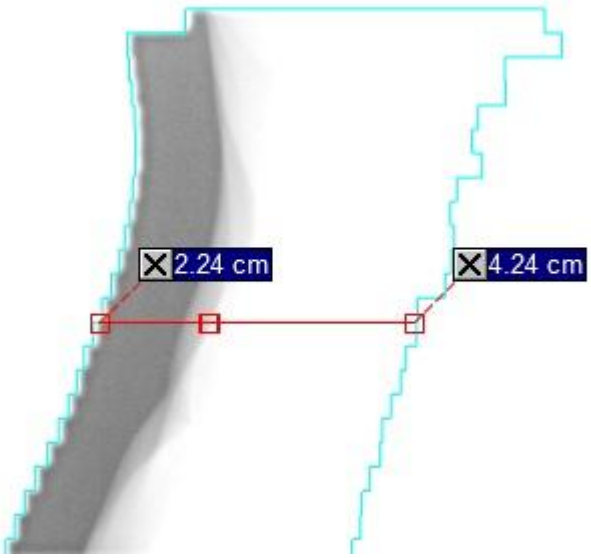


Figure 11. CIW and CBESD measurements on a tangential field electronic portal image.

Figure 2 and 3 show tangential field electronic portal images (EPIs). The window and its gray levels were adjusted to optimize contrast for clear visualization of the lung border and skin border for the required measurements. The length of the treatment field was noted and distances were measured at the centre of the irradiated field. A single observer i.e. the principal investigator evaluated all images to remove chances of any inter-observer bias.

The CLD, CIW and CBESD were measured perpendicular to the chest wall along the central axis on medial and lateral tangential field DRR and EPIs. The average of the medial and lateral image values was taken for all measurements. The variation of lung tissue irradiated (CLD variation) was calculated by subtracting the CLD measured on electronic portal images (EPID) from the CLD measured on the DRR.

CLD Variation = CLD(EPID) - CLD(DRR)

The inter-fraction motion was correlated with patients' anxiety scores and other parameters like age, tumor location, type of surgery and duration of treatment.

Statistical Analysis

Categorical variables were summarised using counts and percentages. Quantitative variables were summarised using mean and standard deviation or median and range. Group systematic error (M), standard deviation of the systematic error (∑), and standard deviation of the random error (σ) were calculated using Van Herk method (101).

Chi square test was used to compare the proportions between categorical variables. Two sample t tests was used to compare means between the two groups. Pearson correlation coefficient was used to find the correlation between two quantitative variables. For non-normal variables, Mann Whitney's U test was carried out. For all the analysis, 5% level of significance was considered to be significant. All the statistical analysis were done using stata/ic 13.1.

RESULTS

From February 2016 to August 2016, 27 breast cancer patients seen in the Department of Radiotherapy who received adjuvant post mastectomy or whole breast radiation therapy with or without regional nodal irradiation by conformal technique were enrolled in the study after an informed consent. Baseline data was collected including age, address of the patient, occupation, co-morbidities and any known history of anxiety disorder. Disease factors like clinical stage, pathological stage, type of surgery, neoadjuvant or adjuvant chemotherapy were recorded. These variables were obtained from the subjects by a direct interview and from their clinical records.

Table 3 Patient characteristics

PATIENT CHARACTERSTICS	Number of patients (n=27)	%
Age (years)	Mean = 44 Range:22-74	
< 35	5	18.5
35-45	9	33.3
46-55	10	37.0
> 55	3	11.1
Occupation		
Housewife	22	81.5
Employed	5	18.5
Stage		
I	2	7.4

IIA	2	7.4
IIB	7	25.9
IIIA	5	18.5
IIIB	5	18.5
IIIC	2	7.4
Tx	4	14.8
Side of breast cancer		
Right	11	40.7
Left	16	59.2
History of anxiety disorder		
Yes	1	3.7
No	26	96.3
Co-morbidities		
Hypertension	6	22.2
Diabetes Mellitus	6	22.2
Thyroid disorders	3	11.1
Bronchial asthma	0	0
Surgery		
Mastectomy	22	81.5
Breast conservation	5	18.5
Axillary radiation		
No	16	59.2
Yes	11	40.7
No of Fractions		
15	16	59.2
25	11	40.7

All patients had received systemic chemotherapy before being enrolled in this study.

The patients in this study were of varied age group, ranging from 22-74 years with mean age of 44 years. The maximum number of women were in the age group of 35-55 years (70.3%). 19% (n=5) women were working.

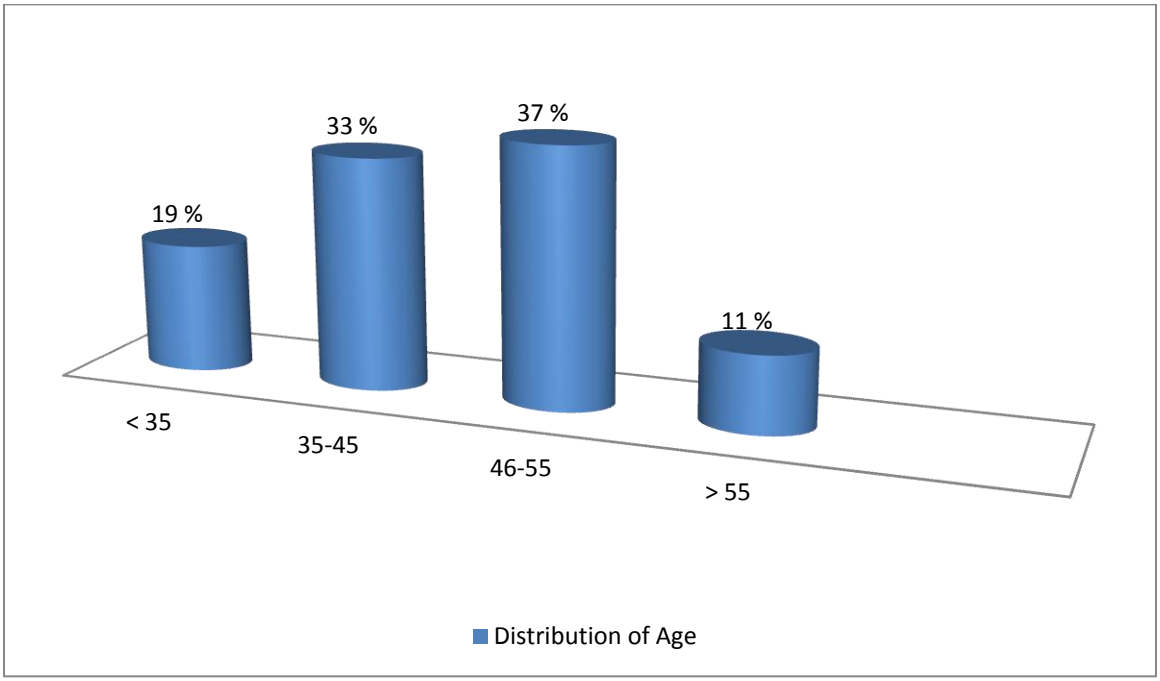


Figure 12. Percentage distribution of Age

Majority of patients (77.7%) had Stage II - Stage III disease. 15 % patients (n=4) had an early stage breast cancer while 70% (n=19) patients presented with locally advanced breast cancer. Remaining 4 patients had undergone lumpectomy elsewhere and had presented to our institute for further management. Their initial staging was not known. Left sided breast cancer was more (59%, n=16) among our study patients.

Six patients were known to have hypertension and six patients had diabetes mellitus. They all were on regular medications for the same. Three patients had thyroid disorders,

one of them had hyperthyroidism and remaining two were hypothyroid. None of the patients were known asthmatics. One patients was known to have an underlying anxiety disorder and was under follow up in Psychiatry department for the same.

Most of the patients (81%) had undergone mastectomy, while only five (19%) patients underwent breast conservation surgery.

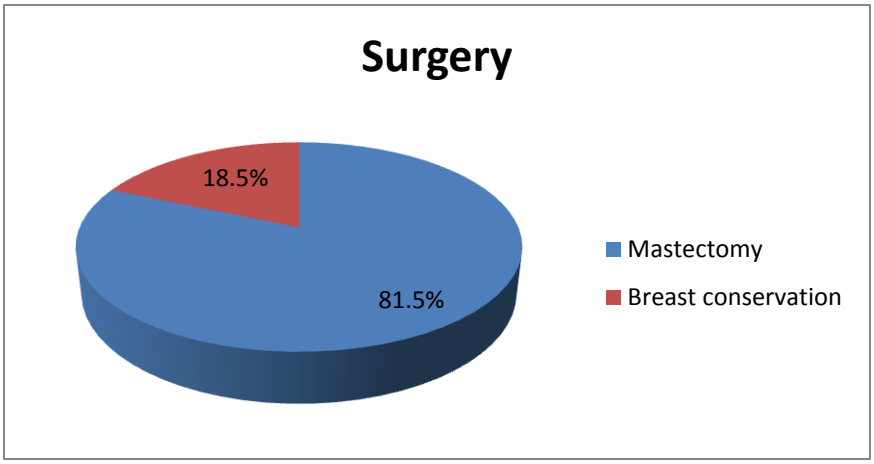


Figure 13. Type of surgery

All patients received neo adjuvant or adjuvant chemotherapy and had completed their chemotherapy prior to being referred for loco regional radiation therapy. It was ensured that there was a gap of at least 3-4 weeks from date of completion of chemotherapy to the commencement of radiotherapy. Most of the patients had received anthracycline and taxane based chemotherapy. Some patients with triple negative breast cancer had also received platinum based chemotherapy. The patients with positive ER/PR receptor status were started on hormonal therapy prior to being referred for radiation therapy. They were continued on the same during the course of RT. Tamoxifen or Letrozole was started

depending on whether they were premenopausal or postmenopausal. Trastuzumab was also continued during the course of radiation therapy if the patients were Her2Neu positive.

All patients received loco-regional radiation therapy with conformal technique. Field in field (FIF) technique with single isocentre was used for planning and treating all the patients. Prior to starting radiation therapy, pulmonary function test was done for all patients and an echocardiogram was done for left sided breast cancer patients.

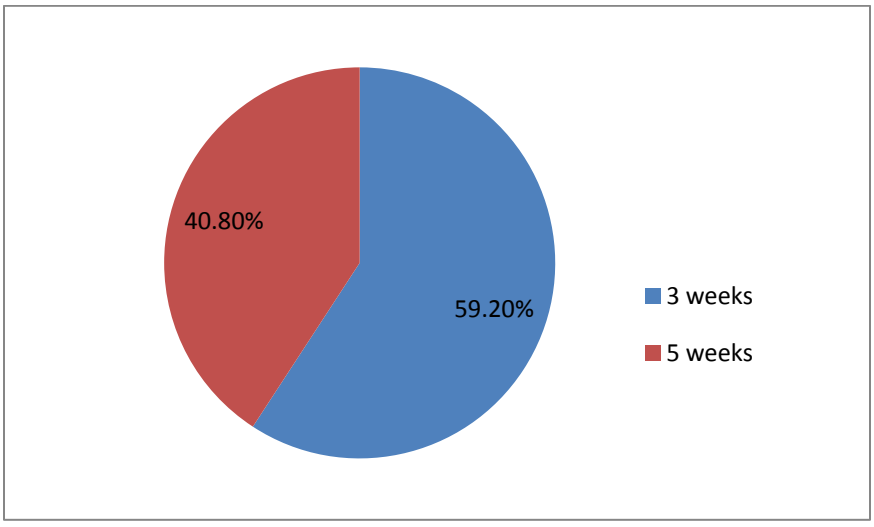


Figure 14. Duration of Radiation therapy

About 60% (n= 16) of the patients received hypofractionated radiotherapy 40 Gy in 15 fractions over three weeks, while remaining 40% received conventional fractionation with a dose of 50 Gy in 25 fractions over 5 weeks. The mean duration of treatment for patients who received hypofractionated radiotherapy was 20.1 ± 2.3 days (excluding 5

more days of lumpectomy cavity boost) and mean duration of treatment for patients who received conventional fractionation was 37.6 ± 9.2 days.

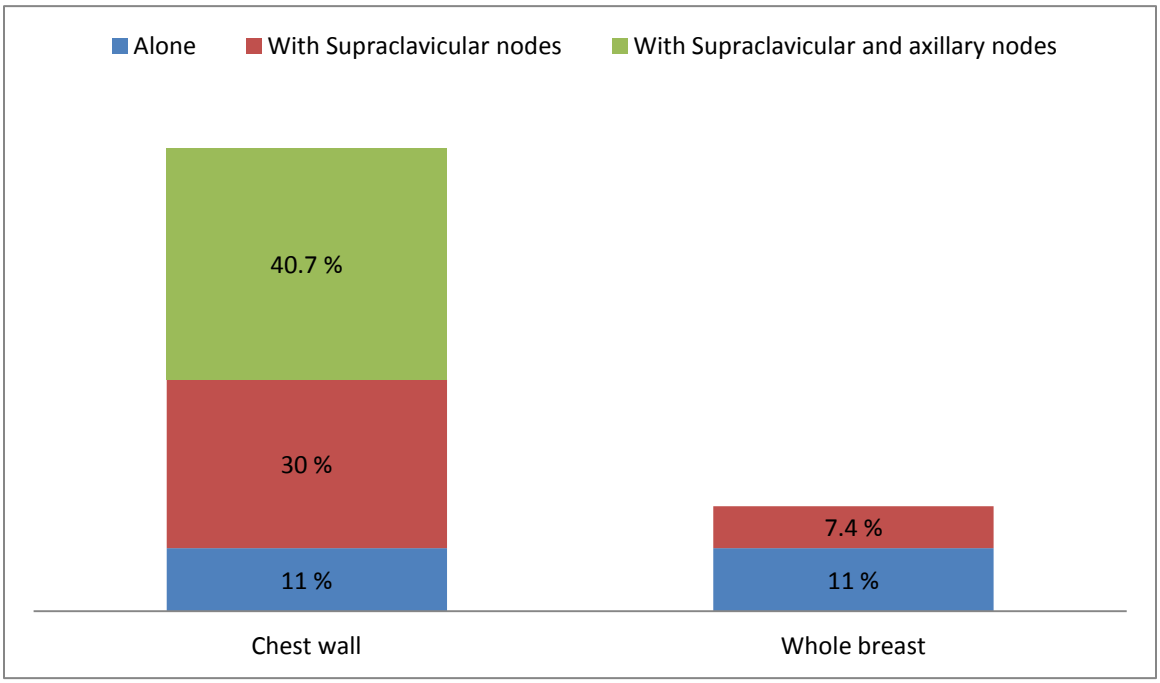


Figure 15. Sites of Radiation therapy - chest wall or whole breast alone or with regional nodal irradiation.

Among all the patients enrolled in this study, nearly 18% (n= 5) underwent whole breast irradiation, out of which 7% received an additional supraclavicular field irradiation in view of post neoadjuvant chemotherapy status. None of the patients in this hypofractionated group received axillary radiation. All the patients who had undergone a breast conservation surgery received hypofractionated radiotherapy. Out of 82% (n=22) of patients who received chest wall irradiation, half of them received axillary radiation due to various high risk factors like extranodal extension or incomplete axillary dissection. None of the patients received internal mammary nodal radiation.

Level of anxiety

Beck Anxiety Inventory (BAI) score was calculated for each patient and level of anxiety was assessed. The baseline anxiety level of patients was considered on the basis of their anxiety score at the time of simulation. 45% of the patients had mild to moderate anxiety level at the baseline, while nearly 55% patients had minimal anxiety. None of the patients had severe anxiety at baseline.

Anxiety level	**Number of patients (%)**
Minimal	15 (55.5)
Mild	11 (40.7)
Moderate	1 (3.7)
Severe	0

The variation of anxiety score over the course of treatment was noted for each patient. The median anxiety score at the time of simulation and on the first day of radiation therapy delivery was 7. It showed a decreasing trend in the subsequent days. The median score was 4 and 3 for second and third day of treatment respectively. Figure 16 shows the mean and range of anxiety score for all patients during the course of treatment.

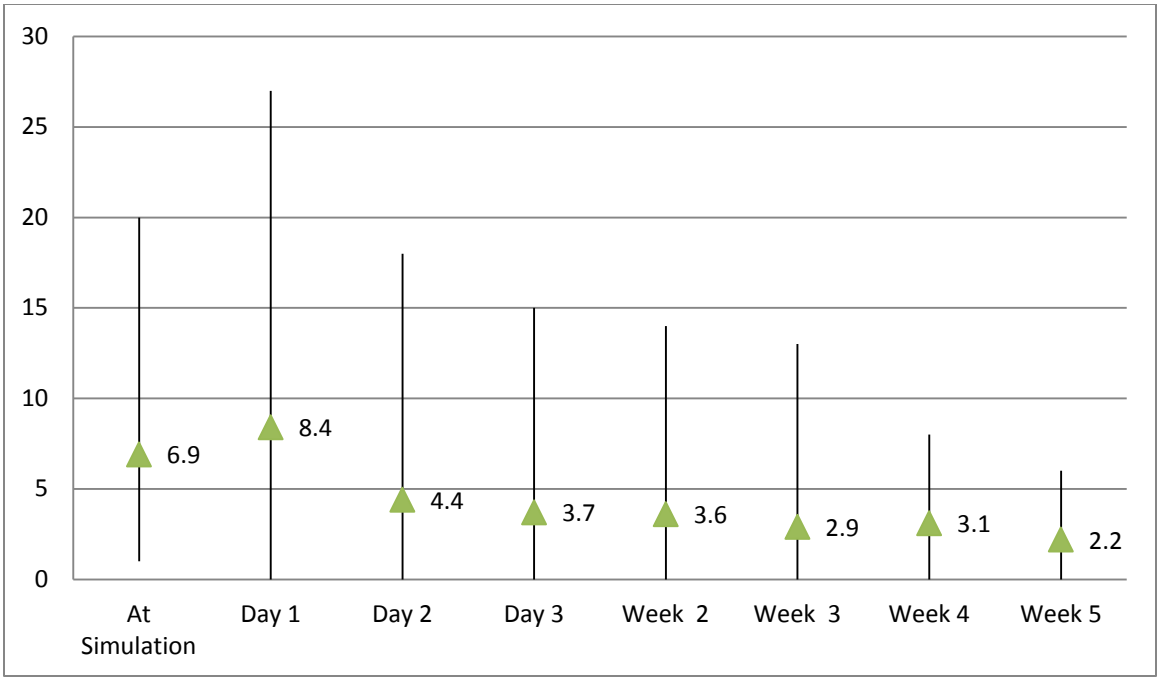


Figure 16. Mean and range of anxiety score during the course of treatment. Triangle represents the mean anxiety score for that particular day.

Nearly half of the patients had mild to moderate anxiety level at the time of simulation and first day of treatment with 7% patients developing severe anxiety on the 1st day (Day 1) of radiation therapy. As the radiation therapy course progressed, the proportion of patients with mild to moderate anxiety reduced. All patients had a very low anxiety score during the last week of treatment. This is depicted in the following table 6 and figure 17.

The patient with an underlying anxiety disorder had mild anxiety at simulation. Her anxiety score was constant throughout the course of treatment with no typical decline as seen in other patients.

Table 4. Percentage of patients in each anxiety group during simulation and course of treatment.

Anxiety level	Minimal %	Mild %	Moderate %	Severe %

At simulation	56	41	4	0
Day1	56	37	0	7
Day2	78	22	0	0
Day3	89	7	4	0
Week 2	85	15	0	0
Week 3	89	11	0	0
Week 4	91	9	0	0
Week 5	100	0	0	0

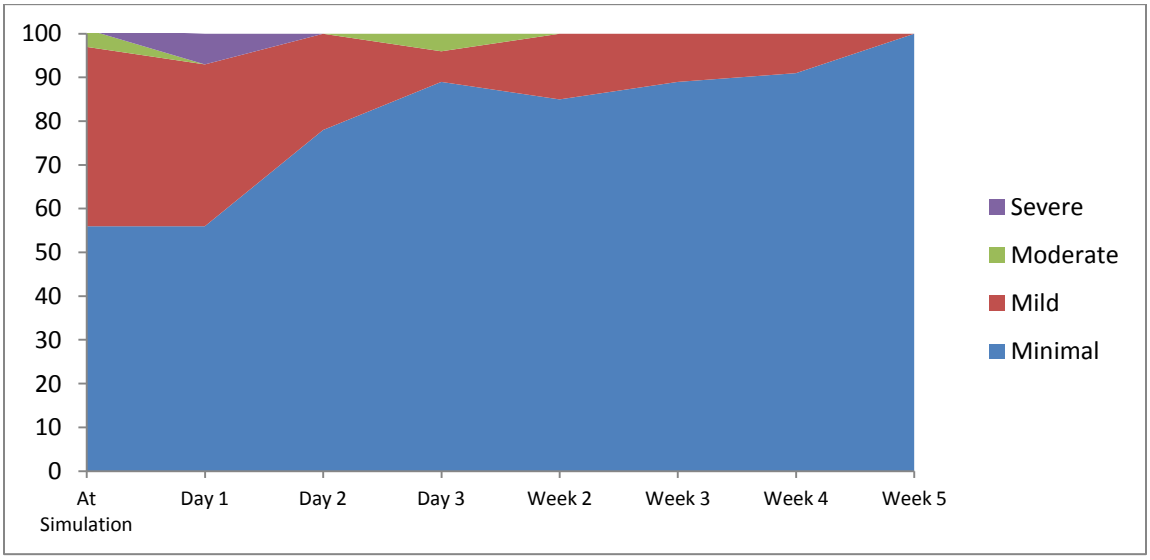


Figure 17. Variation of anxiety level among patients during radiation therapy.

Each color shade is representative of an anxiety level and the width of each color represents the percentage of patients with that anxiety level on a particular day of treatment. The blue are is seen to be increasing with time, while red area reduces, green and purple areas are seen only during the initial days of treatment.

There is a rapid decline in the anxiety from the first day of treatment to the end of treatment. Following figure 18 shows this rapid decline for 2 of our patients who had score of more than 26 on the first day of treatment.

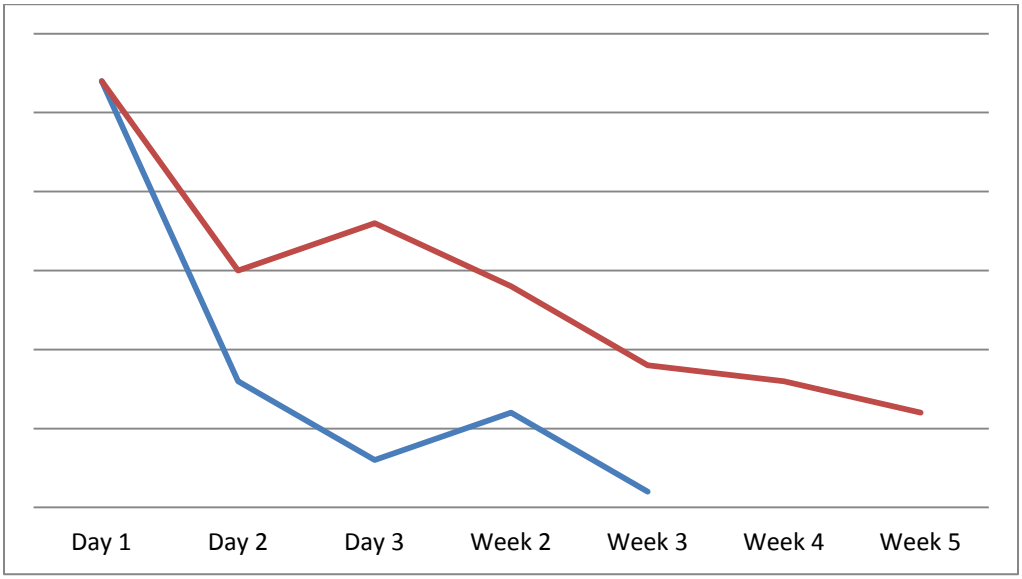


Figure 18. Rapid reduction in anxiety score for 2 of our patients who had severe anxiety level at the start of treatment.

Inter-fraction variations

A total of 27 pair of DRRs and 577 Electronic portal images (EPI) were evaluated. Mean central lung distance on DRR was 2.34 cm (Range: 1.4-3.5 cm). Table 7 shows the results for inter-fraction variability observed in these 27 patients.

Table 5. Group Systematic error (M), Standard deviation of systematic error(∑) , Standard deviation of random error (σ) (mm)

Parameter	M	∑	σ	Maximum deviation
Vertical	3.4	1.8	2.8	11.4
Lateral	3.4	1.8	2.8	11.5
Longitudinal	3.0	1.0	2.4	11.2
CLD variation	3.1	1.8	3.1	11.8

The vertical, lateral and longitudinal shifts varied with a mean and SD of 3.4±1,8mm, 3.4±1.8 mm and 3.0± 1.0 mm respectively. The variation detected was similar in all directions. The random error varied from 2.4 to 2.8 mm.

CLD variation which represented the inter-fraction variation of lung involvement was calculated from electronic portal images by comparing with baseline CLD measured on the reference DRR. The average systematic deviation was 3.1±1.8mm, ranging from 0.11-0.88mm among the patients. The maximum deviation observed was 11.8mm. The random error observed (σ) was 3.1mm.

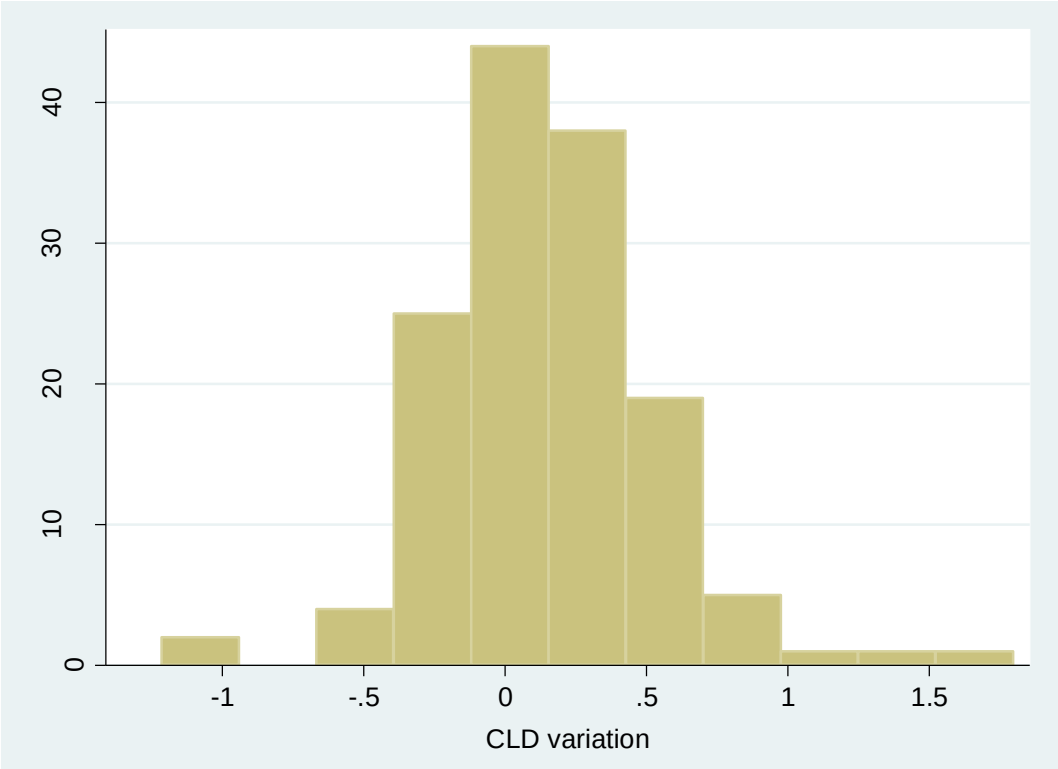


Figure 19. Histogram showing CLD variation for all patients had a normal distribution with 95% of values between -0.5 mm and 6.7 mm.

Table 6. Magnitude of all CLD variation. Only 2.8% values were more than 10mm.

	< 5mm	5-10mm	>10mm
CLD difference (n=140)	80.7 %	16.4%	2.8%

Figure 20 shows the vertical, lateral and longitudinal variation during the course of treatment. It was almost the same and did not show any variation with decrease in anxiety level. The figure also shows that the CLD variation showed a downward trend over the first three days of treatment, with a mild increase in the second week of treatment and thereafter remained almost similar during subsequent weeks.

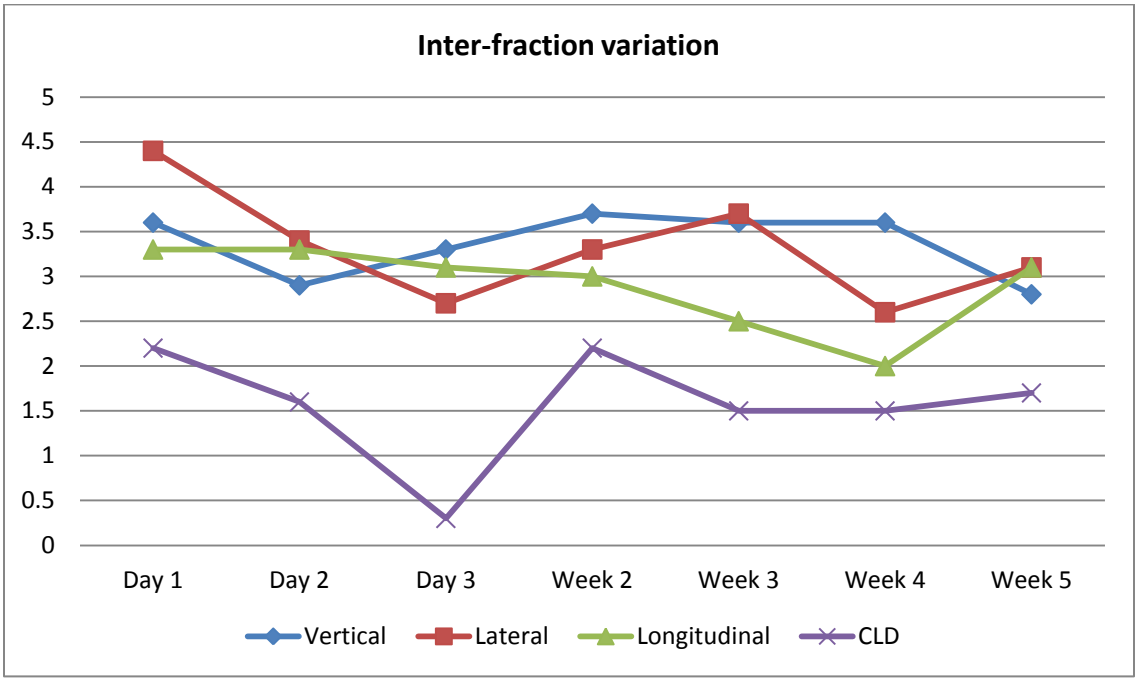


Figure 20. Variation in mean of different parameters during the course of treatment

Mean CIW for chest wall irradiation was 4.6 cm and mean CIW for whole breast irradiation was 7.6 cm. The average day to day variation observed was 3.3 mm (Range: 0.7 - 9.6 mm).

Mean CBESD was 2 cm. The maximum variation observed was up to 6 mm. This central flash distance or CBESD was kept 2 cm during the planning. Thus, with an average variation of 2.3 mm observed in our patients, there are no chances of missing the target.

Table 7. Day to day variation of parameters (mm)

	Average variation	Range of variation
CIW	3.3	0.7 - 9.6

CBESD	2.3	0.8 - 6.1

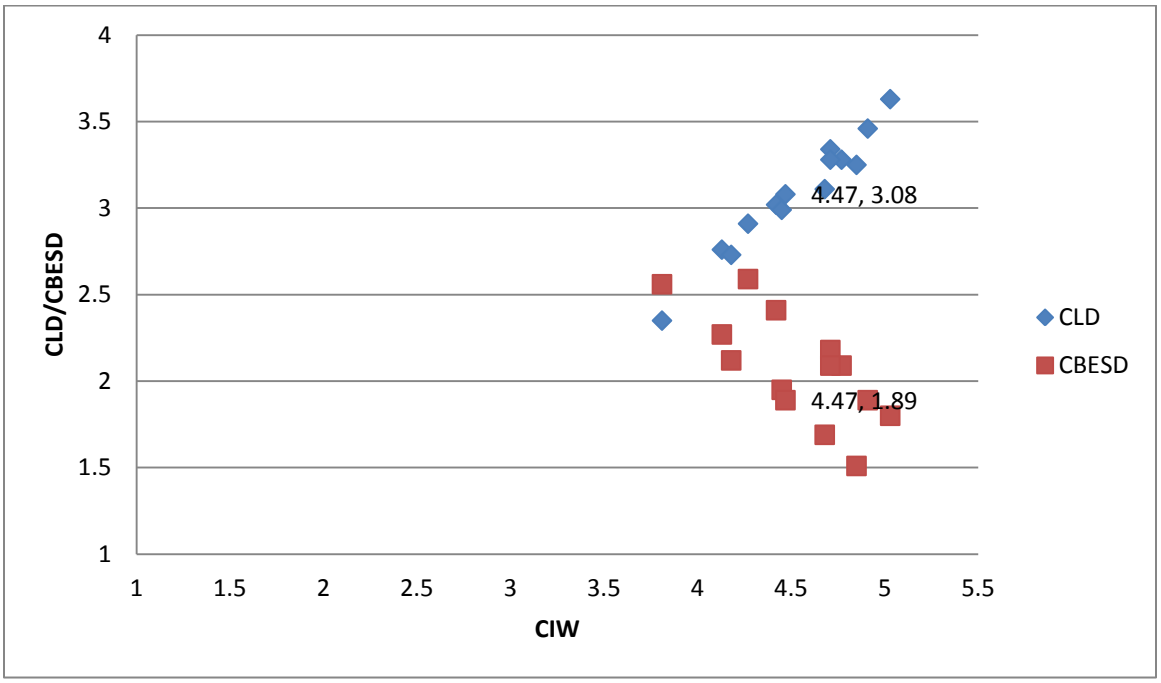


Figure 21. Correlation between CIW and other two parameters (CLD and CBESD) measured for a single patient. (r= 0.97 and -0.72)

Correlation of anxiety score with CLD variation

The anxiety score on the first day of treatment was found to be significantly correlating with CLD variation observed on the first day of treatment (r=0.45, p=0.02). The correlation between the two variables was not significant for the subsequent days.

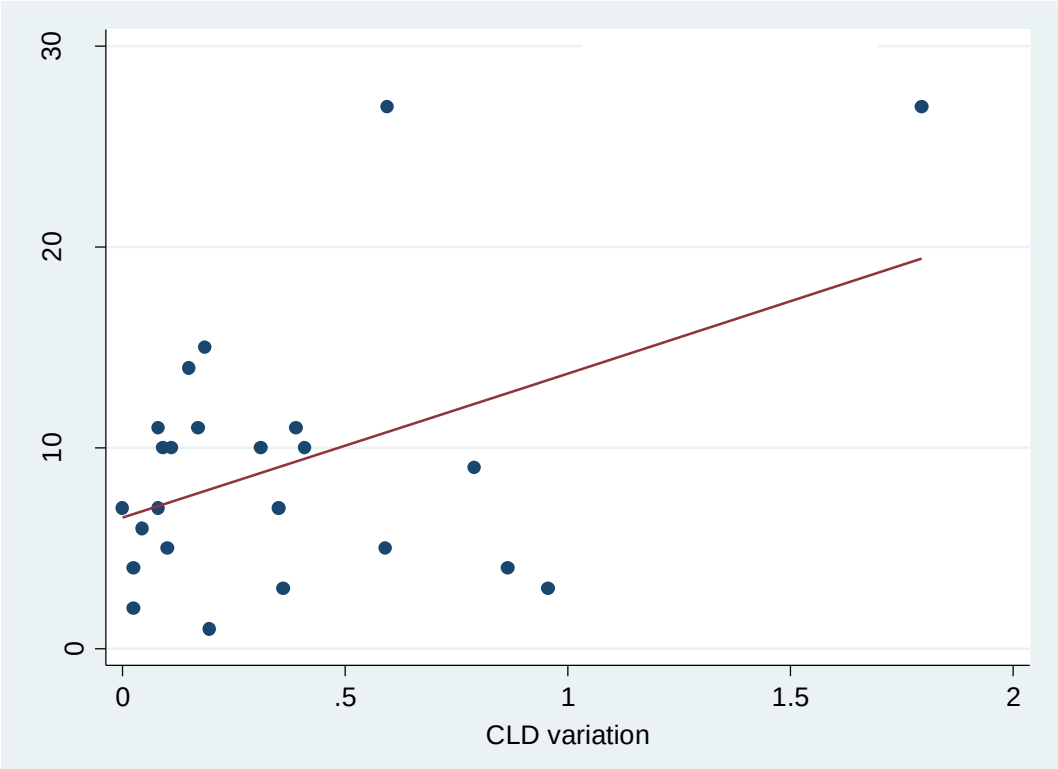


Figure 22. Scatter plot of Day 1 anxiety score variation with Day 1 CLD variation.

Inter-fraction CLD variation when compared with baseline anxiety level of minimal versus mild to moderate anxiety was not found to be significant. (p =0.38).

Table 8. Mean, median and range of CLD variation for patients with minimal versus mild to moderate baseline anxiety level

	Mean systematic error	Median	Range
Minimal anxiety	3.0	2.8	1.7-5.0
Mild to moderate anxiety	3.2	2.4	1.1-8.8

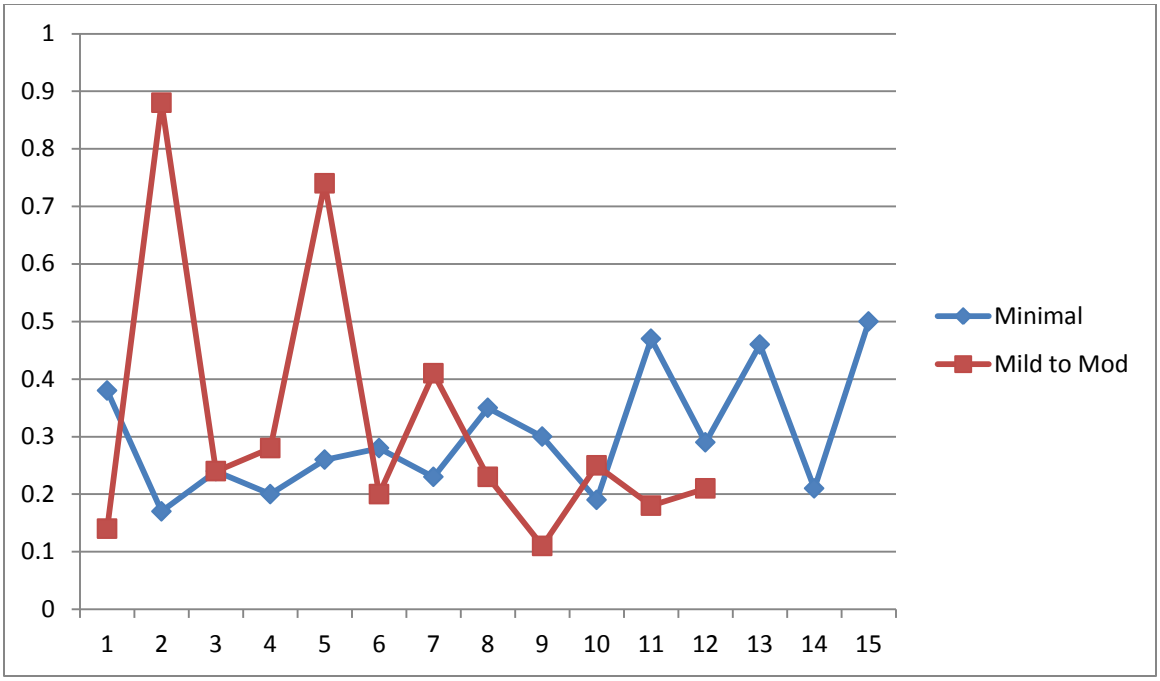


Figure 23. Mean CLD variation for patients with minimal versus mild to moderate anxiety level.

Anxiety score and other parameters

An attempt was made to find any predictable factors of anxiety level noted in patients. There was no significant correlation found between anxiety score and age (r=0.16, p= 0.4). Anxiety level among patients with mastectomy versus breast conservation surgery did not show any significant difference (p= 0.43). No significant difference was found between anxiety level and duration of radiation therapy (p=0.48).

Anxiety level among working women and housewives was not significantly different. 27% women with minimal anxiety level were working while 9% women with mild anxiety level were working.

CLD variation and other parameters

The CLD variation recorded was not significantly different for the type of surgery or the duration of treatment. No significant differences could be found in the inter-fraction motion observed between patients with left or right-sided breast cancer.

The following two Figures 24 and 25 show the inter-fraction variability in terms of CLD for each patient over the course of treatment. It is represented separately for 3 weeks versus 5 weeks of treatment. The CLD variability did not show any pattern and was found to be random. For majority of the patients, the values lied within 5mm and it varied less among patients who received 5 weeks of treatment compared to those who received 3 weeks of radiation therapy. However, with statistical analysis, the p value was not significant (p=0.4).

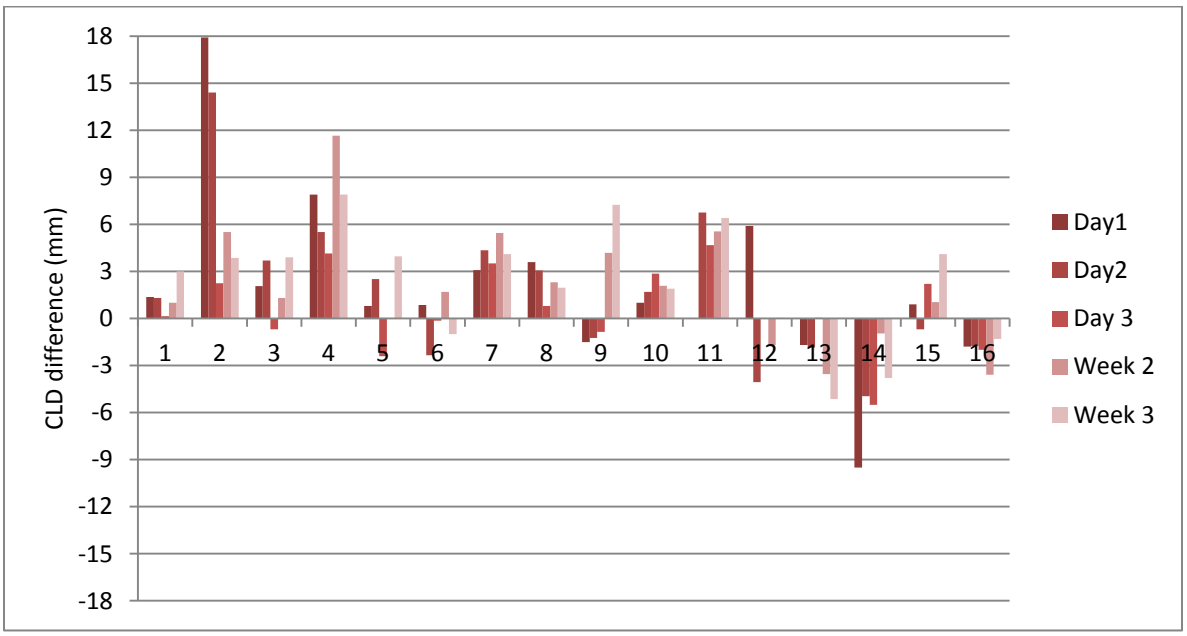


Figure 24. CLD setup variability for each patient who received 3 weeks of treatment

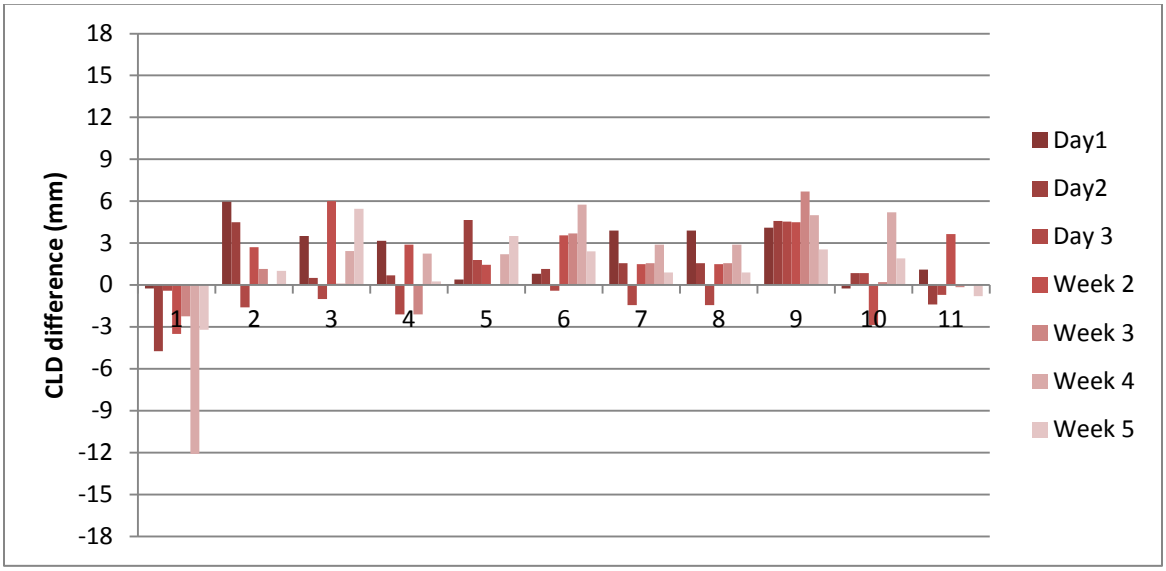


Figure 25. CLD setup variability for each patient who received 5 weeks of treatment

The correlation coefficient between age and CLD variation showed an inverse relation (r= -0.26), however it was not found to be significant (p = 0.18).

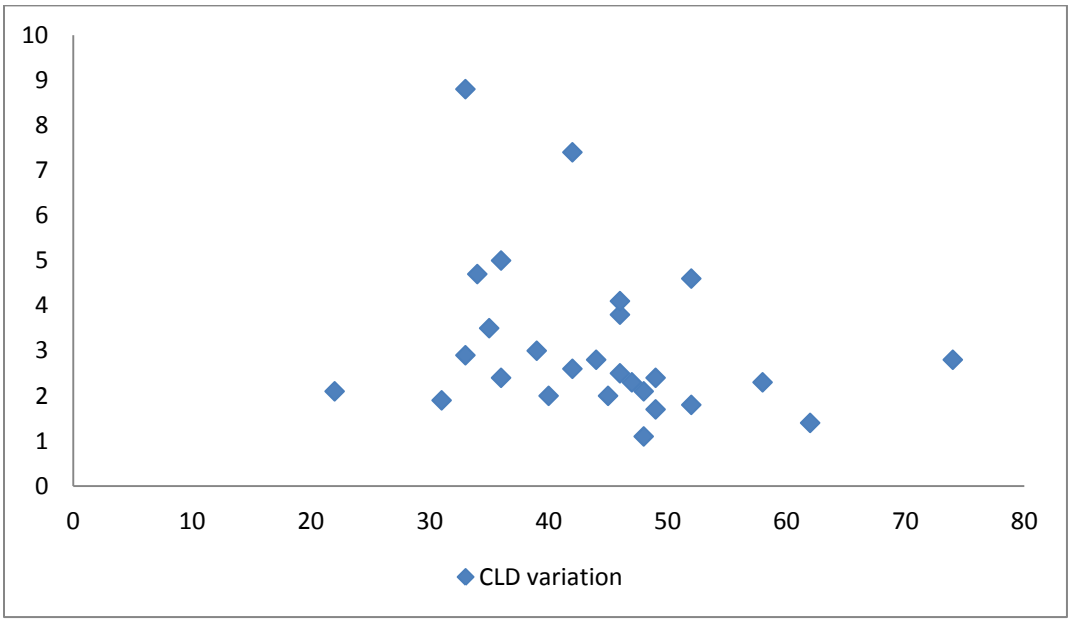


Figure 26. Scatter plot to show CLD variation (mm) with increasing age (years).

There was a significant correlation between baseline CLD values and mean variation in CLD. As the baseline CLD value increased, it showed a higher mean inter-fraction variation (r=0.56, p= 0.002).

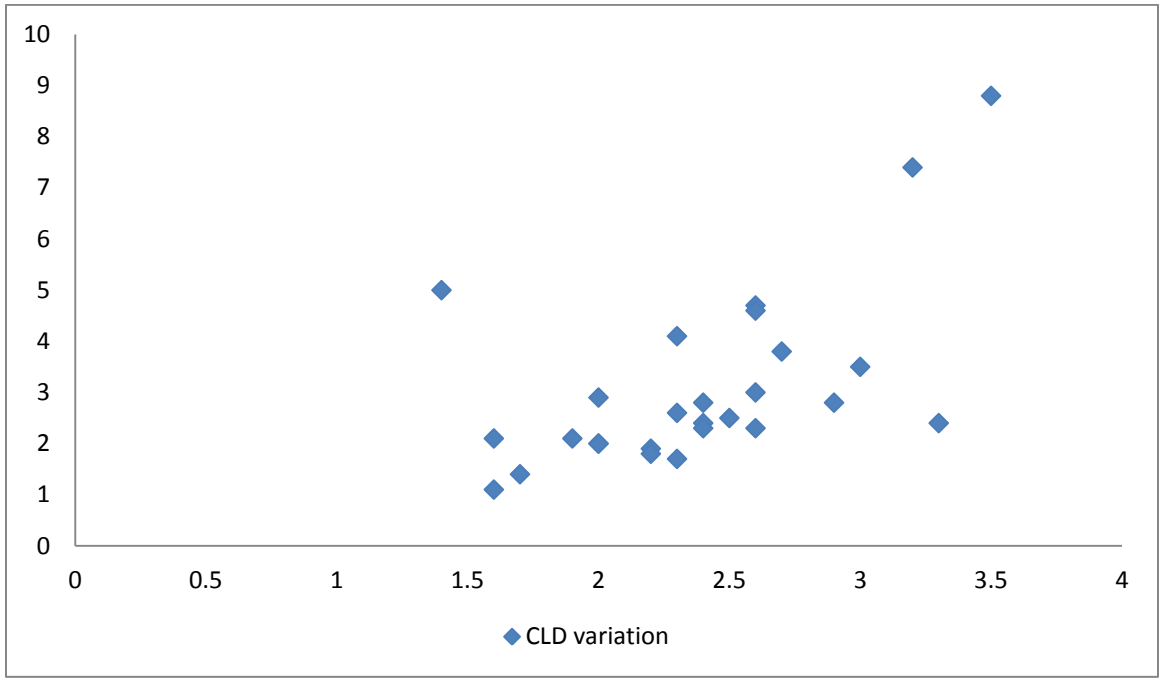


Figure 27. Scatter plot of CLD variation (mm) with baseline CLD values (cm)

DISCUSSION

Radiation therapy has an important role in treatment of breast cancer. It is indicated in all patients after breast conservation surgery and for high risk patients after mastectomy. Non metastatic breast cancer patients referred for loco-regional radiation therapy and who were treated with conformal technique were included in this study.

Most of our patients (70%, n=19) presented with locally advanced breast cancer. These patients and 3 of the 4 patients who had lumpectomy elsewhere(Tx) underwent mastectomy. Only 18% (n=5, including one of those who had lumpectomy elsewhere) of our patients had breast conservation surgery. In our country the psychological factors about having the organ with cancer tissue removed are more significant than cosmetic concerns. Also, the patients come from far off places and have a poor adherence to follow up regimens.

Level of anxiety

Various studies have evaluated and recorded anxiety levels in cancer patients and more so for patients undergoing radiation therapy. Studies have looked into anxiety level for cancer patients of various sites(77).

With our study, we wanted to focus on breast cancer patients which is the most common cancer among women and has a significant morbidity and mortality rate. Breast cancer

requires aggressive treatment of prolonged duration with surgery, radiation therapy, chemotherapy, hormonal therapy during which the patients experience innumerable side effects including psychological distress(76,79).

Our results showed that 44% (n=12) of patients had mild to moderate anxiety levels at the time of simulation and none of the patients had severe anxiety level. However, on the first day of treatment 37% (n= 10) of patients had mild anxiety level with 7.4% (n=2) of patients having severe anxiety level. This anxiety reduced rapidly in the subsequent radiotherapy sessions with only 11% (n=3) and 15% (n=4) of patients having mild to moderate anxiety levels by third day of radiation therapy and second week of treatment respectively. This trend was similar to results of Lewis et al. who showed patients' anxiety levels were highest at radiotherapy simulation and first session with a rapid decline after that (68). Halkett et al. looked into the information needs of breast cancer patients as they proceed through radiotherapy and also found a higher anxiety at baseline which did not drop until after commencement of treatment (80).

Relatively higher anxiety levels seen at the time of simulation and starting of radiotherapy may be explained by the uncertainty among patients about the whole procedure, fear of unknown, fear of pain or damage to body and characteristics of radiotherapy environment. For the treatment, the patients need to change into a different set of clothes and there is a need to expose the tattoos for their accurate positioning on the

machine. There are more number of quality assurance checks with more number of people on the machine during the first day of treatment. All these would have contributed towards increased anxiety among patients. Prior to starting treatment, the patients are explained about the likely acute and late side effects of radiation therapy and an informed consent is taken. They hence have a fear of likely side effects like getting skin burns or damage to lungs or heart with the treatment. Radiation therapy has various nicknames in local languages varying from 'heat' to 'current' treatment. The patients overhear these words while being unfamiliar with the actual technique and machines. This makes them more nervous and overwhelmingly worried about the treatment and this may be manifested as an array of physical symptoms and signs.

The anxiety levels drop rapidly post treatment commencement and during the course of treatment as they become habitual and familiar with the procedure and due to absence of their perceived side effects.

Wide variation in anxiety level was seen among our patients during the planning and start of treatment while there was low anxiety score for all patients by the end of treatment. Fifty six percent patients had only minimal anxiety at the time of simulation and on the first day of treatment. This could be due to the support from the radiation therapy team including the technologists and nursing staff present at the time of planning and treatment delivery which helps them to relax. At our institution, most of the patients are from far

off places and as cancer therapy is a prolonged treatment, they stay back here for months during the course of treatment in nearby hotels during which they tend to interact with other patients undergoing radiation therapy. They discuss with other patients about their experience of radiation therapy and this might have assured them of absence of perceived side effects. This may be a contributory factor to low levels of anxiety level observed in few patients when they first came for radiotherapy planning and treatment. It may be contradictory to other studies where patients may not have had a similar environment of discussion.

The patients are referred for radiation therapy after having completed their systemic chemotherapy. In the current standard of care, anthracyclins, taxanes and platinum based chemotherapy is used for all the patients. We observed that many of our patients had chemotherapy induced neuropathy. This may be a confounding factor in recording the anxiety score as tingling and numbness which is one of the item in BAI questionnaire was found to be severely bothering the patients, which could be likely due to post chemotherapy neuropathy rather than anxiety. The neuropathy improved over the course of treatment.

The type of anxiety experienced by the patients in our study was more due to stress of a new event and it settled with habituation of the situation. Thus, it is more likely an anticipatory anxiety seen in breast cancer patients during radiotherapy.

We attempted to further look into factors which may predict the level of anxiety among patients like their age, occupation, type of surgery and duration of treatment. However, no significant difference was found in the anxiety level and these specific parameters.

Inter-fraction variations

Treatment delivery precision is the backbone of radiotherapy treatment in this era of conformal techniques. Breast or chest wall irradiation is one of the most challenging radiotherapy plans due to the complexity in shape of the breast and postoperative chest wall, underlying normal structures like lung and heart and target motion due to respiratory movements. With the multimodality treatment, cure rates in breast cancer are higher and patients live longer. This demands a need to minimize the radiation dose to lung and heart tissue to prevent any long term toxicity in breast cancer survivors. Thus to achieve this, various conformal techniques have evolved and position verification has become an important aspect of treatment. It includes quality assurance measures, ensuring treatment delivery as per the plan, daily reproducibility of position and accounting for target motion due to breathing.

At our institution, machine based and patient based quality assurance measures are practiced. Setup sheets are maintained and each treatment volume and plan is verified by at least two physicists and one radiation oncologist. Breast board is used for immobilization for all breast cancer patients. It has an adjustable incline with varying

wedge angle and is helpful for excluding the lung and heart to the maximum extent possible from the treatment volume. However, due to the incline and hand grip of the breast board, it may allow patients' movement and can produce a difficulty in reproducing exactly the same position. This may account for some inter-fraction variations. Thus, additional supports like knee support and heel lock for some patients or other supports like body cast or Vacloc have been tried at many centers.

Inter-fraction variations are expected to be seen during treatment of breast cancer patients due to the setup changes, patient movements and breathing movements. Small magnitude inter-fraction variations up to 5mm are taken care of in the planning process and has little clinical impact on breast radiation therapy.

Lawson et al (95) had reported systematic error of less than 2 mm with standard deviation of 4.1, 3.1 and 3.7 mm in vertical, lateral and longitudinal direction respectively. In our study, we found that group systematic error was less than 5 mm with standard deviation of 1.8, 1.8 and 1.0 mm in vertical, lateral and longitudinal direction respectively. Only 3.6% shifts were 1 cm or larger with no shifts more than 2 cm unlike Lawson et al who had 13 vector shifts of larger than 2 cm. The shifts that we observed in our study were random with no predictable pattern in the vertical, longitudinal and lateral shifts recorded, and it did not diminish as the treatment progressed. The random errors were within 3 mm for all three directions.

The group systematic error for CLD was 3.1 mm with standard deviation (∑) of 1.7 mm and a maximum deviation of 11.8 mm. We noted that 95% of variation in CLD was between 0.5 - 6.7 mm. This describes the uncertain movement due to breathing motion. The CLD variation observed was higher in our study compared to other similar studies. The average systematic difference observed by Prabhakar et al. for CLD was 1.2 mm (∑ of 0.7 mm with maximum deviation of 2.2 mm). Lirette et al. reported an average difference of 1 mm but a larger standard deviation ∑ of 3.1 mm and maximum deviation of 7.4 mm. In our study, the observed standard deviation of random error (σ) in CLD was 3.1 mm which was similar to that observed by Koseoglu et al. (102). Only 2.8% values showed a CLD deviation of 1 cm or more.

The observed day to day mean variation for CBESD or central flash distance was 2.3 mm with maximum deviation of 6.1 mm. Thus, keeping a margin of 2 cm during planning to account for breathing movements will ensure no cold regions during delivery of radiation therapy due to variation in chest wall expansion. This is similar to previously reported value of 2.5 mm by Prabhakar et al. (103) and 2.2 mm reported by Van Tienhoven et al. (104).

The inter-fraction variation in central irradiated width (CIW) was 3.3 mm in our study and this was slightly more than 2.1 mm reported in study by Prabhakar et al. and similar to value (3.4 mm) reported by Lirette et al. (105).

As infrequently, deviations larger than the acceptable values could occur during treatment and these could significantly change the irradiated volume by under dosage of the target

and high dose to the normal structures. It suggests a need for daily position verification or other methods like DIBH, active breathing control, gating etc to ensure radiation as per the planned volumes. Daily position verification using electronic portal imaging (orthogonal and tangential field images) in our study was useful and a simple technique.

It was hypothesized that inter-fraction variability will be more for patients with a higher anxiety level due to the changes in respiratory rate and tidal volume that is influenced by increased output at the medullary level in anxious patients. Our study found a significant correlation between anxiety score and variations observed in CLD from the baseline on the first day of treatment ($r=0.45$, $p=0.02$). A patient is relatively more anxious at the start of treatment and this influences the breathing pattern during treatment. These variations in breathing pattern translates to more shifts recorded on the first day of radiotherapy. This subsequently reduced during the course of treatment but showed no predictable pattern or significant correlation with the observed anxiety scores.

Kron et al. had conducted a study on 20 patients to look into intra-fraction and inter-fraction variability and found inter-fraction variation to be twice as large as intra-fraction variation. Thus looking at their study, they concluded that as there is a relatively smaller intra-fraction variation, the breast cancer patients may not considerably benefit from breath holding or gated techniques. They reported an inter-fraction variation in lung movement by 1.8 mm with a standard deviation of 0.7 mm. These values were lesser than the observed values in our study. They also looked for any correlation between set-up errors and patient parameters like age, treatment side, weight, height or breast separation.

They found that increasing age was significantly correlated with inter-fraction motion (p = 0.05). They assumed this may be due to more inflexibility and difficult in holding position for longer time in older patients. Contrary to above data, our study showed a negative correlation between increasing age and CLD variation i.e. with increase in age, variation in CLD variation was less (p=0.18). Kron et al. did not find statistical correlation with other parameters. In our study also, the variation in CLD was not significantly different for left and right sided breast cancer, type of surgery undergone and duration of treatment.

There was a significant correlation between the baseline CLD value and variation observed in CLD (p=0.002). A larger CLD showed a greater variation in day to day treatment. This could be likely due to changes in the breathing pattern.

CONCLUSION

- This study has given us an estimate of the anxiety level among breast cancer patients who have undergone radiation therapy using the conformal technique in our department. It has given us an insight into psychological stress of patients just prior to and while on treatment.

- Anxiety alters the breathing pattern and in breast cancer radiotherapy, chest wall movements due to respiratory motion is an important contributory factor to inter-fraction variation. Central lung distance variation compared to baseline was found to be more on the first day of treatment and was significantly correlated with higher level of anxiety seen at starting of treatment.

- .There is a need of care and support of patients by the radiation oncologist and other support staff to reduce anxiety levels which has been shown to peak at the time of simulation and first day of treatment.

- The day before starting of radiation therapy can be the treatment verification day whereby the positioning and other parameters are checked without actual delivery of treatment which could help the patients to get accustomed to the treatment environment.

- Communication with patients is a key factor. Patients should be educated about radiation therapy, its procedure at simulation and treatment. We suggest counseling and use of patient information leaflets with pictorial representation.

- It is also important for the oncology team to be able to recognize patients with higher anxiety levels who may need to be referred to psychiatrist for further evaluation and counseling.

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LIST OF FIGURES AND TABLES

APPENDIX I

AJCC TNM Staging for Breast Cancer

T Staging		
Tx	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Tis	Carcinoma in situ	
Tis (DCIS) **Tis (LCIS)**	Ductal carcinoma in situ Lobular carcinoma in situ	
Tis (Pagets)	Paget disease of the nipple not associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma.	
T1	Tumour 2 cm or less in greatest dimension	
	T1mic	Microinvasion 0.1 cm or less in greatest Dimension
	T1a	More than 0.1 cm but not more than 0.5 cm in greatest dimension
	T1b	More than 0.5 cm but not more than 1 cm in greatest dimension
	T1c	More than 1 cm but not more than 2 cm in greatest dimension
T2	Tumour more than 2 cm but not more than 5 cm in greatest dimension	
T3	Tumour more than 5 cm in greatest dimension	
T4	Tumour of any size with direct extension to chest wall and/or to skin (ulceration or skin nodules)	
	T4a	Extension to chest wall (does not include pectoralis muscle invasion only)
	T4b	Ulceration, ipsilateral satellite skin nodules, or skin oedema (including peau d'orange)
	T4c	Both 4a and 4b
	T4d	Inflammatory carcinoma

N Staging		
cNx	Regional lymph nodes cannot be assessed	
cN0	No regional lymph node metastasis	
cN1	Metastasis in movable ipsilateral Level I, II axillary lymph node(s)	
cN2	Metastasis in ipsilateral Level I, II axillary lymph node(s) that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary lymph node(s) in the absence of clinically evident axillary lymph node metastasis	
	cN2a	Metastasis in axillary lymph node(s) fixed to one another (matted) or to other structures
	cN2b	Metastasis only in clinically detected internal mammary lymph node(s) and in the absence of clinically detected axillary lymph node metastasis
cN3	Metastasis in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement; or in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident Level I, II axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement	
	cN3a	Metastasis in infraclavicular lymph node(s)
	cN3b	Metastasis in internal mammary and axillary lymph nodes
	cN3c	Metastasis in supraclavicular lymph node(s)

M Staging	
Mx	Not assessed
M0	No distant metastasis
M1	Distant metastasis

Pathological N Staging		
pNx	Regional lymph nodes cannot be assessed	
pN0	No regional lymph node metastasis	
pN1	Micrometastasis; or metastasis in 1–3 axillary ipsilateral lymph nodes; and/or in internal mammary nodes with metastasis detected by sentinel lymph node biopsy but not clinically detected	
	pN1mic	Micrometastasis (larger than 0.2 mm and/or more than 200 cells, but none larger than 2.0 mm)
	pN1a	Metastasis in 1–3 axillary lymph node(s), including at least 1 larger than 2 mm in greatest dimension
	pN1b	Internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected
	pN1c	Metastasis in 1–3 axillary lymph nodes and internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastasis in 4–9 ipsilateral axillary lymph nodes, or in clinically detected ipsilateral internal mammary lymph node(s) in the absence of axillary lymph node metastasis	
	pN2a	Metastasis in 4–9 axillary lymph nodes, including at least one that is larger than 2 mm
	pN2b	Metastasis in clinically detected internal mammary lymph node(s), in the absence of axillary lymph node metastasis
pN3	pN3a	Metastasis in 10 or more axillary lymph nodes (at least one larger than 2 mm) or metastasis in infraclavicular lymph nodes
	pN3b	Metastasis in clinically detected internal ipsilateral mammary lymph node(s) in the presence of positive axillary lymph node(s); or metastasis in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected
	pN3c	Metastasis in ipsilateral supraclavicular lymph node(s)

STAGE GROUPING

Stage	T Stage	N Stage	M Stage
0	Tis	N0	M0
IA	T1	N0	M0
IB	T0, T1	N1mic	M0
IIA	T0, T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0, T1, T2	N2	M0
	T3	N1, N2	M0
IIIB	T4	N0, N1, N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

APPENDIX II

RTOG breast contouring guidelines for breast and chest wall

	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Breast	Clinical Reference + Second rib insertion	Clinical reference + loss of CT apparent breast	Skin	Excludes pectoralis muscles, chest wall muscles, rib	Clinical Reference + mid axillary line typically, excluding latissimus dorsi	Sternal-rib junction
Chest Wall	Caudal border of the clavicle head	Clinical reference+ loss of CT apparent contralateral breast	Skin	Rib-pleural interface. (Includes pectoralis muscles, chest wall muscles, ribs)	Clinical Reference/ mid axillary line typically, excluding latissimus dorsi	Sternal-rib junction

RTOG contouring guidelines for regional nodal volumes for breast cancer

	Cranial	**Caudal**	**Anterior**	**Posterior**	**Lateral**	**Medial**
Supraclavicular	Caudal to cricoid cartilage	Junction of brachiocephalic-axillary veins/ caudal edge of clavicle head	Sternocleidomastoid (SCM) Muscle	Anterior aspect of the scalene muscle	*Cranial:* lateral edge of SCM muscle *Caudal:* junction of 1st rib-clavicle	Excludes thyroid and trachea
Axilla Level I	Axillary vessels cross lateral edge of pectoralis minor muscle	Pectoralis major muscle insert into ribs	Plane defined By anterior surface of Pectoralis major muscle and Latissimus dorsi muscle	Anterior surface of subscapularis muscle	Medial border of latissimus dorsi muscle	Lateral border of Pectoralis minor Muscle
Axilla level II	Axillary vessels cross medial edge of Pectoralis Minor muscle	Axillary vessels cross lateral edge of Pectoralis minor muscle	Anterior surface of Pectoralis minor muscle	Ribs and intercostal muscles	Lateral border of Pectoralis minor Muscle	Medial border of Pectoralis minor Muscle
Axilla level III	Pectoralis Minor muscle insert on cricoid	Axillary vessels cross medial edge of Pectoralis minor muscle	Posterior surface Pectoralis major muscle	Ribs and intercostal muscles	Medial border of Pectoralis minor Muscle	Thoracic Inlet

APPENDIX III

INFORMATION SHEET AND CONSENT FORM

Level of anxiety in breast cancer patients receiving locoregional radiation therapy and its correlation with inter-fraction variations observed during delivery of treatment

Department of Radiotherapy

Christian Medical College, Vellore

Patient Information Sheet

Breast cancer treatment is a multimodality approach where surgery is followed by adjuvant therapy with chemotherapy, radiation therapy and hormonal therapy based on the risk factors. You have been referred for radiation therapy after the surgery. Radiotherapy is an important part of the breast cancer treatment as it helps to prevent recurrent disease and this has been proven by various studies in the past.

You are expected to be anxious about the radiation therapy and may have various questions in your mind. Radiation therapy to breast cancer patients is directed either on the residual breast tissue (in cases of early breast cancer following lumpectomy) or to the chest wall (in cases radiation therapy is being delivered following removal of the whole breast). It is given using X rays and the treatment is not painful. The procedure requires you to lie down as instructed using an immobilisation device. Prior to starting the

treatment, you will be required to come for planning for 1 day which will be done in the same position as the treatment followed by a CT scan for treatment planning. Once the plan is ready, your treatment will be started.

The radiotherapy planning and execution in breast cancer patients depends on the amount of chest wall expansion and therefore during planning adequate margins are given so that there are no areas in planning field that are missed. You are being given the most accurate form of radiation therapy. Prior to starting treatment images will be taken for verification of your position and to assess any deviation from the original radiotherapy plan. These images will be taken again weekly. This will ensure that treatment is being delivered correctly to the target volumes.

This observational study will help us to understand the levels of anxiety of breast cancer patients undergoing radiation therapy and will help us to suggest the need of suitable interventions to decrease anxiety. This will also try to see if the level of anxiety correlates with the change in respiratory pattern of the patients.

We request you to participate in this study. Being part of the study you will be required to fill up a questionnaire on the day of planning, first three days of radiation treatment and weekly once to assess the level of anxiety. The standard protocol for treatment is followed with no change in the delivery of treatment if you agree to be a part of this study. The only difference is the extra images taken for verification of position prior to treatment. This may ensure more accurate delivery of radiation to target volumes.

What is radiotherapy?

It is a treatment given using X-rays and it is not painful. It requires you to lie down as instructed using an immobilisation device.

How does radiotherapy help in breast cancer?

Radiotherapy is an important part of the breast cancer treatment as it helps to prevent local recurrence of the disease

What are the side effects with radiation?

Acute side effects may occur while you are undergoing radiotherapy. These include darkening of the skin, peeling of the skin and ulcers over the radiated region.

Late side effects may occur months or years after completion of radiation therapy. These include skin tightness due to fibrosis, lymphedema, lung problems like radiation pneumonitis and heart problems (for left sided breast cancer patients) like cardiomyopathy.

What is this study?

This study tries to understand the levels of anxiety of breast cancer patients undergoing radiation therapy and help to suggest the need of suitable interventions to decrease anxiety. This will also try to see if the level of anxiety correlates with the change in respiratory pattern of the patients.

If you take part what will you have to do?

If you agree to participate in this study, you will have to sigh the consent form. You will be required to fill up a questionnaire on the day of planning, first three days of radiation treatment and weekly once to assess the level of anxiety.

Will there be any difference in treatment in this study?

The standard protocol for treatment is followed with no change in the delivery of treatment if you agree to be a part of this study. The only difference is the extra images taken for verification of position prior to treatment. This may ensure more accurate delivery of radiation to target volumes. The radiation dose delivered due to the extra images is very minimal and will be delivered only to the treatment field. Thus, no extra side effects are expected.

Will you get more side-effects if you participate?

As there is no difference in the treatment, no extra side effects are expected.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

What will happen if you develop any study related injury?

Since this is an observational study, no particular study related side effects are expected.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, people associated with the study may review your medical notes without your additional permission.

Whom will you contact for study related queries?

If you have any further questions, please ask **Dr. Shina Goyal.**

Ph No: +91-9843673938, email: shina.goyal@cmcvellore.ac.in

Informed Consent

Study Title: Level of anxiety in breast cancer patients receiving locoregional radiation therapy and its correlation with inter-fraction variations observed during delivery of treatment

Study Number: _____

Subject's Initials: _____

Subject's Name: __

Date of Birth / Age: _____

i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

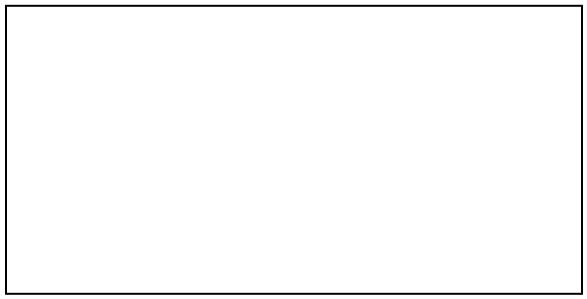
(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____

Signature:

Or 

Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

APPENDIX IV

Beck Anxiety Inventory

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom.

	Not At All	Mildly but it didn't bother me much.	Moderately - it wasn't pleasant at times	Severely – it bothered me a lot
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of worst happening	0	1	2	3
Dizzy or lightheaded	0	1	2	3
Heart pounding/racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky/unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint/lightheaded	0	1	2	3
Face flushed	0	1	2	3
Hot/cold sweats	0	1	2	3
Column Sum				

APPENDIX V

Data Sheet

uniqueid	age	occupation	diagside	ct	cn	pt	pn	surg	ht	dm	thy	ba	oth	anxiety	sites	dose	frac	dosim	dos	doc	b4sim	anxiety level	basd1
1	62	1	1			1	0	2	2	2	2	2	2	2	4	1	1	04/04/2016	15/04/2016	05/05/2016	8	mild	0
2	46	1	1	4	1	1	1	1	2	2	2	2	2	2	3	2	2	30/03/2016	12/04/2016	16/05/2016	2	minimal	4
3	33	1	1	1	0	1	0	2	2	2	2	2	2	2	4	1	1	15/02/2016	29/02/2016	18/03/2016	10	mild	27
4	36	1	1	5	0	1	1	1	2	2	2	2	2	2	3	2	2	08/02/2016	25/02/2016	31/03/2016	20	moderate	27
5	74	1	2	4	1	3	2	1	1	2	1	2	1	2	3	2	2	26/02/2016	18/03/2016	25/04/2016	8	mild	7
6	49	2	2	2	1	2	1	1	2	2	1	2	2	2	3	2	2	02/03/2016	17/03/2016	22/04/2016	5	minimal	7
7	49	2	2	2	1	2	0	2	1	2	1	2	2	2	4	1	1	16/03/2016	29/03/2016	26/04/2016	1	minimal	0
8	40	1	1	2	2	2	2	1	2	2	2	2	2	2	3	2	2	22/02/2016	10/03/2016	14/04/2016	1	minimal	6
9	42	1	2	4	1	2	3	1	1	1	2	2	2	2	3	2	2	06/04/2016	21/04/2016	25/06/2016	7	minimal	7
10	42	1	2	2	1	1	2	1	2	2	2	2	2	2	2	1	1	28/03/2016	08/04/2016	28/04/2016	12	mild	9
11	45	1	2	2	0	3	1	1	2	2	2	2	2	1	2	1	1	08/04/2016	25/04/2016	13/05/2016	9	mild	11
12	44	1	1	5	0	0	0	1	2	1	2	2	2	2	2	1	1	04/04/2016	19/04/2016	09/05/2016	4	minimal	4
13	46	1	2	2	1	2	1	1	2	2	2	2	2	2	2	1	1	10/02/2016	26/02/2016	17/03/2016	9	mild	10
14	58	1	1	2	1	2	0	1	2	1	2	2	2	2	1	1	1	15/04/2016	04/05/2016	24/05/2016	5	minimal	3
15	35	1	1	4	1	2	3	1	2	2	2	2	2	2	3	2	2	18/04/2016	28/04/2016	01/06/2016	2	minimal	1
16	39	1	2	3	1	1	0	1	2	2	2	2	2	2	2	1	1	02/05/2016	12/05/2016	01/06/2016	6	minimal	14
17	31	2	2	2	1	5	1	1	2	2	2	2	2	2	1	1	1	22/04/2016	11/05/2016	31/05/2016	7	minimal	5
18	34	1	2	2	2	2	1	1	2	2	2	2	2	2	2	1	1	20/04/2016	04/05/2016	24/05/2016	2	minimal	7
19	33	1	2	5	0	5	1	1	2	2	2	2	2	2	2	1	1	02/05/2016	20/05/2016	10/06/2016	2	minimal	5
20	47	1	2	4	3	2	1	1	1	1	2	2	2	2	3	2	2	23/05/2016	07/06/2016	13/07/2016	13	mild	11
21	52	1	2	4	3	4	2	1	1	2	2	2	2	2	3	2	2	18/05/2016	06/06/2016	09/07/2016	6	minimal	10
22	22	1	2	3	1	2	1	1	2	2	2	2	2	2	3	2	2	27/05/2016	14/06/2016	18/07/2016	1	minimal	2
23	48	2	2	4	1	1	2	1	1	2	2	2	2	2	3	2	2	06/06/2016	22/06/2016	26/07/2016	8	mild	10
24	46	1	1	3	1	1	0	1	2	1	2	2	2	2	2	1	1	22/06/2016	05/07/2016	25/07/2016	9	mild	11
25	36	2	1	2	1	1	0	2	2	2	2	2	2	2	5	1	1	01/07/2016	11/07/2016	28/07/2016	6	minimal	3
26	52	1	2	2	0	1	0	1	2	2	2	2	2	2	1	1	1	20/06/2016	30/06/3016	20/07/2016	9	mild	10
27	48	1	1	5	0	2	1	2	2	1	2	2	2	2	5	1	1	04/07/2016	15/07/2016	04/08/2016	13	mild	15

basd2	basd3	baswk2	baswk3	baswk4	baswk5	apd1	apd2	apd3	apwk2	apwk3	apwk4	apwk5	latd1	latd2	latd3	latwk2	latwk3	latwk4	latwk5	ccd1	ccd2
0	0	0	0			0.1	0	0	0	0.2			0	0.1	0	0	0.2			0.5	0.1
8	2	3	3	6	3	0.2	0.1	0.2	0	0.1	0.3	0	0.1	0.2	0.1	0.3	0.3	0.2	0.1	0.7	0.1
8	3	6	1			0.1	0.1	0	0	0.5			0.3	0.1	0.4	0.3	0.7			0.4	0.7
15	18	14	9	8	6	0.1	0	0.4	0	0	0.5	0.5	0.7	0.1	0.3	0.5	0.2	0.2	0.1	0.4	0.1
2	2	2	2	2	0	0.6	0	0.2	0.6	0.3	0.3	0.3	0	0	0.1	0.6	0.4	0.2	0.6	0	0.2
5	5	9	4	5	5	0.5	0.4	0.2	0	0.1	0.3	0.1	0.2	0.1	0.2	0.4	0.2	0.1	0.3	0.3	0.2
0	4	2	0			0.4	0.1	0.5	0.2	0.3			0	0.6	0.4	0.6	0.1			0.1	0.4
0	0	0	1	0	0	0.2	0.2	0.3	0.8	1	0.4	0.3	0.1	0.2	0	0.4	0.1	0.2	0.3	0.5	0.5
3	0	1	2	2	2	0	0.8	0.5	0.5	0.2	0.2	0.5	0.6	0.7	0.6	0.3	0.1	0.2	0.5	0	0.1
8	3	8	8			0.1	0.1	0.7	0.2	0			0.3	0.3	0.4	0.5	0.3			0.3	0
4	10	10	13			0.8	0.2	0.2	0.1	0.1			0.3	0.6	0	0	0			0.3	0.3
4	3	3	4			0	0.2	0.6	0.6	0			0.6	0.2	0.3	1	0.6			0.3	0.6
3	6	3	3			0.2	0.1	0.5	0.3	0			0.7	0.2	0.5	0.2	0.9			0.2	0.1
4	1	0	0			0.3	0.2	0.4	0	0			0.7	0	0.2	0	0.2			0.7	0
0	1	0	1	1	0	0.5	0.3	0.6	0.3	0.5	0.1	0.3	0.7	0.7	0.5	0.6	0.4	0.7	0.9	0.5	0.1
4	3	6	4			0.7	0.1	0.3	0.3	1.3			1.1	0.2	0.1	0.5	0.3			0.7	0.4
0	0	0	0			1.2	0.6	0.1	1	0.3			0.4	0	0.5	0	0.4			0.1	0.4
4	1	2	2			0.3	0.7	0.7	0.5	1.4			0.2	0.2	0.3	0.2	0.9			0.2	0.8
2	3	5	2			0.6	0.6	0	0.7	0			0.8	0.9	0	1.2	1.4			0	0.5
4	3	4	1	1	1	0.4	0.4	0	0.5	0.8	0	0.2	0.1	0	0.3	0.1	0.3	0.7	0.3	0.4	0
7	2	1	1	2	1	0.5	0.5	0.5	0	0	1	0	1.5	1.5	0.5	0.3	0.1	0	0.3	0.7	0.7
1	3	1	1	1	2	0	0.1	0.2	0.8	0.5	0.1	0.1	0	0.5	0.1	0.3	0.6	0.1	0	0	0.2
5	7	5	4	6	4	1	0.7	0.4	0.4	0.1	0.8	0.8	0	0.1	0.4	0	0.2	0.3	0	0	0.4
3	2	3	3			0.5	0.8	0.5	1	1			0.9	0.9	0.6	0.3	0			0.5	0.4
0	1	1	3			0.2	0	0.3	0.3	0			0.5	0.2	0.2	0	0.2			0.9	0.4
9	7	6	5			0.1	0.3	0.3	0.4	0.6			0.8	0.2	0.2	0.4	0.4			0	1
15	9	2	2			0		0.4	0.6	0.3			0.3		0	0	0.4			0.3	

ccd3	ccwk2	ccwk3	ccwk4	ccwk5	drrm	drrl	cld1m	cld1l	cld2m	cld2l	cld3m	cld3l	clwk2m	clwk2l	clwk3m	clwk3l	clwk4m	clwk4l	clwk5m	clwk5l	ciwd1m	ciwd1l
0.2	0	0			1.48	1.83			1.25	1.8	1.39	1.89	1.28	1.83	1.08	1.63						
0.3	0	0.5	0.2	0.1	2.56	2.85		2.73	3.11	3.25	2.82	2.67	3.07	3.04	2.93	2.93	3.92	3.92	2.85	3.2		5.17
0.3	0.1	0.3			2.3	4.77	1.74		2.09		2.12	4.5	1.74	4.22	2.15	4.15					6.92	
0.1	0.4	0.2	0.3	0.1	3.57	2.99	3.02	2.35	2.91	2.76	3.63	3.25	3.28	2.73	3.34	2.99	3.46	3.11	3.28	3.08	4.42	3.81
0.1	0.4	0.2	0.5	0.2	2.73	2.11	2.48	1.66	2.83	1.91	2.95	2.09	2.23	1.4	2.78	2.04			2.26	1.49	4.59	3.7
0.4	0.4	0.8	0.2	0.5	2.54	2.12			2.51	2.01	2.88	2.2	2.35	1.73	2.54		2.33	1.88	2.65	1.96		
0.1	0.2	0.2			1.37	1.45			1.02	1.05	1.48	1.48	1.25	1.31	1.02	1.02						
0.5	0	0.1	0.1	0.1	2.16	1.88	1.85	2.1	1.4	1.71		1.84	1.76	1.99	1.92	2.12	1.63	1.97	1.58	1.75	5.01	5.1
0	0.4	0.1	0.2	0.7	2.3	2.27	2.48	1.93	2.17		2.56	2.09	2.17	1.69	2.17	1.66	1.91	1.51			4.98	4.44
0.3	0.8	0.1			3.51	2.87	2.73	2.07	2.97	2.31	3.08	2.47	2.32	1.73	2.65	2.15					4.79	4.04
0.1	0	0.2			2.31	1.69	2.31	1.53	1.99	1.5	2.55	1.93	2.31	1.69	1.78	1.43					4.6	3.54
0.8	0.6	0.3			3.03	2.74		2.02	3.26	2.98	3.01	2.73	2.88	2.55	3.11	2.86						4.17
0.8	0.6	0.4			2.34	2.22	2.08	1.86	1.96	1.73	1.93		1.77	1.7							4.72	4.39
0.3	0.3	0.3			2.62	2.14	2.05	1.99	2.11	2.04	2.36	2.24	2.19	2.11	2.21	2.16					4.12	3.88
0.8	0	0.3	0	0.4	3.2	2.91	3.25	3.25	3.1		2.65	2.92	2.18	2.27	3.11	3.37		2.71	2.35	2.59	5.72	5.7
0	0.5	0.2			2.49	2.65	2.79	2.65	2.71	2.68	2.55	2.76	2.15		1.78	1.91					5.18	5.52
0.1	0.2	0.6			2.65	1.7	2.7	1.45	2.58	1.43	2.43	1.35	2.58	1.35							4.98	3.59
0.3	0.3	0.3			2.44	2.71	2.39	2.76	1.98	1.82			2.03	2.01	1.93	1.94					5.05	4.89
0	0.3	0			2.06	1.89	1.51	1.26	2.53	2.23			2.21	2.09	1.97	1.97					4.74	4.39
0.3	0.5	0.3	0.2	0.1	2.88	2.26		2.18			3.05	2.38						2.28	2.78	2.18		5.54
0.5	0.1	0.6	0	0.5	2.96	2.3		2.22			2.54	1.81			2.34	1.58	2.58	1.68	2.73	2.02		4.82
0.1	0.6	0	0.4	0.1	1.95	1.9	2.02	1.88					2.29	2.13	2.13	1.68	1.61	1.2	1.79	1.68	3.51	3.35
0.5	0.7	0.1	0.1	0.6	1.7	1.6	1.65	1.43	1.79		1.9	1.54	1.56	1.01	1.9	1.43	1.7	1.6	2.09	1.38	4.24	4.02
0.1	0.4	0.3			2.67	2.43	2.7	2.74	2.73	2.74	2.62	2.47	2.88	2.93	2.93	3.2					5.38	5.6
1.2	0.3	0			1.46	1.32	2.44	2.25			1.84	2.05	1.22	1.75	1.79	1.75					8.76	9.22
0	0	0.3			2.24	2.24	2.18	2.12	2.41	2.21	1.89	2.15	2.18	2.09	1.92	1.74					4.39	4.59
0.3	0.1	0.1			1.48	1.69		1.77	1.6	1.92	1.39	2.18	1.74	2.15	1.45	1.98						7.67

ciwd2m	ciwd2l	ciwd3m	ciwd3l	ciwwk2m	ciwwk2l	ciwwk3m	ciwwk3l	ciwwk4m	ciwwk4l	ciwwk5m	ciwwk5l	cbd1m	cbd1l	cbd2m	cbd2l
6.68	7.12	6.68	7.18	6.57	7.09	6.51	7.03							1.89	1.74
5.64	5.58	5.35	5.03	5.42	5.36	5.32	5.2	6.26	6.25	5.03	5.38		2.82	1.83	2.41
6.86		7.44	9.99	6.98	9.99	7.47	9.99					2.47		2.56	
4.27	4.13	5.03	4.85	4.77	4.18	4.71	4.45	4.91	4.68	4.71	4.47	2.41	2.56	2.59	2.27
4.99	4.02	5.24	4.25	4.43	3.46	5.09	4.12			4.97	4.02	1.74	1.81	1.32	1.46
4.37	3.66	4.58	3.77	4.13	3.3	4.6		4.08	3.49	4.29	3.49			1.73	1.83
6.49	6.65	6.45	6.57	6.94	7.06	6.19	6.33							2.39	2.47
4.28	4.93		5.1	4.72	5.06	4.95	4.95	5.08	5.28	5.08	5.14	1.92	1.72	2.61	1.88
4.83		5.06	4.44	4.78	3.99	4.75	4.15	4.73	4.09			1.65	1.56	1.76	
5.09	4.36	5.2	4.46	4.36	3.75	4.77	4.2					2.38	2.5	2.01	2.21
4.52	3.62	4.92	4.04	5.08	4.12	3.85	3.22					2.21	2.82	2.31	2.69
5.65	5.03	5.48	4.9	5.4	4.83	5.5	5						2.96	2.11	2.15
3.4	3.35	3.72		3.79	3.41							1.48	1.56	2.76	2.6
3.83	3.6	4.02	3.83	3.98	3.68	4.17	3.91					0.37	0.7	0.62	0.94
5.7		5.48	5.78	5.14	5.11	5.81	6.04		5.54	5.15	5.18	2.5	2.5	2.5	
5.79	5.89	5.15	5.71	4.54		4.09	4.59					2.31	2.52	1.7	1.91
4.86	3.59	4.69	3.5	4.96	3.49							1.59	1.85	1.69	1.82
3.81	3.78			4.69	4.31	5.03	4.84					1.39	1.65	2.64	2.69
5.23	5.15			4.79	5.03	4.44	4.29					1.54	1.83	0.99	1.08
		6.31	5.54						5.3	5.79	5.16		1.44		
		5.56	4.65			5.2	4.13	5.52	4.41	5.8	4.77		1.79		
				3.9	3.67	3.97	3.6	3.15	2.86	3.58	3.69	2.47	2.63		
4.49		4.38	4.02	4.38	3.79	4.18	3.82	4.02	3.96	4.55	3.85	1.65	1.83	1.53	
5.49	5.67	5.11	5.74	5.61	5.89	5.84	6.26					1.25	1.14	1.16	1.01
		9.52	9.45	8.23	8.42	8.18	8.95					1.66	2.17		
4.77	4.91	4.24	4.47	4.79	4.77	4.33	4.45					2.5	2.38	2.18	2.03
7.67	7.93	7.61	8.22	7.87	8.25	7.35	7.73						2.93	2.91	2.67

cbd3m	cbd3l	cbwk2m	cbwk2l	cbwk3m	cbwk3l	cbwk4m	cbwk4l	cbwk5m	cbwk5l
1.86	1.71	2.03	1.83	2.06	1.89				
2.12	3.93	2.06	2.59	2.12	2.79	1.13	1.69	2.41	2.62
1.98	1.6	2.44	1.51	1.95	1.68				
1.8	1.51	2.09	2.12	2.18	1.95	1.89	1.69	2.09	1.89
1.07	1.27	1.87	2.06	1.19	1.37			1.34	1.49
1.52	1.73	1.96	2.17	1.44		2.01	2.01	1.8	2.01
2.45	2.62	1.95	2.12	2.7	2.82				
	1.71	2.16	1.8	1.96	1.86	1.86	1.53	1.83	1.69
1.57	1.53	1.83	1.98	1.83	1.8	1.88	1.9		
1.99	2.11	2.72	2.82	2.38	2.31				
1.89	2.32	1.7	2.22	2.95	3.11				
2.33	2.22	2.34	2.33	2.27	2.06				
2.47		2.38	2.51						
0.42	0.75	0.5	0.87	0.29	0.65				
2.5	2.35	3.08	2.96	2.41	2.18		2.56	3.07	2.92
2.34	2.34	2.92		3.4	3.45				
1.86	1.91	1.49	1.92						
		1.76	2.18	1.44	1.7				
		1.45	1.25	1.82	1.97				
1.44	1.46						1.7	1.94	1.82
1.94	1.98			2.3	2.49	2	2.22	1.7	2
		2.09	2.31	2.02	2.38	2.83	3.11	2.4	2.27
1.65	1.8	1.65	2.08	1.81	2	1.95	1.88	1.51	1.97
1.48	1.51	1.02	0.79	0.78	0.42				
0.83	1.9	2.14	2.98	2.19	2.45				
2.67	2.5	2.12	2.18	2.59	2.5				
2.93	2.38	2.64	2.35	3.23	2.88				