IMPACT OF RESPIRATORY MOTION ON IMRT (INTENSITY MODULATED RADIOTHERAPY) OF THE CHEST WALL IN POST-MASTECTOMY BREAST CANCER PATIENTS: A DOSIMETRIC COMPARISON WITH 3D CONFORMAL RADIOTHERAPY

DISSERTATION

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CONTENTS

1. INTRODUCTION

The field of oncology has expanded drastically in the past decade, in terms of both treatment options and expertise. Most of these options while improving overall survival and / or quality of life have increased the total expenditure of cancer treatment.

The treatment options in breast cancer, a common cancer among women, are an example of this expansion that has occurred in the world of oncological treatments. We have moved from the era of radical surgeries to breast conservations, from CMF regimen of chemotherapy to anthracyclines and taxanes, various hormonal and targeted therapies, conventional radiation therapy and 3D conformal tangents to intensity modulated radiotherapy with image guidance, tomotherapy and gated radiotherapy.

Various studies have portrayed the benefits of intensity modulated radiotherapy over 3D conformal tangents as the technique of radiation delivery for post-mastectomy chest wall, while mentioning that respiratory movement is a major area of concern(1). Hence, before moving on to higher technologies such as IMRT or Tomotherapy, it was important to compare the new technology (IMRT) with the standard technique (3D conformal tangents) taking into account the effect of respiration. This was increasingly important in our society where finances are still limited.

It is predicted that the effect of respiratory motion on IMRT plan may be more in patients with larger chest wall movement or tidal volume while respiratory motion may not affect 3D-CRT as much. Hence, this study was designed to correlate the magnitude of respiratory motion and its effect on IMRT versus 3D-CRT plan.

2. REVIEW OF LITERATURE

2.1 BREAST CANCER WORLD WIDE

Cancer of the breast in women is a major health burden worldwide. It is the most common cancer among women as well as the primary cause of cancer death among women globally (22.9% of all new cancers in women and 13.7% of cancer deaths)(2). The incidence of breast cancer has increased considerably over the past few decades. It doubled between 1975 and 2000 and seems to double again between then and 2030(3). There is no population around the world with a low risk for breast cancer and this doubling is predicted to affect the lower income and lower middle income countries the most.

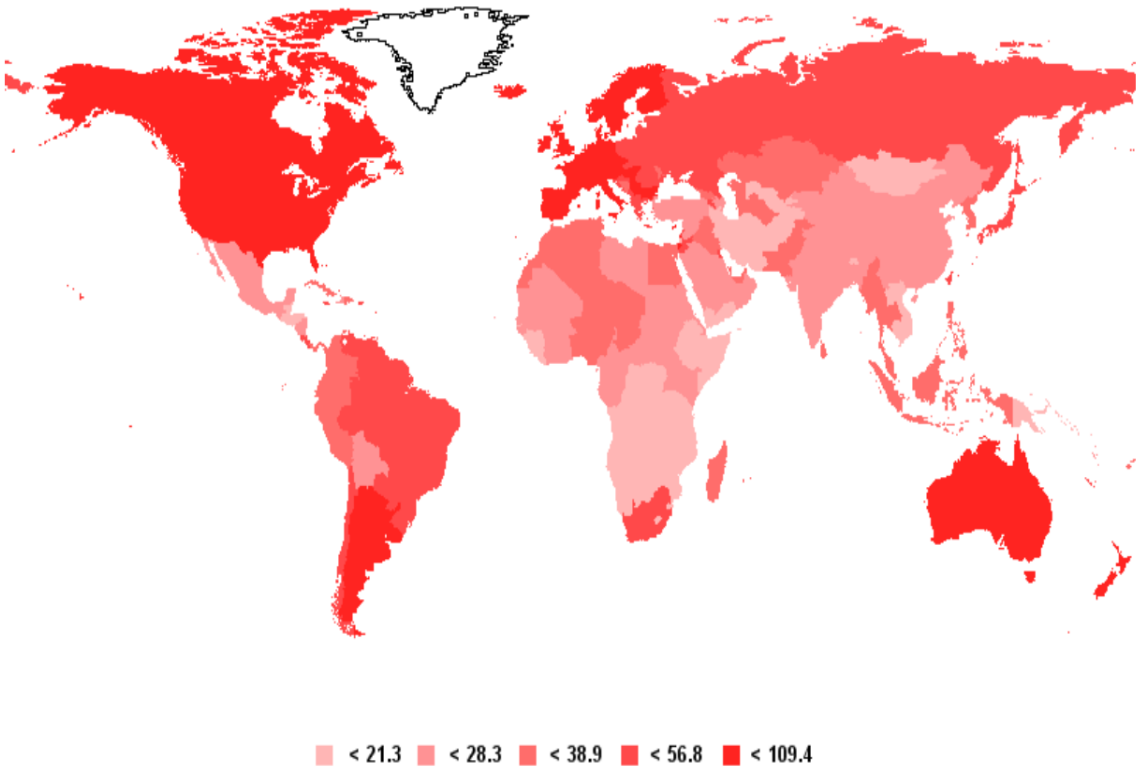


Figure 2.1: Estimated age standardised incidence rate of breast cancer per 100,000 population around the World, all ages (4)

2.2 INDIAN SCENARIO

In the past the incidence of breast cancer in India was low. But with the turn of the century incidence of breast cancer has been steadily rising. The Indian cancer registries have shown a hike of about 0.5% per year incidence between the years 1991-2005 and it varies greatly between the urban and rural areas of India. The Mumbai cancer registry shows an increase of 1.1% per annum over a 30 year period from 1975-2005(5). National Cancer Registry Program (2006- 2008) reported an incidence of 33 and 32.1 per 100000 population in Mumbai and Chennai, while Pune and Bhopal had an incidence of 24.4 and 25.5 per 100000, and the rural India had an incidence of 7.4 per 100000 (NCRP, unpublished data). This variation across our country has hindered the widespread use of newer technologies in the treatment of breast cancer.

Unlike the western population, most patients have locally advanced disease at presentation. Hence, modified radical mastectomy is the most commonly practiced surgery for breast cancer in India.

Table 2.1: The stage at presentation of breast cancer in various cities of India(6)

Stage	**Frequency in Percent**			
	Mumbai	**Trivandrum**	**Chennai**	**Lucknow**
I	7.8	4.4	1	4
II	57.4	42.3	23	33
III	28.9	40.5	52	47
IV	5.9	12.8	24	9

2.3 OVERVIEW OF BREAST CANCER MANAGEMENT

The management of invasive breast cancer is based on the clinical extent and pathological characteristic of tumour, in addition to the age of patient (menopausal status), biological prognostic factors and preference of the patient.

Although surgery is the mainstay of treatment in non-metastatic breast cancers, the other modalities including chemotherapy, endocrine therapy, targeted therapy and radiation therapy have added benefits if administered according to the indications. There are various prognostic factors which determine the sequence and combinations of therapy. Introduction of multimodality treatment (surgery, chemotherapy and radiation therapy) reduced breast cancer mortality by 18% and improved overall survival(7).

In the recent years a paradigm shift has occurred in the surgical management of breast cancers, from radical mastectomy to breast conservation surgeries in the early stage breast cancer and issues regarding quality of life are given equal importance to overall survival. The novel molecules (hormonal / targeted therapies) and chemotherapeutic drugs have improved overall survival with tolerable side effects. At the same time, advanced radiation therapy techniques have made treatment of post-mastectomy chest wall and post breast conservation whole breast treatments more effective.

2.4 ROLE OF RADIATION THERAPY IN BREAST CANCER

The use of radiation therapy in the treatment of breast cancer dates back to as early as 1890’s. The first X-ray machine was assembled in Chicago in 1896 by Emile Grubbe and it has been documented that a patient with recurrent breast cancer was treated in the same year.

In the present era, radiation therapy plays a major role in the treatment of both early stage and locally advanced breast cancers. In early stage of breast cancer, it forms a major part of breast conservation therapy while in locally advanced stage, post mastectomy radiotherapy is indicated only in high risk patients (especially for tumours > 5cms in size and > 4 nodes positive disease).

However, in India, mastectomy is still the most common and this is because of the following factors

1. Tumour factors**:** locally advanced nature of disease at presentation

2. Patient factors: -

- Concerned about disease free survival than cosmetics
- Finances
- Poor adherence to follow up regimes

3. Physician factors: -

- Surgical skill and radiotherapy equipment required for breast conservative therapies are not easily accessible across centres in India.

Adjuvant radiation therapy in breast cancer not only involves treatment of chest wall/ breast, but also the draining lymph nodal regions according to specific indications. Radiation to chest wall/ breast in itself is challenging as it involves treatment of a strip of curvilinear structure while sparing the underlying lungs and heart. Treatment of adjacent lymph node regions makes radiation therapy planning in breast cancers more complex.

Post mastectomy radiotherapy: - The indications for post mastectomy radiation therapy have been defined from the results of various randomized trials like the Danish trial and British Columbia trial. Benefit in terms of local control and survival was found in

stages II / III and node positive breast cancers(8,9). Studies showed that the addition of post mastectomy radiotherapy reduced loco regional recurrence rate by 2/3rd to3/4th when compared to the groups that did not receive radiotherapy(10,11)

On the other hand, the role of post mastectomy radiotherapy in T1/T2 tumour, grade 1 / grade 2 with 1-3 lymph nodes positive is still debatable. The indications in this group of breast cancers is expected from the results of the on-going Supremo trial(12). Various factors such as size of tumour (>4 cm), close/positive margins, lymph vascular invasion, extra capsular extension, ER/PR/Her2 neu status, grade of tumour are known to affect the loco regional recurrence rate, and these factors contribute significantly towards the decision making.

Various techniques of post mastectomy radiation therapy are available, such as external beam therapy with photons / electrons. Single or a combination of techniques is used and all modalities aim at maximizing dose to chest wall while minimizing dose to underlying critical structures such as lungs and heart.

Within external radiotherapy, the technological improvement has provided us with various approaches to deliver the radiation dose. A few of them are:

- Conventional therapy with tangential beams
- Electron Therapy
- Conformal therapy
- Intensity modulated radiotherapy
- Image guided radiotherapy
- Arc therapy (Volumetric Modulated Arc Therapy –VMAT)
- Tomotherapy

Organs at risk in post-mastectomy radiotherapy and its effect:

1. **Lungs-**

The incidence of radiation pneumonitis is low in chest wall only radiotherapy but the addition of supraclavicular and axillary radiation has shown to increases its incidence. Hockey stick radiation field which includes inter-mammary lymph nodal irradiation further increases its incidence. In the British Columbia experience, it has been documented that 1/164 patients treated with sequential chemotherapy and radiotherapy developed symptomatic radiation pneumonitis requiring corticosteroid therapy(13). The characteristic clinical features of radiation pneumonitis are cough, fever and non-specific infiltrates on Chest X-ray.

Table 2.2: RTOG clinical grading of Radiation pneumonitis

Grade	Definition
1	Mild dry cough or dyspnoea on exertion requiring clinical intervention
2	Cough requiring narcotic anti-tussives or dyspnoea not at rest
3	Severe cough not responding to narcotics or dyspnoea at rest; Intermittent oxygen or steroids may be required
4	Continuous oxygen or assisted ventilation
5	Fatal

2. **Heart-**

Though infrequent, acute and subacute complications of post-mastectomy radiotherapy such as pericarditis and cardiac failure have been reported. At the same time, long term complication of cardiac related morbidity has been reported more commonly. A

meta-analysis of 10 randomised trial of PMRT has shown that the standard mortality ratio for heart disease was 1.62 times higher for irradiated patients ($p<0.01$)(14). Though there are various factors such as chemotherapeutic regimen used and patient's comorbid illnesses that add to the risk of long term cardiac toxicity, the most important treatment related factor is the volume of heart irradiated. Volume of heart irradiated increases considerably when internal mammary lymph nodal irradiation is done.

Recent studies have shown that the doses to the heart from PMRT can be considerably reduced by using megavoltage energies and modern planning techniques.

3. **Brachial plexus-**

Injury to brachial plexus in patients treated for breast cancer may be multifactorial (axillary surgery, radiation therapy and chemotherapy). However incidence of brachial plexopathy due to radiation therapy is rare and is related to the use of a third field (supraclavicular +/- axillary fields) and dose to axilla. In the JCRT (Joint centre for Radiation therapy) experience, where axillary dose was less than or equal to 50 Gy, the incidence of plexopathy was only 0.6% in the absence of chemotherapy and 4.5% with chemotherapy(15). The rate of permanent plexoplathy was also dependent on delivered dose and fraction size

4. **Contralateral breast**

Women with breast cancer have a baseline risk of developing contralateral breast cancer at the rate of 0.3% to 1% per year(16,17). Various cancer registries and case control studies have revealed a slightly increased risk in women treated with radiation therapy(18). This increased risk may be due to the small dose of scattered radiation deposited in the contralateral breast during radiation. However, this increased risk seems to be confined to

patients younger than 40-45 years of age at the time of treatment. The analysis of Connecticut Tumour registry, revealed that patients of age 45 or younger at the time of radiation exposure had an increased relative risk of 1.59 (95% confidence interval- 1.07 to 2.36) and, at an average dose of 1 Gy delivered to contralateral breast, the estimated relative risk was 1.21(19).

2.5 RADIATION THERAPY TECHNIQUES IN BREAST CANCER (POSTMASTECTOMY SETTING)

1. **Conventional therapy - Tangents**:

The chest wall has been conventionally treated with 2 tangential beams in contrast to AP-PA beams, in order to reduce the dose to lungs and heart. Various parameters such as Central Lung Distance (CLD), Maximum Lung Distance (MLD), Average Lung Distance (ALD) and Maximal Heart Distance (MHD) are measured from a simulator film to predict the volume of lung and heart being irradiated, which in turn predicts the probability of radiation induced pneumonitis or cardiac toxicity. A CLD of 1.5cm, 2.5cm and 3.5 denotes the involvement of 6%, 16% and 26% of lung respectively and a CLD of than 3 cm in left side breast cancer, resulted in irradiation of a significant volume of heart. Similarly, grouped ALD (average of superior and inferior lung distance) values of < 2 cm, 2-3 cm and > 3 cm show an increasing trend of radiation pneumonitis of 4%, 6% and 14% respectively, though not statistically significant(20).

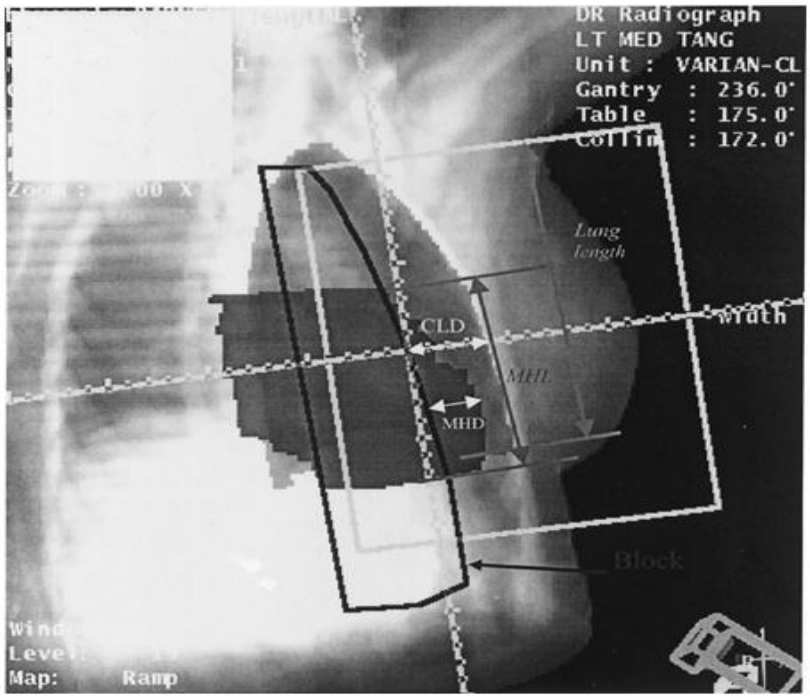


Figure 2.2: Computerised radiograph showing medial tangential view of a whole breast radiotherapy plan with the various parameters of plan evaluation such as CLD (central lung distance) and MHD (maximum heart distance) marked.

2. Conformal Radiotherapy

The concept of CT based volume delineation and planning was introduced in the late 80's when a CT extension of X-ray simulator was enabled. This improved field set up and dose calculations, though only limited CT slices were available. However, the optimal use of 3D based planning became possible when CT simulators replaced X-ray simulators and dose calculations were no more based on target volume alone but also on normal tissue constraints.

A conformal therapy plan employs the use of multiple tangential beams of varying weightage to produce homogenous coverage of target volume as well as sparing of normal tissues.

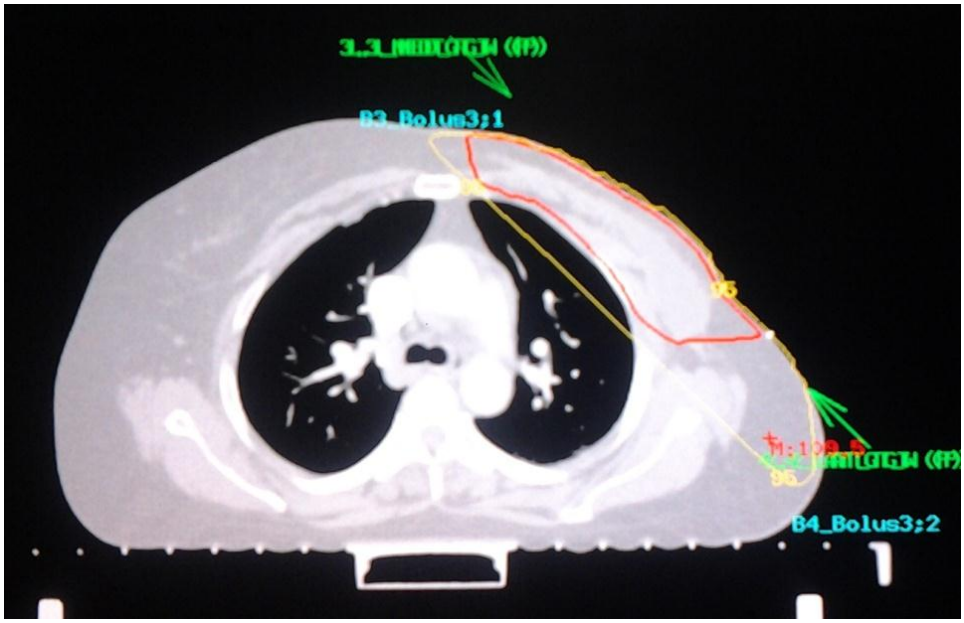


Figure 2.3: An axial section of thorax showing a 3D conformal therapy dose distribution. The 95% isodose line is covering the target as well as neighbouring normal tissue.

The assessment of dose delivered to target volume or normal tissue by conventional two dimensional planning is highly inadequate as it is based on rough estimates. Meanwhile, 3 dimensional treatment planning allows more accurate analysis of dose to target as well as normal tissue with the aid of dose volume histograms (DVH). In addition to the availability of DVH, analyses of plans allows the use of biologic effect models, such as normal tissue complication probability (NTCP) models to estimate toxicity risk. Therefore, 3D treatment planning is a powerful tool that can compare treatment techniques for adequacy of target coverage and complication risk.

Treatment of chest wall and regional lymph nodes pose many challenges to Radiation Oncologists. There is no single technique accepted as gold standard and hence multiple complex field arrangements have been used for treatment. These have led to high radiation dose to large volumes of heart and resulted in increased rates of pericarditis(21). Radiation induced ischemic heart disease is also a significant treatment related morbidity(14).

Similarly, risk of radiation pneumonitis also limits the choice of radiation techniques depending on the body habitus and in field lung volumes.

The risks of cardiac and pulmonary toxicities are highly dependent on the dose received by the organ and this is dependent on the technique of radiation delivery. Hence accurate estimate of these risks are crucial for decision making when selecting the fields arrangement for treatment. Though theoretically 3D conformal tangents technique involves a reduction in the volume of normal tissue receiving high dose, these beams of uniform intensity result in lung toxicity which is directly proportional to the volume of lung within the radiation field.

3. Intensity modulated radiotherapy

Since 1960's physicists have attempted to develop ways and means of altering the spatial distribution of the intensity of treatment beams. Initially, metallic beam modifiers were used for this purpose. These resulted in better coverage of dose to targets. Beam blocks, wedge filters, bolus and beam compensators were the beam modifying devices that were used in 2- dimensional and 3- dimensional radiotherapy till the 1990's. It was then that computer controlled Linear Accelerators with fully motorised Multi-Leaf Collimators were launched and 3D treatment planning computers with inverse planning algorithms for optimisation of dose were developed. New Linear Accelerator based IMRT treatment delivery systems including binary multi-leaf intensity modulating collimator, step and shoot MLC, dynamic MLC and intensity modulated arc therapy were developed. Two other types of IMRT equipment, namely Cyber Knife and Helical Tomotherapy have also been launched and are commercially available.

Dosimetrically, IMRT has the ability to deliver the prescribed dose to the delineated target volume with precision, while sparing the adjacent normal tissue structures. It

basically differs from common tangent based plan by having multiple beams which are directed to the target from all around and these beams are further modulated in their intensity by the moving multi-leaf collimators. A computer aided optimization process is used to determine customized non uniform fluence distributions to attain certain specified dosimetric and clinical objectives.

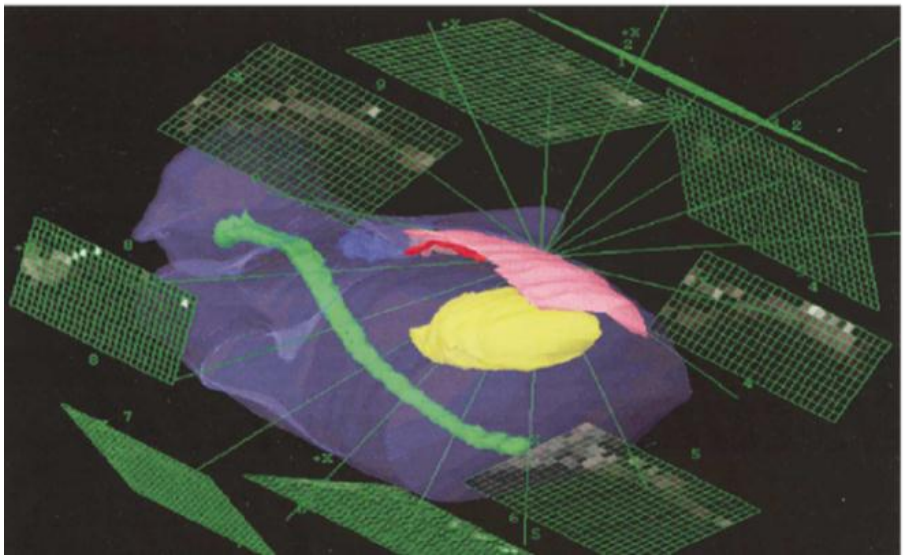


Figure 2.4: A three dimensional view of nine axial beams showing beamlet intensities around the chest wall target (pink). Other structures shown are heart (yellow), supraclavicular nodal region (blue), internal mammary chain (red) and spinal cord (green)(22)

Benefits of intensity modulated radiotherapy in post mastectomy breast cancer:

There is a significant body of literature showing that inverse planned intensity modulated radiotherapy leads to a more favourable dose distribution compared to 3 dimensional planned conformal radiotherapy of whole breast after breast conservation (23–28)]. Data on IMRT of the chest wall in post-mastectomy breast cancer patients are scarce in literature. However, there are distinct differences in the target volume of conserved breast and chest wall. The shape of the target (chest wall) is usually shallower. In addition, while contouring for whole breast radiotherapy, the pectoralis muscles, chest wall muscles and ribs may be excluded in stage I-IIA breast cancers, whereas these structures are included

in the target volume of chest wall. Due to these differences, results of a dosimetric study on radiotherapy to whole breast are not completely applicable to radiotherapy of the chest wall.

Hence, a focussed literature review on intensity modulated radiotherapy in post mastectomy breast cancer was done and it revealed that there was definite benefit of the same when compared to 3DCRT, such as:

1. Tangential field IMRT reduces the ipsilateral lung dose volume (D30 by 43%) when compared to 3DCRT tangents.
2. Tangential field IMRT reduces the heart dose volume in the left sided breast cancer patients (V70 by 46%) when compared to 3DCRT tangents(1).
3. Further search projected the benefits of IMRT technique when regional lymph nodal irradiation was required along with chest wall irradiation.

The known pitfalls in conventional radiotherapy in this setting are:

1. Under / over-dosage at the junction of the matched chest wall and supraclavicular fields
2. Inhomogeneous distribution due to matching of separate fields for regional lymph nodes irradiation
3. Under-coverage due to the routine mean depth to which the dose to regional lymph nodes is prescribed- as the depth varies from person to person.

IMRT technique was able to overcome these pitfalls and provide a homogenous dose to the various targets (chest wall and regional nodal area) while maintaining a similar dose to normal tissues. In fact, IMRT technique was able to reduce the V20 (volume receiving 20 Gy) of ipsilateral lung to 28% when compared to 32% - 45% with 3D conformal technique(29).

Issues in clinical implementation of Intensity modulated radiotherapy, especially in post mastectomy treatment are:

1. High cost
2. Complex and time consuming procedures
3. Dedicated quality assurance programs
4. Management of inter-fraction changes- set up errors
5. Management of intra-fraction changes- movement with respiratory motion

Hence, though IMRT is theoretically capable of delivering conformal dose with high degree of precision, it may not be true clinically due to various uncertainties in the radiotherapy process.

2.6 UNCERTAINTIES IN RADIATION THERAPY FOR BREAST CANCER

1. **Set up errors:**

Studies have shown wide variations in systematic errors of 1.0-14.4 mm and random errors of 1.7-5.8 mm in tangential breast / chest wall radiotherapy(30). The use of immobilisation devices have significantly improved set up reproducibility in breast cancer treatments. Various immobilisation devices have been examined, such as wedge boards with or without arm supports, cushion with arm handle, plastic mask, vac-fix etc. It was also established that arm handles further reduced set up errors(31).

2. **Respiratory motion induced errors**:

Breast / chest wall is mobile during respiration with a motion amplitude as high as 0.8 to 10 mm in the antero-posterior direction(32). This movement is capable of contributing significantly to geometric uncertainties.

Most research on respiratory motion in breast cancer radiotherapy has been done on conserved breasts. One of them established the set up deviation as well as breast movements during normal and deep breathing with and without respiratory training. The mean set up deviation was 1.3 mm (SD+/-0.5 mm), 1.3 mm (SD +/- 0.3 mm) and 4.4 mm (SD +/- 2.6 mm) in the medio-lateral, supero-inferior and antero-posterior dimensions respectively. The mean set up deviation was added to the post training breast movement to give the cumulative maximum movement error (CMME). The mean CMME was recorded for a group of 5 patients as 3.4 mm, 4.5 mm and 7.1 mm in the medio-lateral, supero-inferior and antero-posterior dimensions respectively(33). Though these values aren't directly applicable in the post-mastectomy setting it gives an idea regarding set up deviation as well as breast movement with respiration.

2.7 RESPIRATORY MOTION AND IT EFFECT ON RADIATION THERAPY FOR BREAST CANCER

1. **Image acquisition limitations**

If respiratory motion is not accounted for during imaging, motion artefacts are created which distort the target volume.

2. **Treatment planning limitations**

Planning Target Volumes (PTV) should be large enough to ensure target coverage through the treatment delivery. In case of post mastectomy breast cancer, expanding the target volume to account for respiratory motion would mean extending anteriorly into air and posteriorly into lung. This increases lung dose. This expansion is not entirely possible in IMRT planning. A technique of skin flash is used to account for anterior shift with respiration.

3. **Radiation delivery limitations**

Radiation delivery in the presence of organ motion causes an averaging or blurring of static dose distribution over a path of motion. This displacement results in deviation between intended and delivered dose distribution. For non IMRT / conventional radiation where the dose gradient in the center of field is small, the effect is manifested by blurring of dose distribution with anatomy moving near the beam edge. This effect may be exacerbated in IMRT delivery due to its conformal nature and steep fall off of dose gradient.

Analysis of inter-fraction and intra-fraction variation during tangential breast radiotherapy using Electronic Portal Imaging Device (EPID) revealed the effect of respiratory motion and movement during treatment was minimal. The maximum range of central lung distance for any patient on one day was 0.25 cm. However, the day to day set up variation was greater, with CLD values ranging from 0.59 cm to 2.94 cm and it resulted in change in corresponding lung and heart areas during individual treatment fractions(34).

2.8 MAGNITUDE AND MEASUREMENT OF RESPIRATORY MOTION

1. **Mechanics of breathing**

The lung primarily functions to facilitate gas exchange (O_2 and CO_2) between blood and air, thereby maintaining normal pressure in arterial blood. Respiration being an involuntary movement continues even if the person is unconscious and breathing is non-rhythmic, unlike cardiac motion. Nevertheless, it is possible to control the pattern of breathing.

Respiration is composed of 2 components, inspiration and expiration. The diaphragm is the most important muscle of inhalation. As the diaphragm contracts it forces the abdomen inferiorly and anteriorly, thereby increasing the size of chest cavity in the supero-inferior direction. The intercostals muscles which connect the ribs also play a part in normal inspiration. Contraction of these muscles, cause the chest wall to expand antero-posteriorly. Exhalation on the other hand is a passive process where in the lungs recoil into their pre inspiration position.

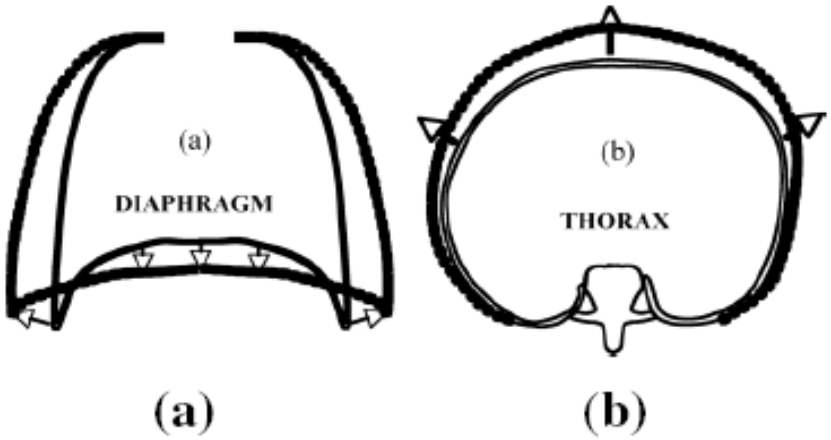


Figure 2.5: (a) During inhalation, the diaphragm contracts, the abdomen is forced down and forward, and the rib cage is lifted. (b) The intercostal muscles also contract to pull and rotate the ribs, resulting in increasing both the lateral and anterior- posterior (AP) diameters of the thorax(35)

2. **Measuring respiratory motion:**

Person's breathing pattern varies in magnitude, regularity and period. It varies from person to person as well as time to time in the same person. Respiratory motion varies markedly between persons that an individual approach to respiratory management is advised. Audio-visual feedback has demonstrated to improve respiratory reproducibility.

3. **Motion observables**

There is no fixed pattern of respiratory behaviour for a particular person prior to observation and treatment. Each person differs in terms of quiet versus deep, chest versus abdominal and healthy versus compromised. Hence, it has been shown that every person's respiratory pattern has to be analysed prior to treatment.

Both surface markers and spirometers provide signals that are surrogate of tumour motion. Their applications should be validated by performing fluoroscopic and CT imaging studies.

2.9 RESPIRATORY MOTION AND ITS EFFECT ON INTENSITY MODULATED RADIOTHERAPY FOR BREAST CANCER

As mentioned earlier, IMRT is gaining popularity owing to its ability to conform the spatial distribution of the dose deposited in a patient more effectively especially in case of targets in thoracic cavity and abdominal cavity where the organs at risk are many. However respiratory motion is thought to hinder the actual benefit of IMRT. In IMRT, beam intensity gradients are not limited to beam edges. Thus respiratory motion may result in major dose variations. This effect will be exacerbated by the interplay between motion of leaves of multileaf collimators and component of target motion perpendicular to the beam.

Various studies have also documented dosimetric errors using single MLC based IMRT treatment, summing upto 20% within the field (in low dose gradients) and even higher in the edge of the field (high dose gradient region). These studies were film based and didn't take into account target deformation(36,37). Thus effect of respiratory motion on dose is of prime concern in IMRT.

Yu et al demonstrated that fluence variations within the target tend to average out over a typical course of 25-30 fractions(38).]. This was confirmed by other studies also. However, these studies assumed 1 dimensional movement and didn't take into account target deformation. Thus it was concluded that fractionation alone cannot be relied upon, especially for movement > 1cm.

From the literature we know that the mean amplitude of chest wall movement with respiration is 8-10 mm. Considering the small amplitude, the influence of respiratory motion on dose may not be marked. However, it can be postulated that patients with large chest wall movement with respiration (8 mm) are likely to have significant target under-coverage. This may also reflect as over-dosage to organs at risk.

2.10 RESPIRATORY MOTION MANAGEMENT TECHNIQUES AND ITS BENEFITS IN BREAST CANCER RADIOTHERAPY

Techniques:

1. **Motion encompassing methods**

   The 3 techniques possible for acquiring CT scan that accounts for motion are

   - Slow CT scan
   - Inhale and Exhale breath hold technique
   - 4D CT scan

2. **Respiratory gating methods**

Respiratory gating involves delivering radiation only within a particular predetermined phase of breathing cycle. The position and width of this phase also called a gate is determined by monitoring the patient's respiratory motion, using an external surrogate marker or internal fiducial. It requires special equipment to track the target in the

form of external markers or internal fiducials and increases the overall treatment time. This is more pronounced in case of IMRT where the overall treatment time increases by 4-15 fold over a conventional treatment.

3. **Breath hold methods**

It was found that breath hold techniques (in deep inspiration) facilitated the movement of heart posteriorly and inferiorly away from the chest wall thereby reducing the cardiac and pulmonary toxicity. However, these techniques required meticulous training of the patient and the compliance was poor.

It is possible to incorporate breath holds into IMRT delivery sequence, that is to segment the leaf motion sequence into active and inactive periods corresponding to the breath hold and rest periods.

4. **Real time tumour/ target tracing methods**

More sophisticated than breath-hold technique incorporated into IMRT delivery sequence are methods that involve synchronization of IMRT delivery with respiratory motion. The advantage of this method is that patient is allowed to breathe freely, and linear accelerator operation may not be interrupted.

Benefits of respiratory motion management techniques:

The use of respiratory gating technique has proven to reduce the dose delivered to the heart in breast radiotherapy especially in left sided breast cancer patients. There was a 15.5% decrease in average mean dose to the heart(39). Similarly Korreman et al showed that DIBH (deep inspiratory breath hold) technique and IG (inspiratory gating) technique decreased the incidence of pneumonitis(40).

2.11 RESPIRATORY MOTION MANAGEMENT TECHNIQUES IN THE INDIAN SCENARIO OF BREAST CANCER

As seen above, respiratory motion management techniques either needs meticulous patient training, patient cooperation and/ or sophisticated tumour tracking equipment. In addition, it is a time consuming process which requires considerable human resource as well as machine time. Thus its relevance in the Indian scenario of high patient load and poor finances is questionable.

2.12 CHOICE OF RADIATION THERAPY TECHNIQUE FOR BREAST CANCER ON THE BASIS OF RESPIRATORY MOTION

As respiratory motion management techniques are still limited to a few selected patients especially in India, the options of radiation therapy technique is restricted to 3D conformal tangents and Intensity modulated radiotherapy. This study aims at formulating a protocol for selection of appropriate radiation therapy technique on the basis of patient's respiratory pattern.

3. MATERIALS AND METHODS

3.1 AIMS AND OBJECTIVES

Aim: To study the dosimetric effect of respiratory motion on intensity modulated radiotherapy to the chest wall in patients with carcinoma breast and compare it with the respiratory motion effect on 3D conformal tangents based plan.

Null Hypothesis**:**

"The impact of respiratory motion on IMRT of the chest wall in post-mastectomy breast cancer patients is not significant compared to 3D conformal tangents."

Primary Objective:

1. To determine the reduction in target coverage that can occur with respiratory motion when treated with IMRT and 3D CRT

2. To generate criteria for the selection of patients requiring post-mastectomy radiation for choosing techniques of delivering radiation therapy, on the basis of lung excursion data.

Secondary Objectives:

1. To see whether the lung and cardiac toxicity are under reported as compared to actual, when plans are calculated or evaluated on a free breathing CT scan

3.2 DURATION AND DESIGN OF STUDY

Duration: 12 months

November 2012 to October 2013

Design: Prospective trial

3.3 SETTING

Table 3.1: Time line and setting

Activity	Location	Timeline
Recruitment of patients	Radiotherapy Unit I OPD	November 2012- October 2013
Data collection	Radiotherapy Department	November 2012- October 2013

3.4 PARTICIPANTS

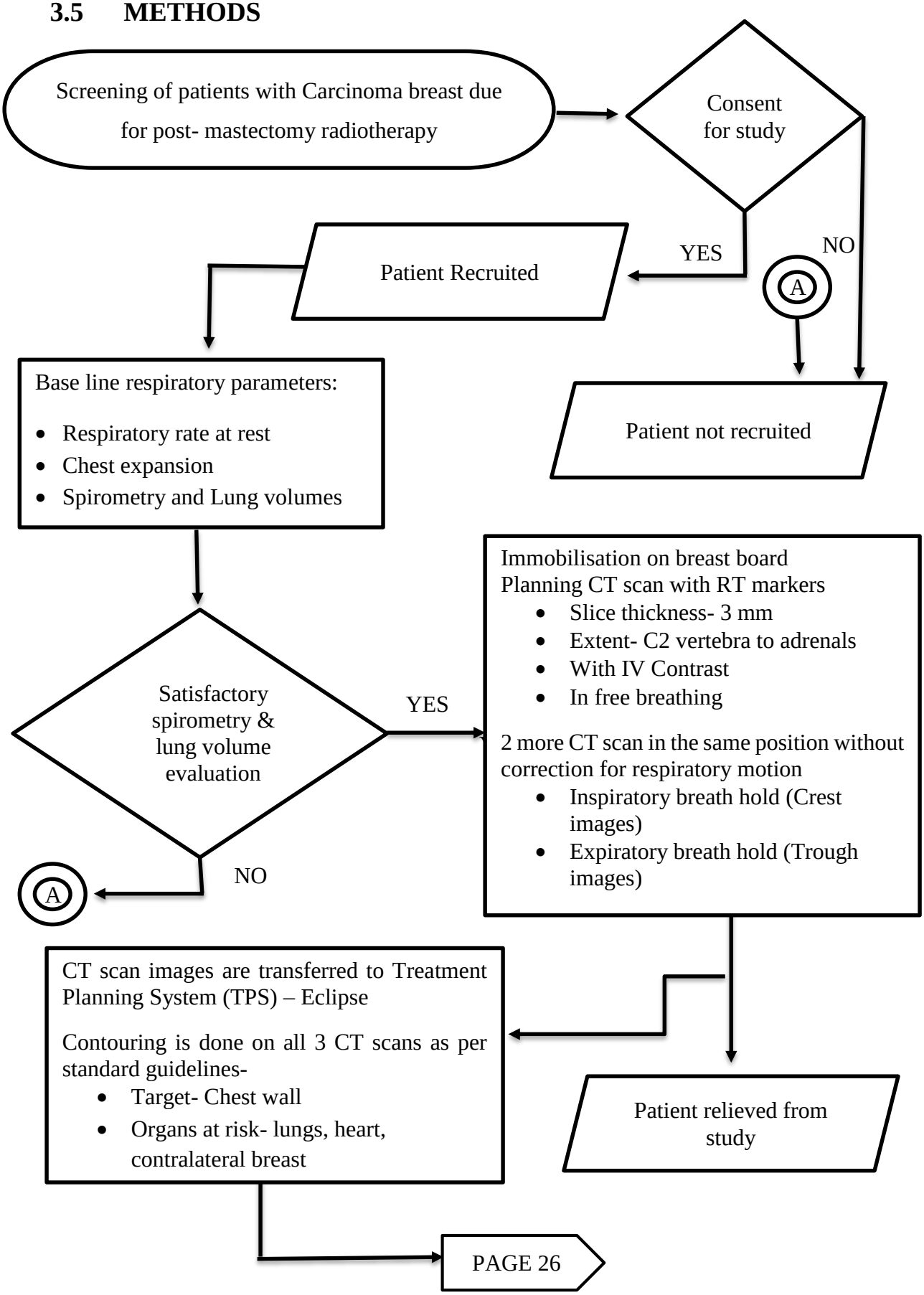
Inclusion criteria:

1. Women with breast cancer who require post mastectomy radiotherapy to chest wall
2. Patients who consent for undergoing 3 sets of CT scan in the same sitting and use of images for study purpose

Exclusion criteria:

1. Persons with restrictive/ obstructive lung disease
2. Reconstruction flaps

3.5 METHODS


Screening of patients with Carcinoma breast due for post- mastectomy radiotherapy
Consent for study
YES
NO
Patient Recruited
A
Patient not recruited
Base line respiratory parameters:
Respiratory rate at rest
Chest expansion
Spirometry and Lung volumes
Satisfactory spirometry & lung volume evaluation
YES
NO
A
Immobilisation on breast board
Planning CT scan with RT markers
Slice thickness- 3 mm
Extent- C2 vertebra to adrenals
With IV Contrast
In free breathing
2 more CT scan in the same position without correction for respiratory motion
Inspiratory breath hold (Crest images)
Expiratory breath hold (Trough images)
CT scan images are transferred to Treatment Planning System (TPS) – Eclipse
Contouring is done on all 3 CT scans as per standard guidelines-
Target- Chest wall
Organs at risk- lungs, heart, contralateral breast
Patient relieved from study
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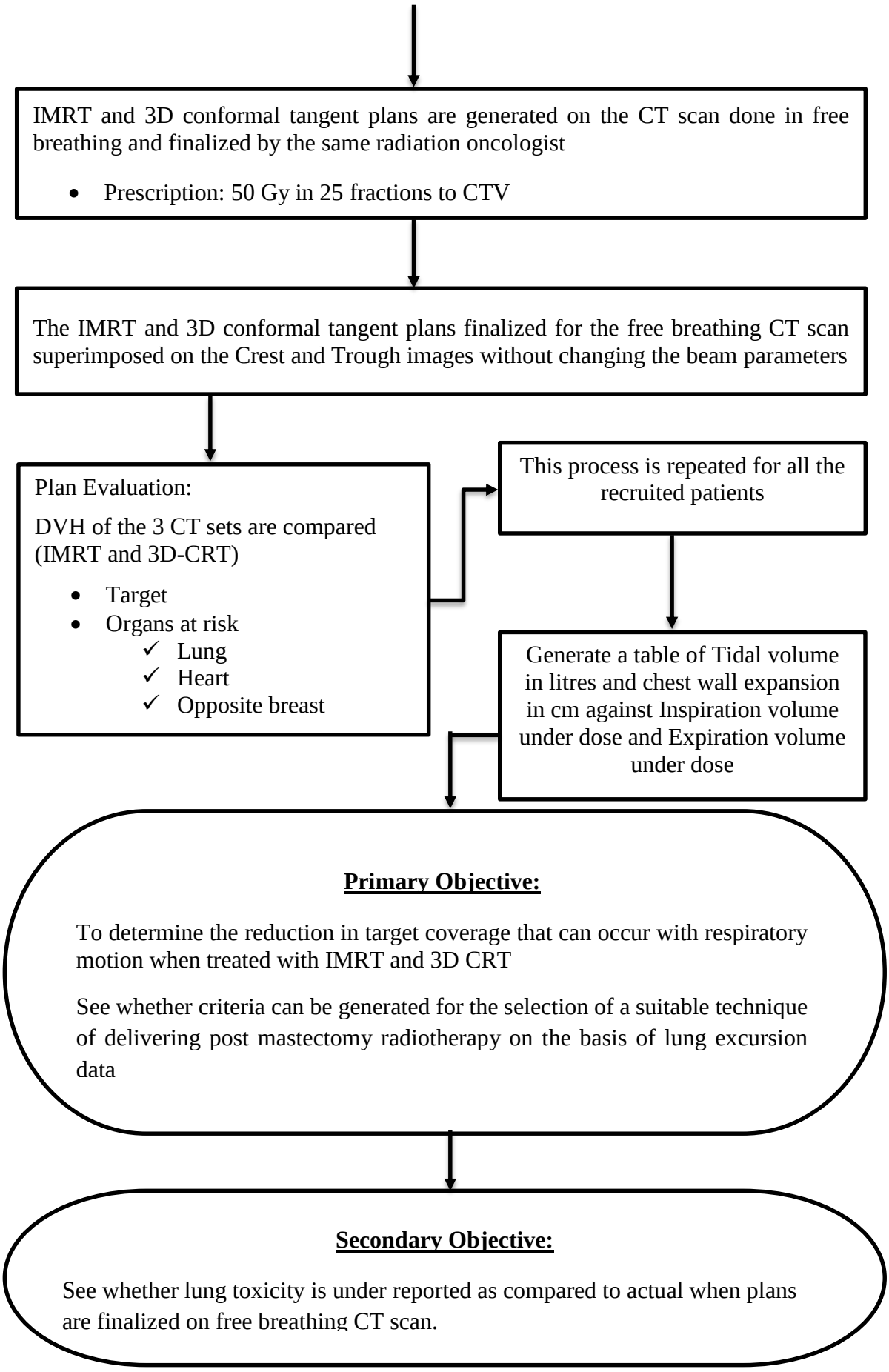

IMRT and 3D conformal tangent plans are generated on the CT scan done in free breathing and finalized by the same radiation oncologist
• Prescription: 50 Gy in 25 fractions to CTV
The IMRT and 3D conformal tangent plans finalized for the free breathing CT scan superimposed on the Crest and Trough images without changing the beam parameters
Plan Evaluation:
DVH of the 3 CT sets are compared (IMRT and 3D-CRT)
• Target
• Organs at risk
✓ Lung
✓ Heart
✓ Opposite breast
This process is repeated for all the recruited patients
Generate a table of Tidal volume in litres and chest wall expansion in cm against Inspiration volume under dose and Expiration volume under dose
Primary Objective:
To determine the reduction in target coverage that can occur with respiratory motion when treated with IMRT and 3D CRT
See whether criteria can be generated for the selection of a suitable technique of delivering post mastectomy radiotherapy on the basis of lung excursion data
Secondary Objective:
See whether lung toxicity is under reported as compared to actual when plans are finalized on free breathing CT scan.

Patients were recruited according to the above criteria and a written consent was obtained. Each study patient underwent the following procedures:

As a baseline, a Spirometry and Lung volume study was done using the Jaegar's Master Screen PFT, to assess the respiratory parameters of each patient recruited in to the trial. The parameters recorded were breathing frequency and tidal volume. They were also trained to hold their breath in inspiration and expiration for a minimum duration of 20 seconds (the time taken to complete a CT thorax study). The Jaegar's Master screen PFT was used to document the breath hold times of each patient.

The second step was CT simulation of each patient in free breathing, inspiratory breath hold and expiratory breath hold. Rest of the study was dosimetric based, and patients were not required.

Planning CT scan:

The planning CT scans was carried out on PET CT Seimens Biograph which had a large bore size (convenient for breast board set up), flat couch and a speed capable of completing a CT thorax in 20 seconds.

Each of the recruited patients were immobilised in supine position on a breast board with arms above the head using arm rests. The scar, chest wall borders, lower limit of contralateral breast were marked using angio-catheters. The 3 CT centers were marked with 2mm lead balls on the body and along the same axial plane 2 mm lead balls were placed on the breast board on either side. The lead balls on the breast board were taken as the reference points to overlap inspiratory and expiratory CT scans, as these points don't move with respiration. 80 ml of intravenous ionic contrast was administered and a free breathing CT scan of 3 mm slice thickness, FOV of 700 mm, extending from hyoid to adrenals was

captured. Subsequently, maintaining the above parameters a CT scan in inspiratory breath hold and another in expiratory breath hold were captured. The three image sets acquired for each patient were then transferred to the Varian Eclipse system.

Contouring:

The following structures were contoured as per guidelines on the free breathing CT scan, inspiratory breath hold CT scan and Expiratory breath hold CT scan

a) Chest wall (CTV- Clinical Target Volume) as per RTOG guidelines (Appendix 2)
b) Lymphnodal regions (CTV) as per RTOG guidelines (Appendix 2)
c) Organs at risk: Lungs, Heart, Contralateral breast, Spine

IMRT planning:

The contouring and planning were done on IMRT Eclipse planning system (External beam planning v10.0.42; Varian Medical System, Palo, Alto, CA). 5-7 coplanar 6 MV photon beams were used (multileaf collimator width of 0.5 mm and dynamic IMRT) to generate the plan rendering a dose of 50 Gy in 25 fractions to target. Various dose constraints used for IMRT planning are shown in Table 3.2.

Table 3.2: Dose constraints utilised in plan evaluation

Organs	**Dose Constraints**
Unilateral Lung	V20<=30%
Combined Lungs	V20 <20%
Heart	V25<10%
Spine	Dmax< 45Gy
Contralateral breast	Mean dose < 5% of prescribed
Target	V95 > 95%

3D Planning

The CT imaging data used for IMRT planning was exported to PLATO RTS Version 2.7.7. No changes were made in the contoured structures. 4 Coplanar opposed tangential beams of 6/15 MV were used to generate a plan rendering 50 Gy in 25 fractions to target volume (chest wall) and separate adjacent fields were planned for lymphnodal CTV.

Both plans were evaluated and approved by an independent radiation oncologist for all ten patients.

Superimposition of Inspiratory and Expiratory images on IMRT and 3D-CRT plans

The final and the most critical task was the superimposition of the Inspiratory and Expiratory images on the planned IMRT and 3D conformal therapy plans. The leaf sequence and the fields applied on the base plan were superimposed on the inspiratory and expiratory sets of images by matching the fiducials on the breast board. The isocentre of the plan may have shifted with reference to the body structures because of the respiratory motion. The dose calculation was run without any change in leaf sequences, field size, shape or angle. The isodose distribution and coverage were compared in the three sets of images for each patient.

3.6 VARIABLES AND SCALES USED IN THIS STUDY

Baseline Respiratory parameters:

1. Respiratory rate at rest
2. Amplitude of respiration / chest expansion
3. Tidal volume in litres

Measurements of respiratory motion:

1. Chest wall expansion –Patient's chest wall circumference at normal inspiration and at normal expiration was measured. The difference between the 2 values was taken as chest wall expansion. These values for all the 10 patients were documented.

Factors that affect set up uncertainties:

1. Height
2. Weight
3. Body mass index

Plan comparison parameters:

1. Target dose coverage

V90: Volume of target in percentage receiving dose above 90% of prescribed dose (45 Gy)

V95: Volume of target in percentage receiving dose above 95% of prescribed dose (47.5 Gy)

V100: Volume of target in percentage receiving dose above 100% of prescribed dose (50 Gy)

V107: Volume of target in percentage receiving dose above 107% of prescribed dose (53.5 Gy) - represents hot spot

D95: Dose in Gy received by more than 95% of target volume (represented target coverage)

D98: Dose in Gy received by more than 98% of the target volume (represents the low dose)

D2: Dose in Gy received by less than 2% of the target volume (represents the high dose)

2. Dose to organs at risk

a. Lung V20: Volume of the combined lungs receiving more than 20 Gy and V10: Volume of the lung receiving more than 10 Gy for ipsilateral and contra lateral lung

b. Heart V25: Volume of Heart receiving more than 25 Gy

c. Opposite breast: mean dose received by opposite breast <5% of prescribed dose

Table 3.3: Data sources and measurement

SOURCE	**VARIABLES**	**MEASURE**
Manual	Respiratory rate	Breaths/min
Lung Volumes	Tidal Volume	Litres
Measuring tape	Chest wall movement	Centimeters
Scales	Body mass index	Kg/m2
Dose volume histogram (DVH)	Target dose coverage	CTV- V90,V95,V100 D95, D98, D2
	Dose to organs 1. Lungs 2. Heart 3. Spine 4. Opposite breast	 V20<20% (Combined lungs) V20<30% (ipsilateral lungs) V25<10% Maximum dose<45 Gy Mean dose<5%

The above parameters were used to compare a conformal tangent plan versus an IMRT plan and assess the influence of respiration on both these techniques of radiation.

3.7 OUTCOME

To find the influence of respiration in IMRT versus 3D conformal plans, patients were categorised according their chest wall expansion as well as tidal volume (quartiles) and the mean target coverage and doses to organs at risk with inspiration and expiration in IMRT versus 3D conformal tangents were compared.

3.8 SAMPLE SIZE

This study was undertaken to understand the variation with respiration in the volume of target organ receiving radiation with IMRT compared to that of 3D CRT (95% to 100% of the volume of target organ receiving 95% of prescribed dose was accepted). Any reduction more than 5% from 95% is seen as significant reduction in the intended exposure. The following table shows if the sample size is 5, the standard error of the sampling distribution will be as high as 4.77(almost 5% which is not acceptable). The proposed sample size of 10 will have a standard error of 2.89 versus 2.27 with a sample size of 15. Since there is only a small incremental improvement in the standard error with an increased sample size of 15 and as it was not feasible to complete the comparison between IMRT and 3DCRT in more than 10 patients during the study period, we proposed to study 10 subjects

Table 3.4: Effect of sample size on 95% 1-tailed confidence interval of volume of target organ receiving the radiation dose

Proposed sample size	SE	Critical value for respective d.f	1- sided 95% probability
5	2.24	2.13	4.77 (90.23 - 95)
10	1.58	1.83	2.89 (92.11 - 95)
15	1.29	1.76	2.27 (92.73 - 95)
20	1.2	1.729	2.07 (92.93 – 95)

3.9 STATISTICAL ANALYSIS

Baseline analyses included calculation of descriptive statistics such as mean, standard deviation and median and quartiles for all the dosimetric variables mentioned above. This was done for IMRT and 3D conformal tangents separately.

Then, comparison between the two groups of data (IMRT and 3D conformal tangents) was carried out by comparison of means. All differences between the 2 groups' two-tailed alpha value less than 0.05 were considered significant.

The outcome analyses included categorisation of the study patients according to the interquartile range calculated for chest wall expansion as well as tidal volume. Following which, a comparison of the means of all dosimetric variables between IMRT and 3D conformal tangents was executed.

4. RESULTS AND ANALYSIS

4.1 OVERVIEW OF PATIENTS RECRUITED IN THE STUDY

Six of the sixteen patients recruited in the study received Intensity modulated radiotherapy, while the rest underwent treatment with 3D conformal radiotherapy.

All the sixteen patients fulfilled the spirometric assessment done to ascertain whether they are able to hold their breath in inspiration/ expiration for the time duration of CT scan thorax (20 seconds).

Table 4.1: Demographic and clinical characteristics

Total number of patient screened	21
Patients who were recruited in to the study	16
Patients who underwent IMRT and 3DCRT planning and data was analysed	10
Patients not recruited	5
	Unable to hold breath for 20 seconds-3 Not consented for study- 2
Age (n=10)	Mean age- 50.1 years Minimum age- 35 years Maximum age- 75 years
Body Mass Index	Mean BMI- 28.79 No: of patients with normal BMI- 2 No: of patients Overweight- 5 No: of patients Obese- 3
Stage	Stage II- 7 Stage III- 3
Laterality	Right- 6 Left- 4
Regions treated	Chest wall only- 2 Chest wall and supraclavicular region- 8

4.2 MAGNITUDE AND MEASUREMENT OF RESPIRATORY MOTION IN THE PATIENTS RECRUITED

Table 4.2: Magnitude of respiratory motion among the study population

Respiratory motion				Quantiles				
Variables	**n**	**Mean**	**SD**	**Min**	**0.25**	**Median**	**0.75**	**Max**
Respiratory Rate	10	20.3	4.11	15	18	20	22	30
Tidal Volume	10	0.66	0.16	0.44	0.49	0.68	0.8	0.85
Chest wall movement	10	0.67	0.28	0.50	0.50	0.50	1	1.2

Respiratory rate of the 10 patients varied between 15/min to 30/min. The tidal volume varied between 0.44 to 0.85 litres with a median of 0.68 and the chest wall movement varied between 0.5 to 1.2 cms with a median of 0.5 cms.

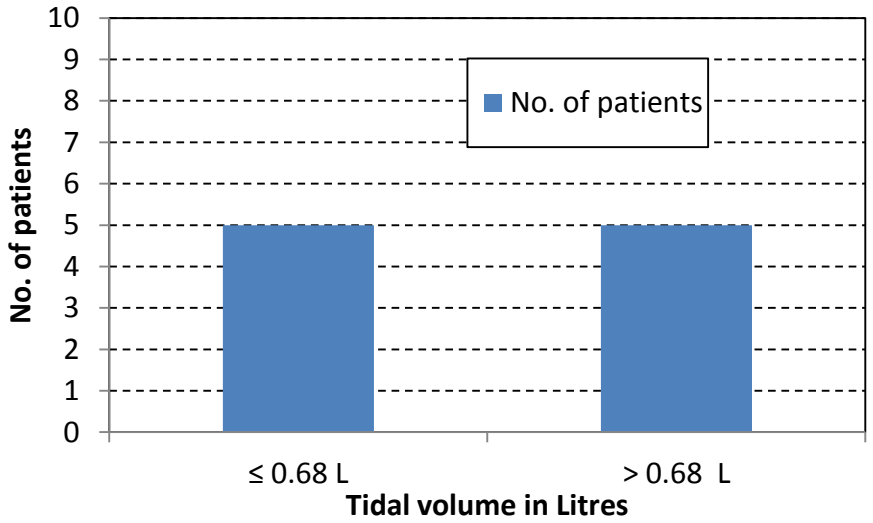


Figure 4.1: Bar graph depicting the distribution of the study population according to tidal volume. Bar 1 shows that there were 5 patients with a tidal volume of ≤0.68 L, Bar 2 shows 5 patients with tidal volume > 0.68 L

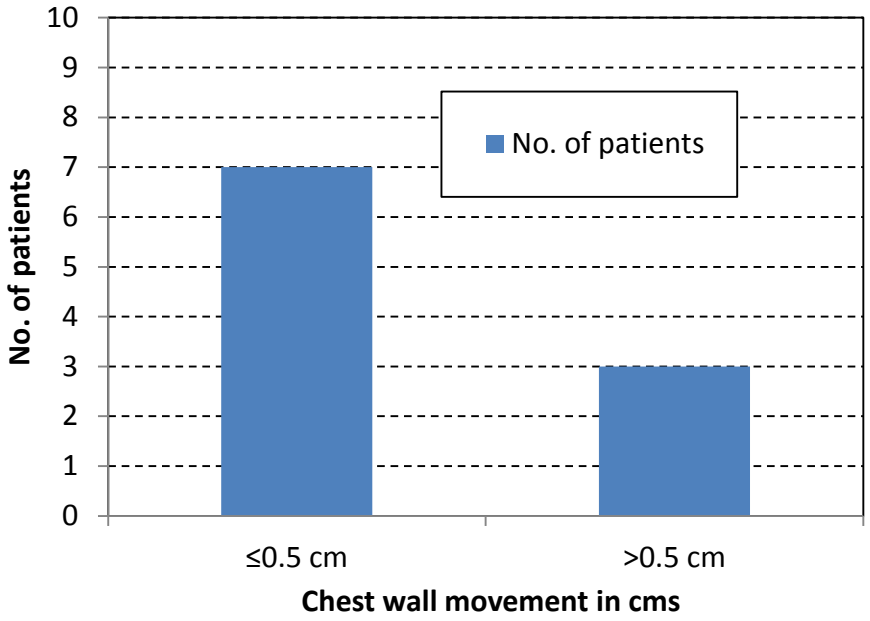


Figure 4.2: Bar graph depicting the distribution of the study population according to magnitude of chest wall movement. Bar 1 show that 7 of the 10 patients had a Chest wall movement of ≤ 0.5 cm and Bar2 shows 3 patients with Chest wall movement of ≥ 0.5 cm

4.3 THE IMPACT OF RESPIRATORY MOTION ON INTENSITY MODULATED RADIOTHERAPY PLAN

Target: Chest wall **Coverage** (Table 4.3- 4.6)

Table 4.3: Comparison of the V90 (Volume receiving 90% of prescribed dose) of chest wall at different phases of respiratory cycle for IMRT technique

V90				**Quantiles**				
Variables	**n**	**Mean**	**S.D**	**Minimum**	**0.25**	**Median**	**0.75**	**Maximum**
Free breathing	10	98.9	0.52	98.0	98.525	98.85	99.35	99.6
Normal Inspiration	10	91.07	6.39	79.6	86.575	90.95	96.6	99.1
Normal Expiration	10	91.92	5.63	83.3	86.7	92.35	97.17	97.8

Table 4.4: Comparison of the V95 (Volume receiving 95% of prescribed dose) of chest wall at different phases of respiratory cycle for IMRT technique.

V95				Quantiles				
Variables	**n**	**Mean**	**S.D**	**Minimum**	**0.25**	**Median**	**0.75**	**Maximum**
Free breathing	10	95.69	1.58	93.5	94.5	95.4	97.6	98
Normal Inspiration	10	86.33	8.09	72.3	81.7	86.45	93.2	96.5
Normal Expiration	10	86.38	7.23	75.2	81	87.65	92.3	94.6

Table 4.5: Comparison of the V100 (Volume receiving 100% of prescribed dose) of chest wall at different phases of respiratory cycle for IMRT technique.

V100				Quantiles				
Variables	**n**	**Mean**	**S.D**	**Minimum**	**0.25**	**Median**	**0.75**	**Maximum**
Free breathing	10	77.03	7.61	63.8	72.4	77.65	80.3	92.5
Normal Inspiration	10	67.58	13.15	48	62	64.25	75.7	90.1
Normal Expiration	10	67.3	7.95	53.5	61.2	68.1	72.6	80.5

Table 4.6: Comparison of the D 95 (Dose in Gy received by 95% of volume) of chest wall at different phases of respiratory cycle for IMRT technique.

				Quantiles				
Variables	**n**	**Mean**	**S.D**	**Minimum**	**0.25**	**Median**	**0.75**	**Maximum**
Free breathing	10	47.81	0.74	46.9	47.27	47.65	48.45	49.3
Normal Inspiration	10	41.47	6.3	28.1	37.7	43.0	46.47	47.3
Normal Expiration	10	43.63	6.7	26.5	42.0	46.45	47.12	48.8

Target coverage with IMRT met the criteria of V95> 95% in 6 out of 10 patients with a mean value of 95.69% and the minimum value being 93.5%. However, when the target coverage with respiration was analysed by the parameter of V90, V95, V100 and D95 it was found that there was mean target under-coverage. The magnitude of target under-coverage was 9.39% and 9.31% with inspiration and expiration respectively in terms of V95. Similarly the mean target under coverage in terms of D95 with inspiration and expiration were 6.34 Gy and 4.18 Gy respectively.

Hot spots (Tables 4.7 & 4.8)

In all the 10 study patients it was possible to achieve a D2 of less than 110% in the free breathing CT scan. When the effect of respiration was analysed, it was found that the mean hot spot increased in the inspiratory and expiratory phases 8.01 Gy and 3.02 Gy respectively. In one of the patients, D2 was as high as 71.2 Gy in inspiration. In terms of V107, the increase in mean hot spot was 19.37% and 11.68% with inspiration and expiration respectively.

Table 4.7: Comparison of the V107 (Volume receiving 107% of prescribed dose) of chest wall at different phases of respiratory cycle for IMRT technique

V107				**Quantiles**				
Variables	**n**	**Mean**	**S.D**	**Minimum**	**0.25**	**Median**	**0.75**	**Maximum**
Free breathing	10	3.03	5.94	0	0.1	0.7	1.9	19.0
Normal Inspiration	10	22.94	17.9	6.1	8.8	16.35	35	58.7
Normal Expiration	10	14.71	14.95	0.1	0.5	8.5	28.1	35.8

Table 4.8: Comparison of the D2 (Dose in Gy received by 2% of volume) which is also termed as "HOT SPOT" of chest wall at different phases of respiratory cycle for IMRT technique

D2				Quantiles				
Variables	**n**	**Mean**	**S.D**	**Minimum**	**0.25**	**Median**	**0.75**	**Maximum**
Free breathing	10	53.14	0.81	52.2	52.6	53.1	53.4	54.8
Normal Inspiration	10	61.15	5.48	54.2	57.6	59.75	64.9	71.2
Normal Expiration	10	58.13	6.14	52.6	52.7	56.1	61.4	70.0

Cold spot (Table 4.9):

In 9 out of 10 study patients it was possible to achieve a D98 of at-least 90%. Comparison of D98 for IMRT technique revealed respiration resulted in cold spots within the target volume, mean of 31.68 to 36.28 Gy in inspiration and expiration respectively. 1 of the patient's D98 was as low as 4.3 Gy in inspiration and 14.6 Gy in expiration.

Table 4.9: Comparison of the D98 (Dose received by 98% of volume) which is also termed as "Cold Spot" of chest wall at different phases of respiratory cycle for IMRT technique

D98				Quantiles				
Variables	**n**	**Mean**	**S.D**	**Minimum**	**0.25**	**Median**	**0.75**	**Maximum**
Free breathing	10	44.6	4.45	32.2	45.3	45.75	46.4	47.5
Normal Inspiration	10	31.68	14.37	4.3	20.5	35.45	42.7	46.6
Normal Expiration	10	36.28	9.87	14.6	31.5	39.6	43.9	44.7

Organs at risk

Lungs (Table 4.10):

It was seen that change in mean ipsilateral lung volume receiving 20 Gy was 6.62% with inspiration and 4.27% with expiration. Similarly the change in mean combined lung volume receiving 20 Gy was 3.28% with inspiration and 1.83% with expiration.

Table 4.10: Comparison of the mean dose delivered to ipsilateral lung, contralateral lung and combined Lungs at different phases of breathing cycle for IMRT technique.

	V20			**V10**		
	FB	**NI**	**NE**	**FB**	**NI**	**NE**
Ipsilateral lung	18.36	24.98	22.63	54.12	59.38	56.43
Contralateral lung	0	0	0.02	0.12	0.37	0.31
Combined lungs	9.53	12.81	11.36	27.94	30.57	29.27

Abbreviations: Vx= percentage of volume receiving x% of prescribed dose; FB, NI, NE refer to respiratory phases of CT scan (free breathing, normal inspiration and normal expiration respectively)

Heart (Table 4.11):

Comparison of mean heart dose (V25) in free breathing, normal inspiration and expiration showed that variation was a maximum of 1.38%. One study patient had a calculated dose of 12.8% with inspiration (crossing the tolerance limit of 10%). 4 of the 10 patients had left sided tumour and the mean cardiac volume receiving dose of 25 Gy of these patients in free breathing, normal inspiration and normal expiration was 5.37%, 7.95% and 3.65% while that of patients with right sided tumour were 0.63%, 1.21% and 1.15% respectively.

Table 4.11: Comparison of the V25 (Volume receiving 25% of prescribed dose) of heart at different phases of respiratory cycle for IMRT technique.

				Quantiles				
Variables	**n**	**Mean**	**S.D**	**Minimum**	**0.25**	**Median**	**0.75**	**Maximum**
Free breathing	10	2.53	3.10	0	0	1.9	4.0	9.6
Normal Inspiration	10	3.91	4.7	0	0	2.25	7.0	12.8
Normal Expiration	10	2.15	2.72	0	0	0.3	4.8	6.3

4.4 THE IMAPCT OF RESPIRATORY MOTION ON 3D CONFORMAL RADIOTHERAY PLAN

Target- Chest wall: **Coverage** (Tables 4.12-4.15):

Table 4.12: Comparison of the V90 (Volume receiving 90% of prescribed dose) of chest wall at different phases of respiratory cycle for 3D conformal tangents

V90				**Quantiles**				
Variables	**n**	**Mean**	**S.D**	**Minimum**	**0.25**	**Median**	**0.75**	**Maximum**
Free breathing	10	97.9	1.22	96.3	96.75	97.8	98.77	100
Normal Inspiration	10	95.14	5.9	79.7	93.75	96.35	99.32	100
Normal Expiration	10	93.84	6.8	78.7	90.55	96.25	98.35	100

Table 4.13: Comparison of the V95 (Volume receiving 95% of prescribed dose) of chest wall at different phases of respiratory cycle for 3D tangents

V95				Quantiles				
Variables	**n**	**Mean**	**S.D**	**Minimum**	**0.25**	**Median**	**0.75**	**Maximum**
Free breathing	10	94.16	1.83	92.2	92.4	93.85	95	98.2
Normal Inspiration	10	91.04	6.52	80.8	84.6	92.2	97.4	99.6
Normal Expiration	10	90.53	5.57	81.5	87.2	92.1	94.7	97.5

Table 4.14: Comparison of the V100 (Volume receiving 100% of prescribed dose) of chest wall at different phases of respiratory cycle for 3D tangents.

V100				Quantiles				
Variables	**n**	**Mean**	**S.D**	**Minimum**	**0.25**	**Median**	**0.75**	**Maximum**
Free breathing	10	65.75	9.45	50.6	54.5	69.55	73.3	74.2
Normal Inspiration	10	60.68	17.20	33.9	44.6	64.4	70.4	84.2
Normal Expiration	10	60.52	16.67	32.4	51.5	59.9	70.9	86

Table 4.15: Comparison of the D 95 (Dose received by 95% of volume) of chest wall at different phases of respiratory cycle for 3D conformal tangents.

				Quantiles				
Variables	**n**	**Mean**	**S.D**	**Minimum**	**0.25**	**Median**	**0.75**	**Maximum**
Free breathing	10	36.87	12.3	7.7	28.22	41.2	46.52	48.1
Normal Inspiration	10	47.12	0.57	46.0	46.8	47.1	47.57	47.9
Normal Expiration	10	41.98	8.7	22.7	36.4	45.9	47.6	48.5

The overall target coverage with 3D-CRT was less (V95 > 95% could be achieved in only 3 out of 10 patients. The analysis of change in parameters such as V90, V95, V100 and D95 with respiration revealed that there was target under-coverage. The mean target under-coverage in terms of V95 with inspiration and expiration were 3.12% and 3.63% respectively.

Hot spots (Table 4.16& 4.17):

Table 4.16: Comparison of the V107 (Volume receiving 107% of prescribed dose) of chest wall at different phases of respiratory cycle for 3D conformal tangents.

V107				**Quantiles**				
Variables	**n**	**Mean**	**S.D**	**Minimum**	**0.25**	**Median**	**0.75**	**Maximum**
Free breathing	10	0.82	1.02	0	0.2	0.3	1.4	2.8
Normal Inspiration	10	2.87	4.01	0	0.4	1.4	1.8	9.9
Normal Expiration	10	2.92	3.64	0	0.2	2.35	3.7	12.2

Table 4.17: Comparison of the D2 (Dose in Gy received by 2% of volume) which is also termed as "HOT SPOT" of chest wall at different phases of respiratory cycle for 3D conformal tangents technique

D2				Quantiles				
Variables	**n**	**Mean**	**S.D**	**Minimum**	**0.25**	**Median**	**0.75**	**Maximum**
Free breathing	10	53.7	0.4	52.6	52.7	53	53.2	53.9
Normal Inspiration	10	53.58	1.17	52.5	52.6	53.35	53.5	56.2
Normal Expiration	10	53.42	0.9	52.6	52.6	53.5	54.1	54.7

It was possible to achieve hot spot of D2 < 107% in all the 10 patients. When the effect of respiration was analysed it was found that mean D2 hardly changed. In terms of V107 the increase of hot spot with inspiration and expiration was 2.87% and 2.92% respectively.

Cold spot (Table 4.18):

Table 4.18: Comparison of the D98 (Dose received by 98% of volume) which is also termed as "Cold Spot" of chest wall at different phases of respiratory cycle for 3D conformal tangents

D98				Quantiles				
Variables	**n**	**Mean**	**S.D**	**Minimum**	**0.25**	**Median**	**0.75**	**Maximum**
Free breathing	10	44.63	1.91	41.9	42.8	44.8	46	47.6
Normal Inspiration	10	40.44	11.49	13.4	36.2	44.55	47	52.2
Normal Expiration	10	38.38	10.89	12.6	35.4	43.35	45.1	47.2

It was possible to achieve a D98 of 90% in only 3 out of 10 patients with 3D-CRT on the free breathing scan. Comparison of D98 with respiration resulted in increase in cold spots within the target volume. The mean D98 was 40.44 with inspiration and 38.38 with expiration. 1 of the patients D98 was quite low, 13.4 Gy in inspiration and 12.6 Gy in expiration.

Organs at risk

Lungs (Table 4.19):

Table 4.19: Comparison of the mean dose delivered to Ipsilateral lung, Contralateral lung and Combined Lungs at different phases of breathing cycle for 3D conformal tangent technique.

	V20			**V10**		
	FB	**NI**	**NE**	**FB**	**NI**	**NE**
Ipsilateral lung	23.63	25.76	23.44	28.22	30.17	27.91
Contralateral lung	0	0	0	0	0.01	0
Combined lungs	11.91	13.12	11.77	14.17	15.35	13.97

Abbreviations: Vx= percentage of volume receiving x% of prescribed dose; FB, NI, NE refer to respiratory phase of CT scan (free breathing, normal inspiration and normal expiration respectively)

It was seen that change in mean lung volume receiving 20 Gy varied by approximately 2% with normal inspiration in ipsilateral lung and combined lungs. There was hardly any change with expiration.

Heart (Table 4.20)

Table 4.20: Comparison of the V25 (Volume receiving 25% of prescribed dose) of heart at different phases of respiratory cycle for 3D conformal tangents technique.

				Quantiles				
Variables	**n**	**Mean**	**S.D**	**Minimum**	**0.25**	**Median**	**0.75**	**Maximum**
Free breathing	10	3.95	5.74	0	0	0.1	8.8	16.3
Normal Inspiration	10	4.6	6.93	0	0	0	9.1	17.8
Normal Expiration	10	4.16	6.14	0	0	0	9.5	17.0

Heart dose variation with respiration in 3D conformal tangents was assessed by comparing mean V25 (volume receiving 25 Gy) of 10 patients in free breathing, normal inspiration and expiration. The mean heart dose was higher by 0.21% and 0.65% in expiratory and inspiratory phases respectively when compared to free breathing. 4 out of 10 patients had left sided breast cancer and their mean cardiac volume receiving 25 Gy in free breathing, normal inspiration and normal expiration was 9.82%, 11.5% and 10.4% respectively while that in patients with right breast tumour was 0.03%, 0%, 0% respectively.

4.5 A COMPARISON BETWEEN THE IMPACT OF RESPIRATORY MOTION ON INTENSITY MODULATED RADIOTHERAPY PLAN VERSUS 3D CONFORMAL RADIOTHERAPY

Target coverage (Tables 4.21, 4.22 and Figure 4.3):

Table 4.21: The dose-volume relationships of Chest wall for each of the 10 study patients using the CT scans acquired during FB and end of NI and NE

Pt No	Technique	V90 (%)			V95(%)			V100 (%)		
		FB	NI	NE	FB	NI	NE	FB	NI	NE
1	3D Tangents	99.6	93.9	99.1	98.2	92.9	97.5	67.9	84.2	86
	IMRT	99.3	83.2	97	98	77	91	92.5	48	64.5
2	3D Tangents	96.6	99.1	97.6	92.4	98.1	96.2	73.3	55.5	78.8
	IMRT	98.9	96.5	85.8	94.6	94.7	76	79.6	90.1	59.4
3	3D Tangents	97.7	97.2	98.1	95.4	97.4	94.7	73.6	80.5	69.7
	IMRT	98.6	99.1	97	94.5	96.5	92.3	78	85.1	73.5
4	3D Tangents	100	100	100	95	91.6	93.4	54.5	44.6	51.5
	IMRT	99.5	87.7	89.1	97.6	82.1	84.4	81.1	63.4	67.3
5	3D Tangents	98.5	95.5	85.3	94.9	80.8	82.1	74.2	70.4	70.9
	IMRT	99.3	96.5	87	96.1	93.2	81	63.8	70.1	53.5
6	3D Tangents	97.9	100	95	93.8	99.6	87.2	52.2	67.3	32.4
	IMRT	98.3	96.9	95.6	95.3	92.9	90.8	75.1	63.3	68.9
7	3D Tangents	96.3	96.3	78.7	93.5	89.5	92.4	69.6	33.9	61.6
	IMRT	98.8	92.1	97.7	95.5	87.6	94	80.3	75.7	80.5
8	3D Tangents	98.2	79.7	92.3	93.9	83.1	81.5	72.1	61.5	58.2
	IMRT	98.8	89.3	88.9	94.2	81.7	84.5	72.4	62	72.6
9	3D Tangents	96.8	96.4	94.8	92.3	92.8	88.5	69.5	70.2	56.2
	IMRT	98	79.6	83.3	93.5	72.3	75.2	70.2	53	61.2
10	3D Tangents	97.4	93.3	97.5	92.2	84.6	91.8	50.6	38.7	39.8
	IMRT	99.6	89.8	97.8	97.6	85.3	94.6	77.3	65.1	72.5

Table 4.21 shows the detailed dose volume information for the chest wall (V90, V95, V100). There was difference between the changes in chest wall coverage with respiration in IMRT versus 3D conformal tangents. However this difference is more

pronounced in some. The table shows that the study participants 1, 2, 4, 6 and 9 have a difference in chest wall coverage (under coverage) between IMRT and 3D conformal tangents of more than 5% in either inspiration or expiration.

Table 4.22: A comparison of means of between the target coverage (V95) for IMRT as well as 3D conformal tangent plans in free breathing versus normal inspiratory/ normal expiratory phases was carried out, to show whether the change in target coverage was significant with respiration

	Paired differences					
	Mean	**SE**	**95% confidence interval of the difference**		**t- test**	**Significance (2 tailed)**
			lower	**upper**		
V95 IMRT FB vs V95 IMRT NI	9.36	2.67	3.31	15.4	3.5	0.007
V95 IMRT FB vs V95 IMRT NE	9.31	2.09	4.56	14.05	4.44	0.002
V95 3D FB vs V95 3D NI	3.12	2.11	-1.66	7.9	1.47	0.174
V95 3D FB vs V95 3D NE	3.63	1.71	-2.38	7.49	2.12	0.063

Target coverage of mean V95 >95% was achieved with IMRT in free breathing CT scan while mean coverage was less than 95% (94.16%) with 3D-CRT. However, when a comparison of means for target coverage in terms of V95 for IMRT and 3D conformal tangents in free breathing versus inspiratory and expiratory phases was carried out, it was found that there was significant change in IMRT with respiration (0.007 and 0.002 respectively) while the change was not significant in 3D conformal tangent plan (0.174 and 0.063 respectively).

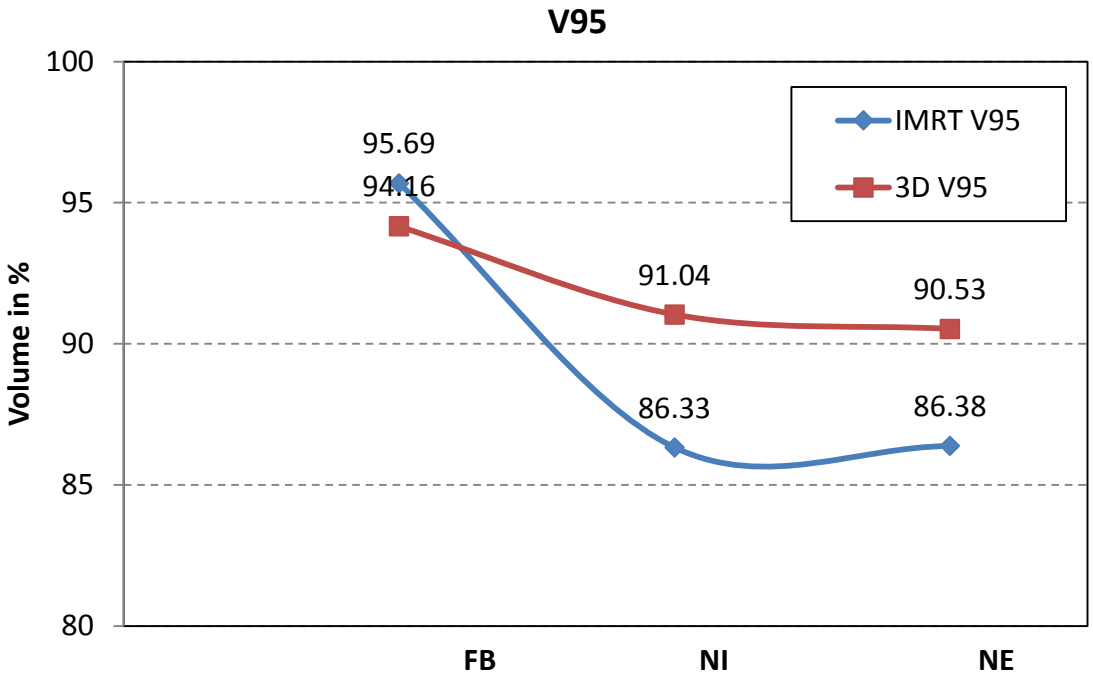


Figure 4.3: Line diagram showing the change in mean target coverage in terms of V95 (volume receiving 95% of dose) with respiration in IMRT versus 3D conformal tangents.

Figure 4.3 is a pictorial representation depicting the drop in target coverage of 4.17- 4.71% in terms of V95 with IMRT when compared to 3D CRT.

Hot spots (Table 4.23 and Figure 4.4):

Though the mean hot spot with IMRT was similar to 3D-CRT (D2 of 53.14 and 53.7 Gy respectively), it was found that hot spots increases with respiration in IMRT plan when compared to 3D conformal tangent plan. However, it was not statistically significant. The line diagram also shows a trend favouring an increase in hot spots in IMRT with respiration of 11.79- 20.07% when compared to 3D conformal tangents.

Table 4.23: A comparison of means of between the hot spots (V107) for IMRT and 3D conformal tangent plans in free breathing versus normal inspiratory/ normal expiratory phases was carried out, to show whether the change in hot spots was significant with respiration

	Paired differences				t- test	Significance (2 tailed)
	Mean	SE	95% confidence interval of the difference			
			lower	Upper		
V107 IMRT FB vs V107 IMRT NI	-19.91	5.95	-33.38	-6.43	-3.34	0.09
V107 IMRT FB vs V107 IMRT NE	-11.68	5.47	-24.07	0.71	-2.13	0.062
V107 TGT FB vs V107 TGT NI	-1.98	1.3	-5.04	1.07	-1.4	0.172
V107 TGT FB vs V107 TGT NE	-2.1	1.11	-4.62	0.42	-1.88	0.092

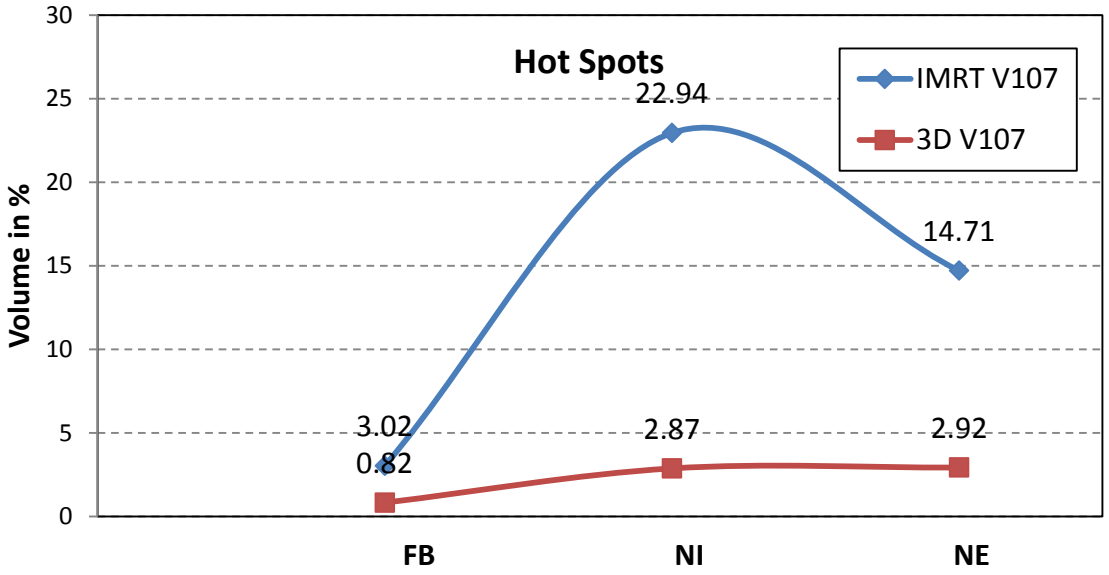


Figure 4.4: Line diagram showing the change in mean HOT SPOTS in terms of V107 (volume receiving 107% of dose) with respiration in IMRT versus 3D conformal tangents.

Cold spots (Table 4.24 and Figure 4.5):

Table 4.24: A comparison of means of between the cold spots (D98) for IMRT as well as 3D conformal tangent plans in free breathing versus normal inspiratory/ normal expiratory phases was carried out, to show whether the change in cold spots was significant with respiration

	Paired differences				t- test	Significance (2 tailed)
	Mean	SE	95% confidence interval of the difference			
			lower	upper		
D98 IMRT FB vs D98 IMRT NI	12.98	4.90	1.87	24.08	2.64	0.027
D98 IMRT FB vs D98 IMRT NE	8.38	3.19	1.14	15.61	2.61	0.028
D98 TGT FB vs D98 TGT NI	4.19	3.71	-4.20	12.58	1.12	0.288
D98 TGT FB vs D98 TGT NE	5.81	3.56	-2.25	13.87	1.63	0.138

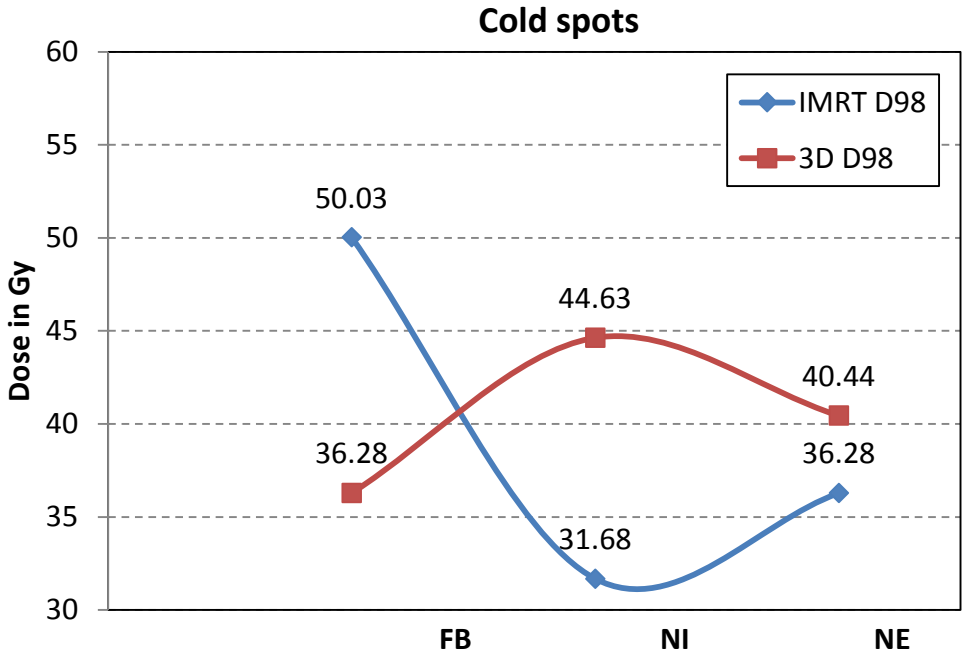


Figure 4.5: Line diagram showing the change in mean COLD SPOTS in terms of D98 (dose received by 98% of volume) with respiration in IMRT versus 3D conformal tangents.

The mean minimum dose received by target was similar in IMRT and 3D-CRT (44.6% and 44.63% respectively). However, when the significance of the increase in cold spots with respiration was checked, it was found that magnitude of cold spots occurring in IMRT with respiration was significant while that with 3D CRT was not.

The line diagram is a pictorial representation which also shows that there is a definite increase in cold spots with IMRT when compared to 3D conformal tangents. The mean D98 of IMRT with inspiration was less than 3D tangents by 12.95 Gy and with expiration by 4.16 Gy.

Organs at risk

Ipsilateral Lung (Table 4.25 and Figure 4.6):

It was seen that change in volume of lung receiving 20 Gy occurring with respiration is significant only in inspiration for an IMRT plan. There seems to be no significant change in expiration for IMRT plan. The effect of respiration on 3D conformal tangents in terms of ipsilateral lung dose is insignificant.

A comparison of the lung dose variation in each patient that occurs with respiration showed that it was more with IMRT than 3D conformal tangents, except in 1. This is depicted in Figure 4.6. A trend line was generated to clarify this finding and it supported the fact that variation in lung dose with respiration in IMRT was more than 3D CRT.

Table 4.25: A comparison of means of between the ipsilateral lung dose (V20) for IMRT as well as 3D conformal tangent plans in free breathing versus normal inspiratory/ normal expiratory phases was carried out, to show whether the change was significant with respiration

	Paired differences					
	Mean	SE	95% confidence interval of the difference		t- test	Significance (2 tailed)
			lower	upper		
V20 IMRT FB vs V20 IMRT NI	-6.62	1.37	-9.72	-3.51	-4.82	0.001
V20 IMRT FB vs V20 IMRT NE	-3.98	1.93	-8.35	0.39	-2.05	0.07
V20 TGT FB vs V20TGT NI	-2.13	2.39	-7.55	3.29	-0.88	0.397
V20 TGT FB vs V20 TGT NE	0.19	1.85	-4.00	4.38	0.102	0.921

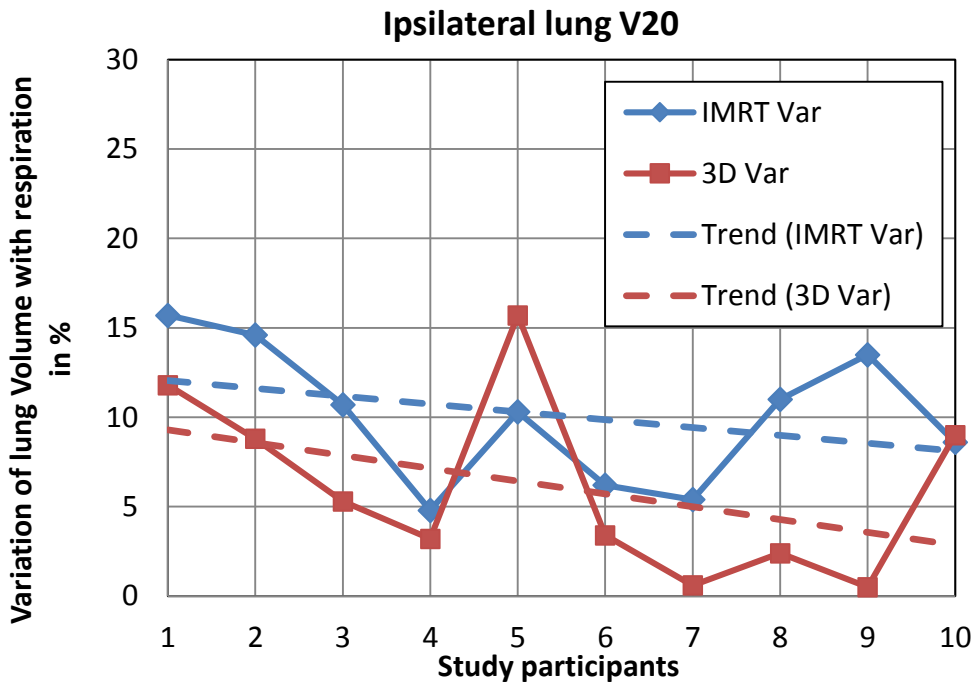


Figure 4.6: Line diagram showing variation of the ipsilateral lung volume receiving 20 Gy with respiration in IMRT and 3D conformal tangents in each of the 10 study participants.

Combined lungs (Table 4.26 and Figure 4.7):

The change in volume of both lungs receiving 20 Gy occurring with respiration was significant only in inspiration for an IMRT plan. There seems to be no significant change in expiration for IMRT plan. The effect of respiration on 3D conformal tangents in terms of combined lung dose is insignificant.

Table 4.26: A comparison of means of between the combined lung dose (V20) for IMRT as well as 3D conformal tangent plans in free breathing versus normal inspiratory/ normal expiratory phases was carried out, to show whether the change was significant with respiration

	Paired differences					
	Mean	**SE**	**95% confidence interval of the difference**		**t-test**	**Significance (2 tailed)**
			lower	**upper**		
V20 IMRT FB vs V20 IMRT NI	-3.28	0.66	-4.79	-1.76	-4.90	0.001
V20 IMRT FB vs V20 IMRT NE	-1.83	0.93	-3.94	0.28	-1.95	0.082
V20 TGT FB vs V20 TGT NI	-1.21	1.39	-4.37	1.95	-0.865	0.409
V20 TGT FB vs V20 TGT NE	0.14	1.10	-2.35	2.63	0.127	0.902

A comparison of the variation with respiration showed that it was more with IMRT than 3D conformal tangents, except in 1 patient. This is depicted in Figure 4.7. It also shows the trend in variation which also supports the same fact in terms of V20 of combined lung.

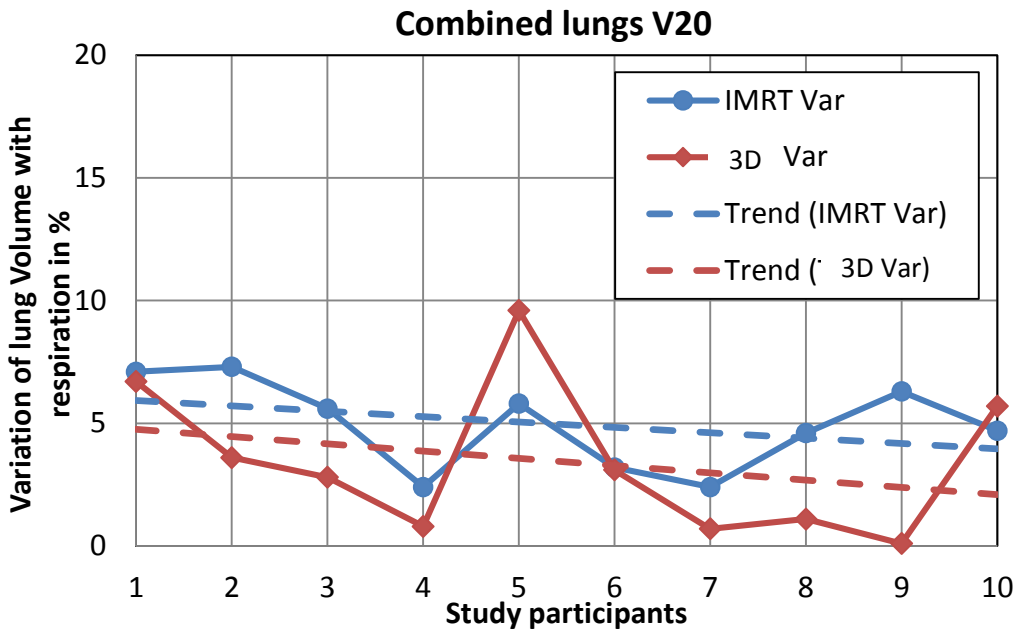


Figure 4.7: Line diagram showing variation of the combined lung volume receiving 20 Gy with respiration in IMRT and 3D conformal tangents in each of the 10 study participants.

Heart (Table 4.27 and Figure 4.8):

Comparing the dose received by heart in left sided breast cancer patients, it was found that the mean cardiac dose was higher with 3D-CRT when compared to IMRT (5.37% vs 9.82%). At the same time, the change in volume of heart receiving 25 Gy occurring with respiration was not significant in either IMRT or 3D conformal tangents. However, the mean percentage volume of heart receiving 25 Gy in 3D-CRT crossed 10% in left sided radiation therapy plans.

Comparison of heart doses in IMRT versus 3D conformal tangents showed that the variation with respiration was more with IMRT than 3D conformal tangents. This is depicted in Figure 4.8. It also showed the trend in variation which supports the fact that effect of respiration on IMRT is more than that on 3D conformal tangents in terms of V25 of heart.

Table 4.27: Comparison of means- Volume of Heart receiving 25 Gy (V25) for IMRT in free breathing versus normal inspiration/ normal expiration as well comparison of Volume of heart receiving 25 Gy (V25) for 3D conformal Tangents in free breathing versus normal inspiration/ expiration.

	Paired differences				t-test	Significance (2 tailed)
	Mean	SE	95% confidence interval of the difference			
			lower	upper		
V25 IMRT FB vs V25 IMRT NI	-1.38	0.64	-2.84	0.08	-2.13	0.061
V25 IMRT FB vs V25 IMRT NE	0.38	0.82	-1.48	2.24	0.46	0.656
V25 TGT FB vs V25 TGT NI	-0.65	0.61	-2.03	0.73	-1.05	0.318
V25 TGT FB vs V25 TGT NE	-0.21	0.17	-0.60	0.18	-1.19	0.263

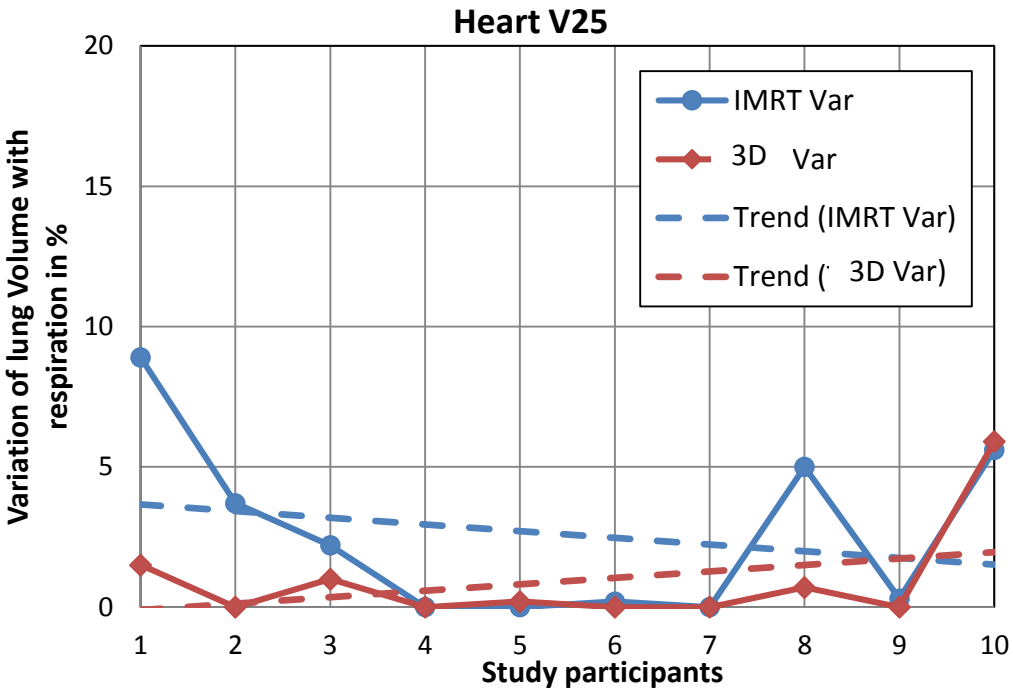


Figure 4.8: Line diagram showing variation of Heart receiving 25 Gy with respiration in IMRT and 3D conformal tangents in each of the 10 study participants.

Contralateral breast

Table 4.28: Comparison of the mean dose in percentage delivered to contra-lateral breast at different phases of breathing cycle for IMRT versus 3D conformal tangent technique.

	FB	**NI**	**NE**
IMRT	3.38	4.16	4.01
3D Tangents	1.56	1.52	1.37

The table 4.28 clearly shows that the overall dose to contralateral breast is higher with IMRT plan when compared to 3D CRT. However, it does not vary with respiration.

Integral dose:

The table 4.29 shows that the mean integral dose is higher with IMRT than 3D CRT. However there is no change in integral dose with respiration in either technique of radiotherapy.

Table 4.29: Comparison of the volume of Body receiving 2%, 5% or 10% of the prescribed dose at different phases of breathing cycle with IMRT technique and 3D CRT.

	FB		**NI**		**NE**	
	IMRT	**3D**	**IMRT**	**3D**	**IMRT**	**3D**
Body 2%	59.18	28.9	62.26	29.1	61.89	28.7
Body 5%	41.78	17.63	43.39	17.68	44.45	16.99
Body 10%	29.59	13.23	30.56	13.3	30.56	12.86

4.6 CORRELATION BETWEEN THE MAGNITUDE OF RESPIRATORY MOTION AND ITS EFFECT ON THE RADIOTHERAPY TECHNIQUES

Target coverage with Tidal volume:

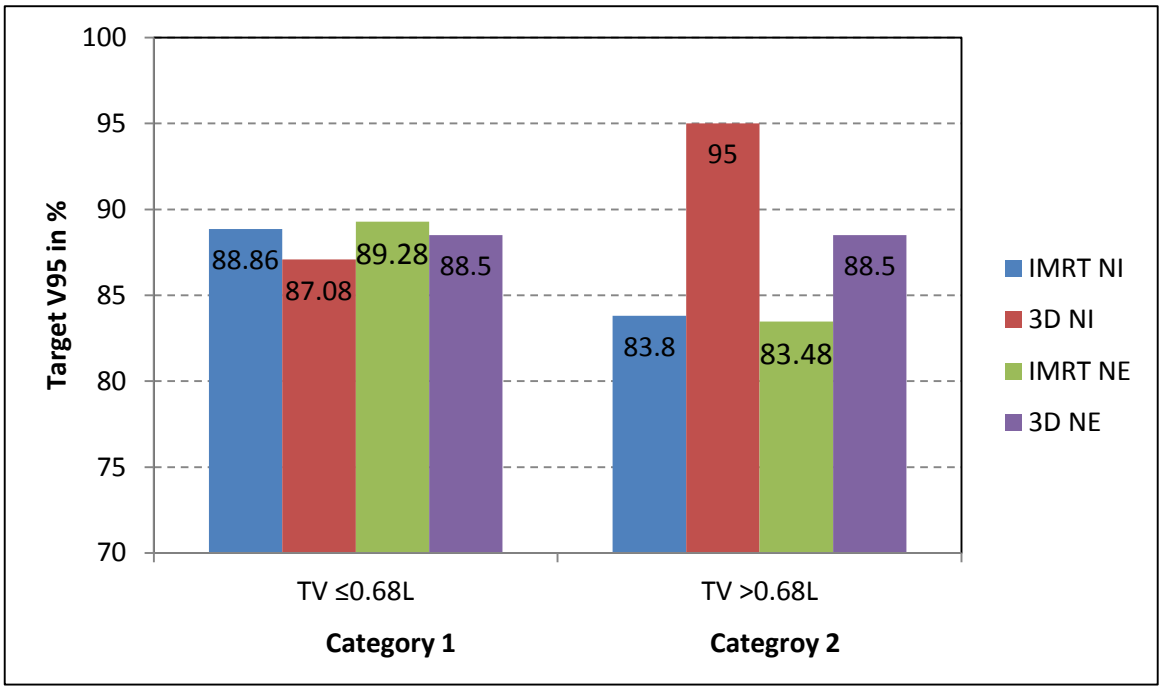
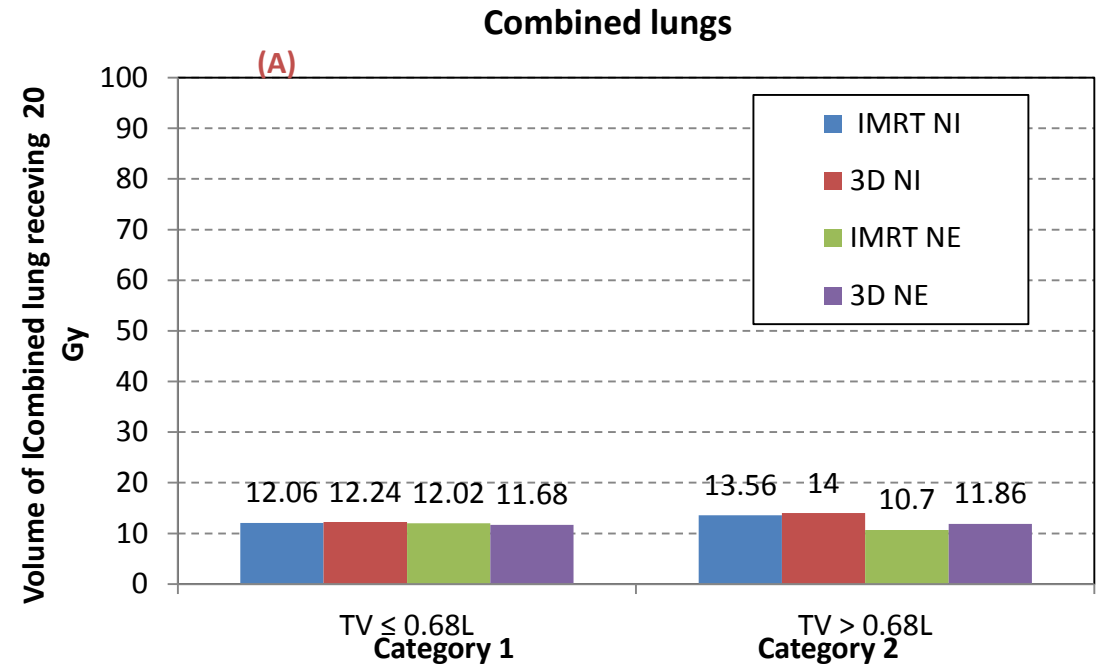


Figure 4.9: The 10 study patients were categorised according to their tidal volume (Category 1- TV ≤ 0.68L, Category 2- TV>0.68L) and their mean target coverage in terms of V95 with inspiration and expiration were used to compare between IMRT and 3D CRT.

It was found that the mean target coverage with inspiration and expiration in IMRT and 3D CRT plan were similar in patients with a tidal volume less than or equal to 0.68 L (the median tidal volume of the 10 patients). However in patients with a tidal volume of more than 0.68 L, there was a difference in the mean under coverage of target between 3D and IMRT of 11.2% in inspiration and 5.08% in expiration, though not statistically significant.

Dose received by organs at risk and Tidal volume

The dose received by organs at risk was similar in both the Categories of tidal volume≤ 0.68L and >0.68 L in IMRT and 3D-CRT.



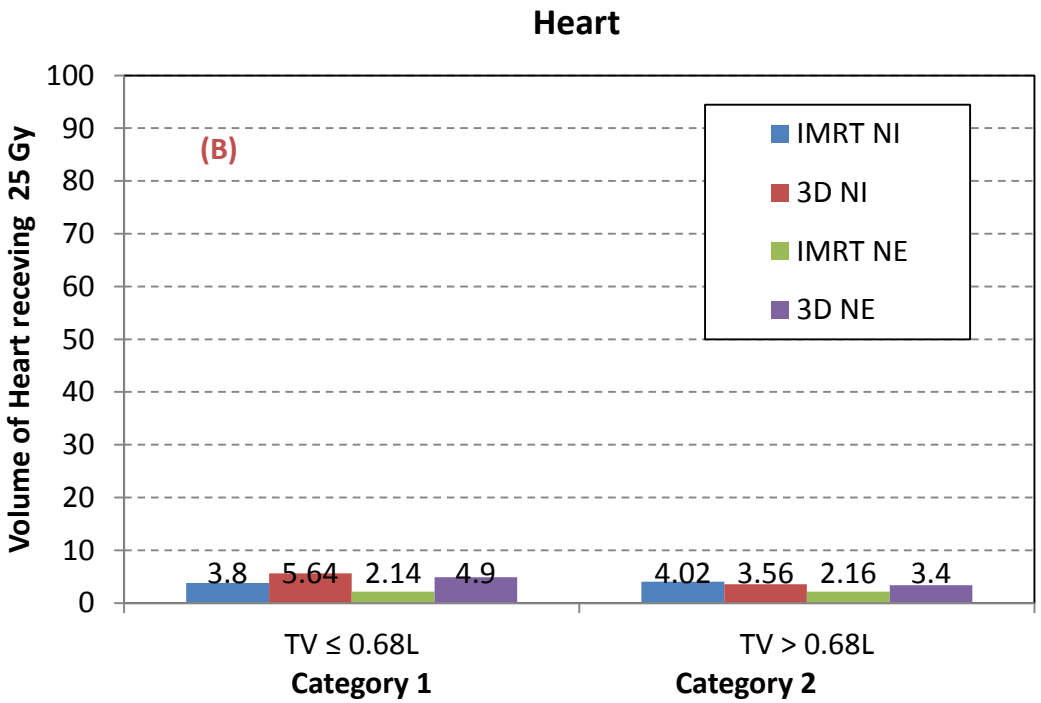


Figure 4.10 a &b: The 10 study patients were categorised according to their tidal volume (Category 1- TV ≤ 0.68 L, Category 2- TV>0.68 L) and their lung and heart volumes in terms of V20 and V25 respectively with inspiration and expiration were compared between IMRT and 3D CRT.

Target Coverage with Chest wall expansion

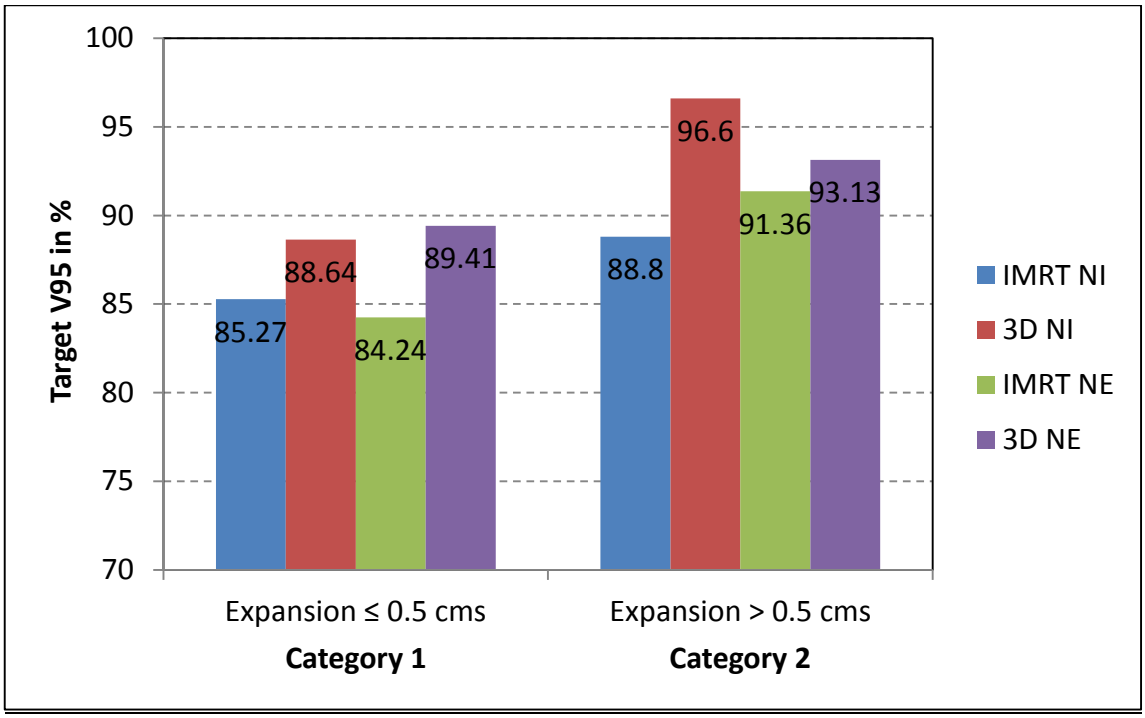


Figure 4.11: The 10 study patients were categorised according to their chest wall expansion (Category 1- Expansion ≤ 0.5cms, Category 2- Expansion>0.5 cms) and their mean target coverage in terms of V95 with inspiration and expiration were used to compare between IMRT and 3D CRT.

Analysis of mean target coverage when patients were divided according to chest wall expansion (Category 1: no. of patients was 7 and Category 2: no. of patients was 3) revealed that the difference between the coverage with 3D CRT and IMRT was 3.37 and 5.17% respectively among patients in Category 1 (IMRT coverage being less than 3D CRT) while the difference in coverage in Category 2 was 1.77 and 7.8% respectively (IMRT coverage being less than 3D CRT). This difference was not statistically significant.

Dose received by organs at risk and Chest wall expansion

Though the dose received by organs at risk did not change much with chest wall expansion, it was noticed that comparatively the heart dose with 3D CRT technique was more when chest wall expansion was more than 0.5 cms

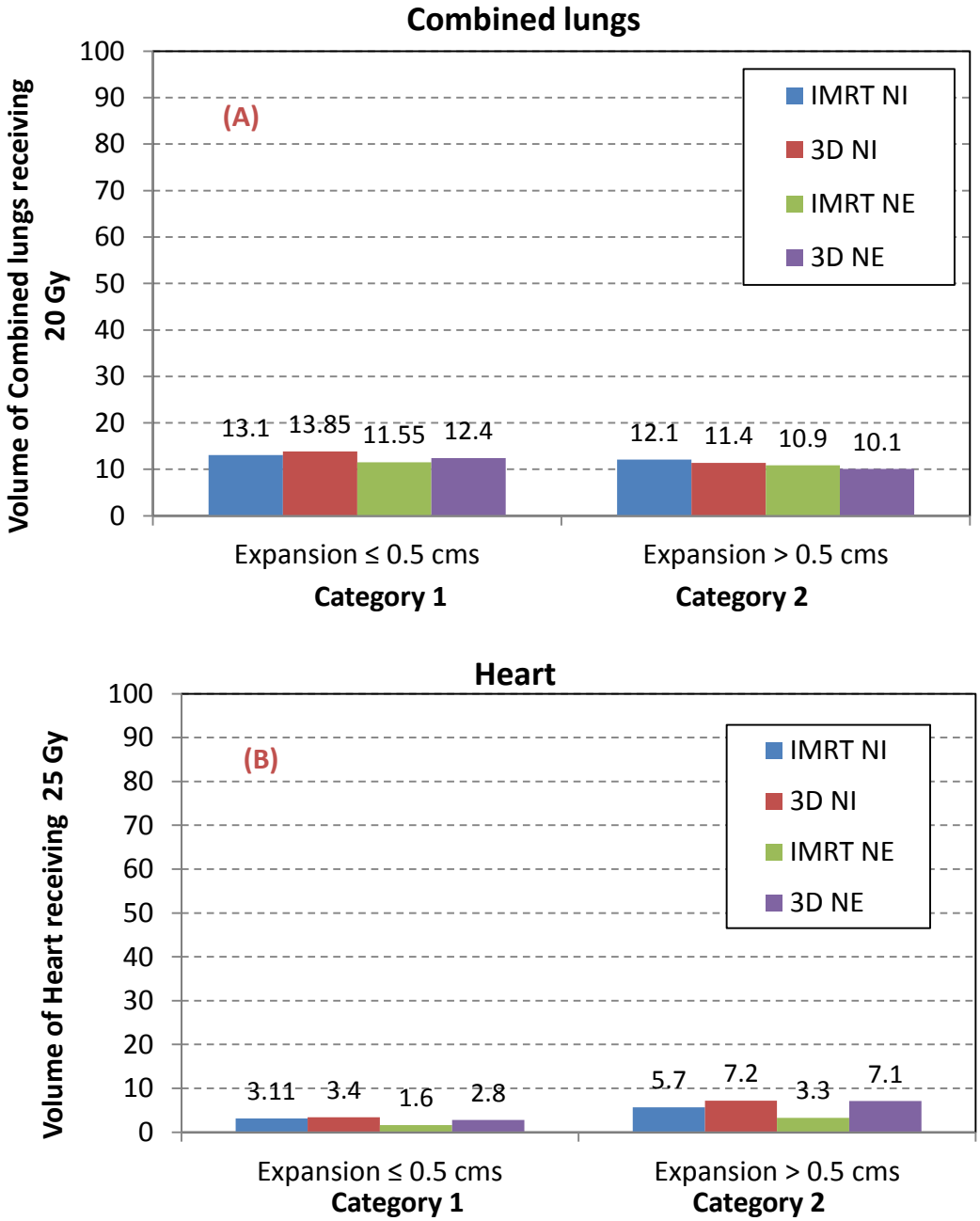


Figure 4.12 a&b: The 10 study patients were categorised according to their chest wall expansion (Category 1- Expansion ≤ 0.5 cms, Category 2- Expansion > 0.5 cms) and their lung and heart volumes in terms of V20 and V25 respectively with inspiration and expiration were used to compare between IMRT and 3D CRT.

4.7 COMPARISON BETWEEN IMRT AND 3D-CRT: TARGET DOSE WASH (V95) IN A PATIENT WITH TIDAL VOLUME > 0.68 L IN FREE BREATHING, NORMAL INSPIRATION AND NORMAL EXPIRATION

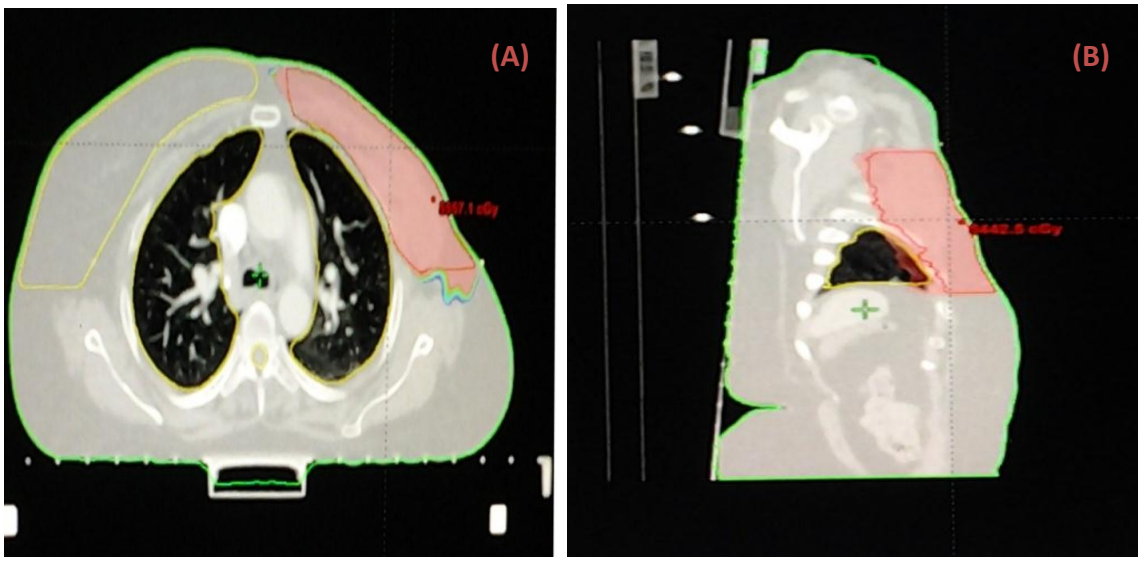


Figure 4.13 a&b: Shows the 95% isodose colour wash in axial and sagittal section at the level of carina and head of humerus respectively on **Free breathing CT scan** with IMRT plan

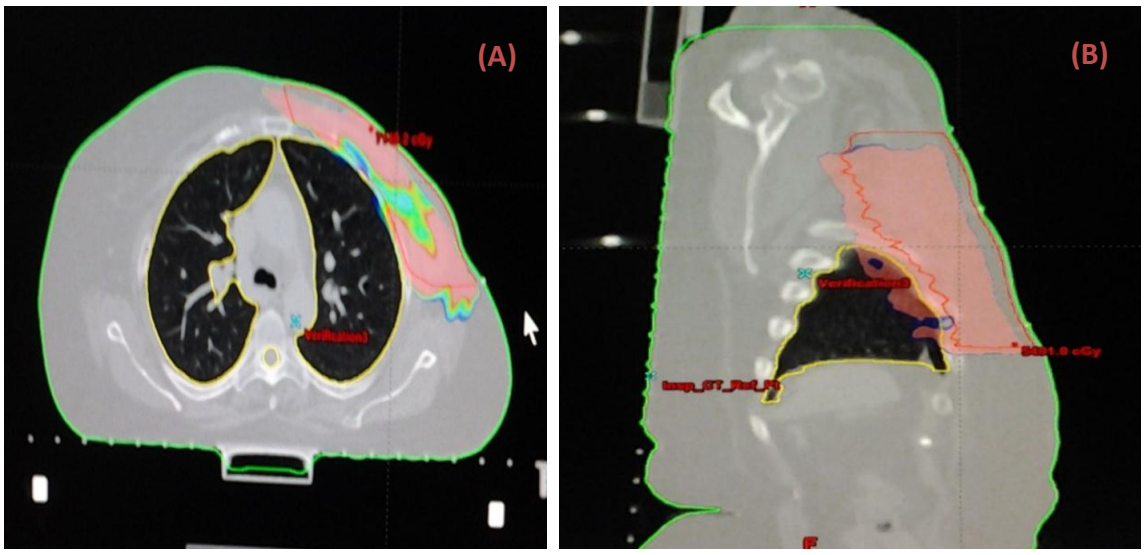


Figure 4.14 a&b: Shows the 95% isodose colour wash in axial and sagittal section at the level of carina and head of humerus respectively on **Normal Inspiration CT scan** with IMRT plan

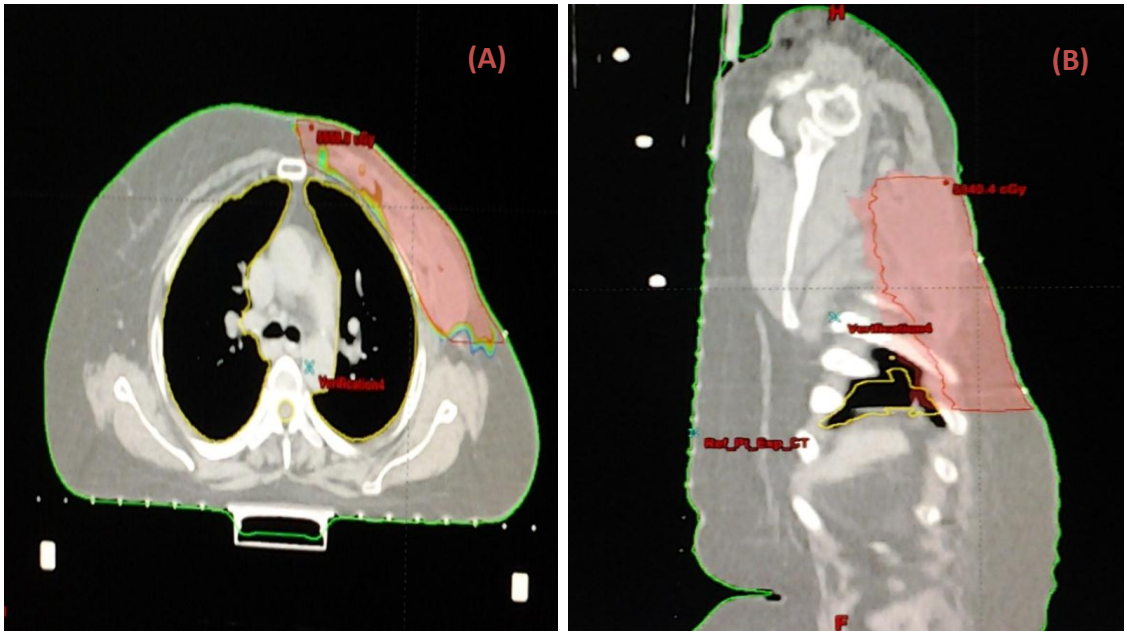


Figure 4.15 a&b: Shows the 95% isodose colour wash in axial and sagittal section at the level of carina and head of humerus respectively on **Normal Expiration CT scan** with IMRT

The above figures 4.13- 4.15 show the 95% isodose colour wash covering the target. As seen, the coverage is good in the Free breathing CT scan. However, in the normal inspiration CT scan, the areas of cold spots can be noticed. The cold spots were predominantly in the anterior and superior portions of the target volume. There were some areas of cold spots in the normal expiration CT scan as well.

The spillage of the 95% isodose colour wash into the ipsilateral lung can also be visualised in the normal inspiration CT scan. However, the heart is spared.

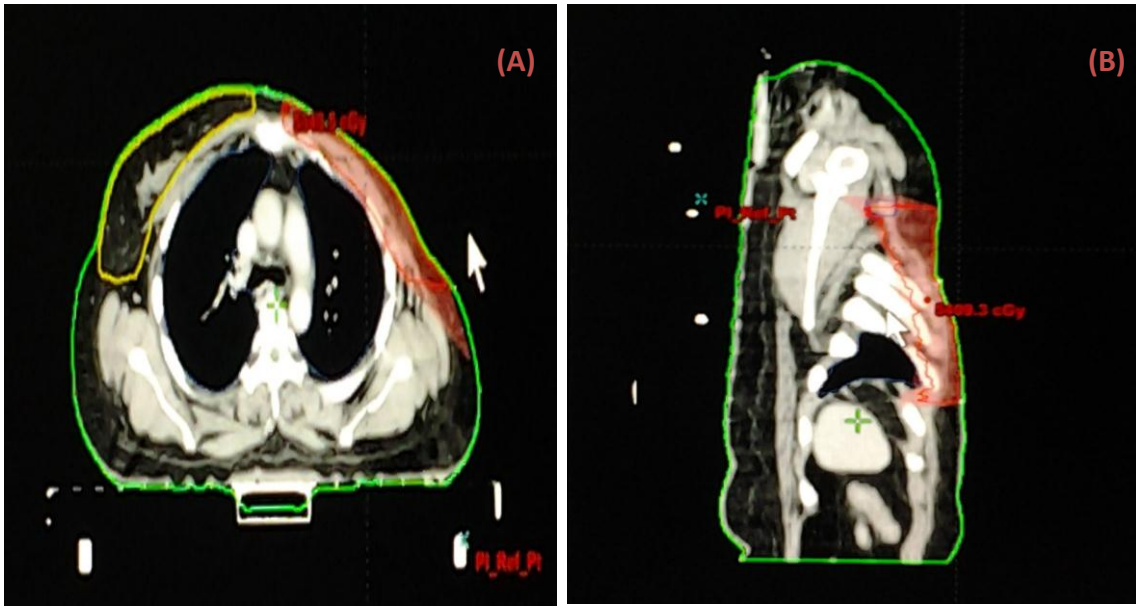


Figure 4.16 a&b: Shows the 95% isodose colour wash in axial and sagittal section at the level of carina and head of humerus respectively on **Free breathing CT scan** with 3D-CRT plan

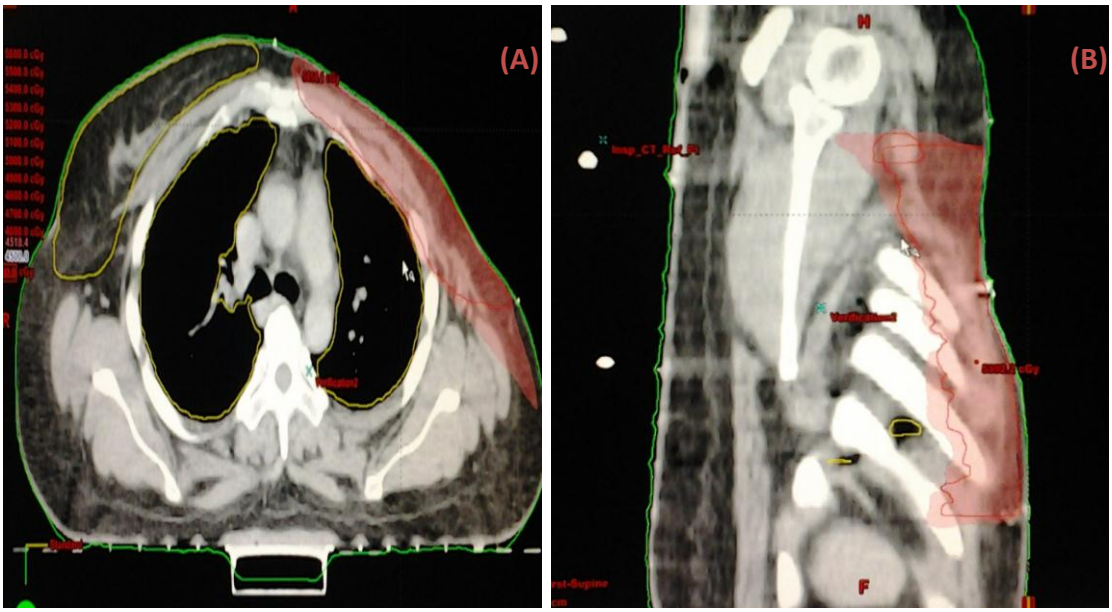


Figure 4.17 a&b: Shows the 95% isodose colour wash in axial and sagittal section at the level of carina and head of humerus respectively on **Normal inspiration CT scan** with 3D-CRT plan

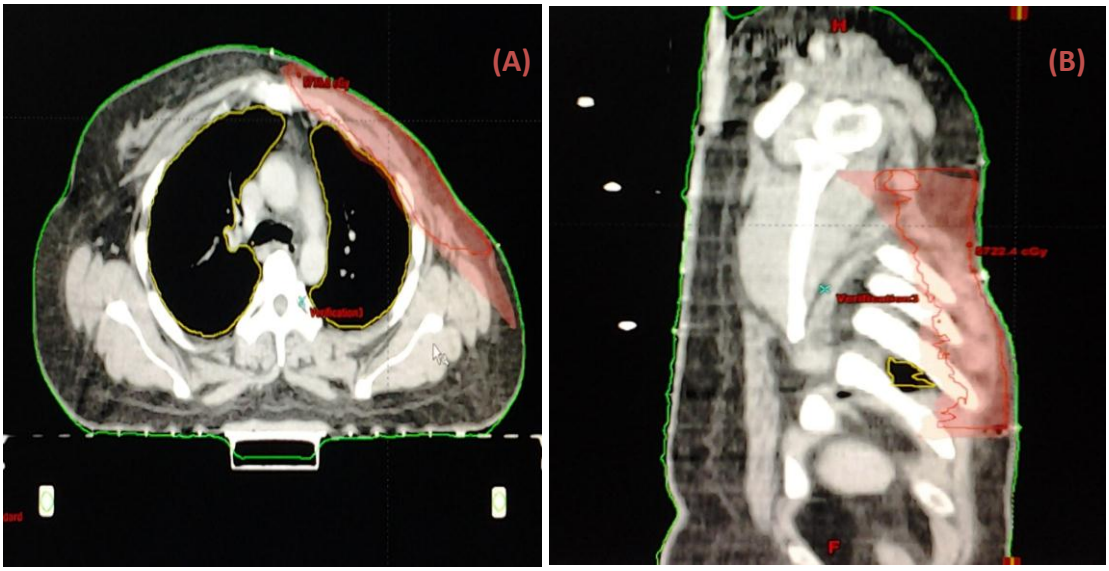
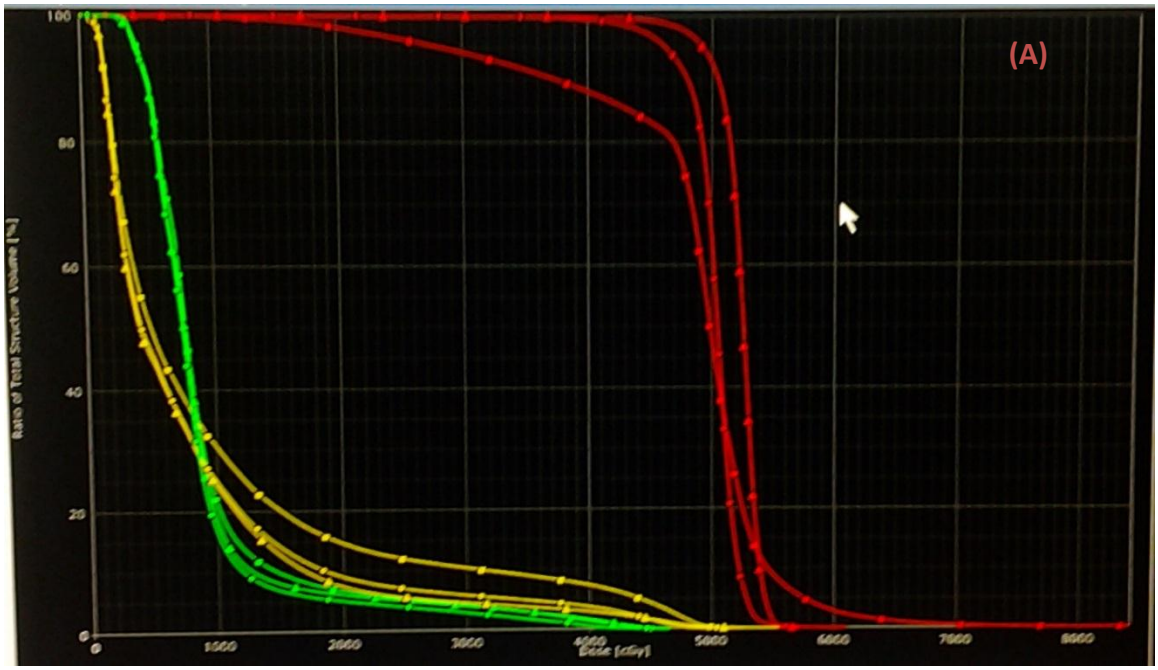


Figure 4.18 a&b: Shows the 95% isodose colour wash in axial and sagittal section at the level of carina and head of humerus respectively on **Normal Expiration CT scan** with 3D-CRT plan

The 3D-CRT plan images are of the same patient as that of the IMRT plan images were taken and it showed that though there were few areas of cold spots in the normal inspiration and expiration images, it was not as clear as that seen with IMRT.

4.8 COMPARISON OF DVH BANDS GENERATED FOR A PATIENT WITH TIDAL VOLUME MORE THAN 0.68L VERSUS A PATIENT WITH TIDAL VOLUME LESS THAN 0.68 L



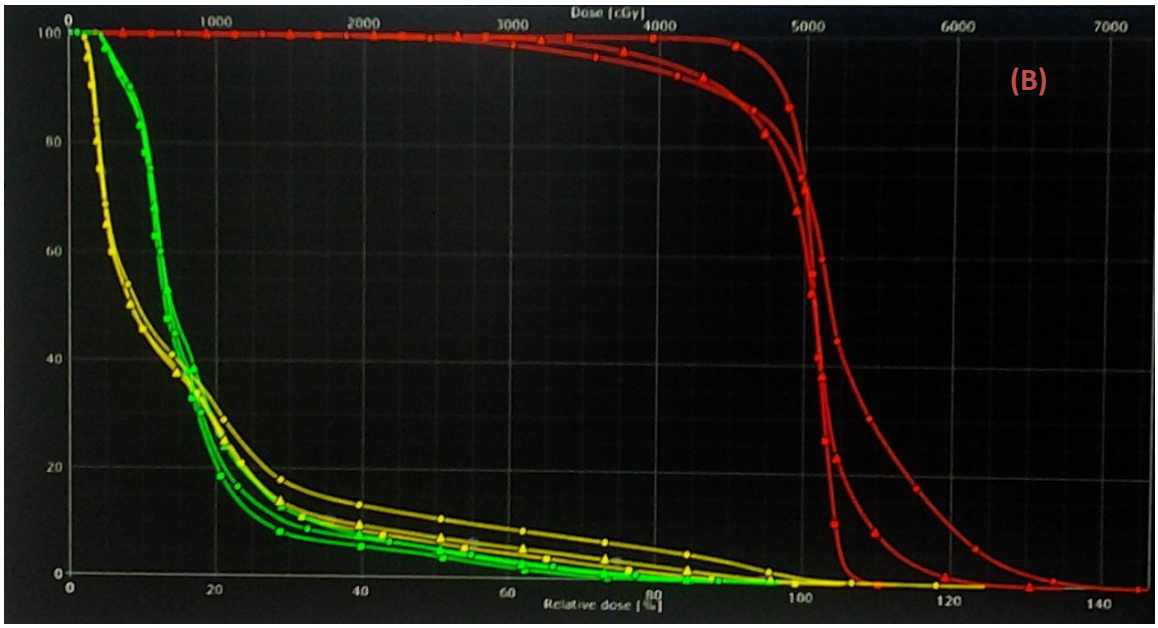


Figure 4.19 a&b: Shows the DVH band of target coverage (red), combined lungs (yellow) and heart (green). **Figure 4.19 a** (patient with TV> 0.68) shows a wider DVH band for target coverage and combined lungs when compared to Figure **4.19 b** (patient with TV <0.68)

5. DISCUSSION

The benefit of inversed planned IMRT over 3D tangential therapy and forward planned IMRT has been studied extensively in whole breast radiotherapy(23,24,26,41–51). However literature on post-mastectomy IMRT is scarce. As we all know, there is definite geometric difference between chest wall and whole breast, and these differences distinctly affect the dose distributions. It is further complicated by the errors in thoracic radiotherapy which consists of both set up error as well as error due to respiratory motion. The effect of respiratory motion has been studied in whole breast treatments but its effect on chest wall radiotherapy is poorly understood(34,52–61).

According to our knowledge, this is the first study which has comprehensively evaluated the dose to target as well as organs at risk and its changes with respiration in both IMRT and 3D conformal tangential therapy in post-mastectomy breast cancer radiation.

All the patients recruited for the study were trained to hold their breath in inspiration and expiration for the duration of planning CT scan of Thorax. Contouring of target and organs at risk in all 3 image sets (free breathing, normal inspiration and expiration) was carried out according to established standards. The IMRT and 3D planning was done for each patient and it was time consuming. Planning of all the patients recruited could not be completed at the time of this report and therefore only 10 patient's data was analysed.

5.1 MAGNITUDE AND MEASUREMENT OF RESPIRATORY MOTION IN THE PATIENTS RECRUITED

The magnitude of respiratory motion differs considerably between patients. We found that the respiratory rate differed between 15 breaths/ minute to 30 breaths/minutes among the 10 patients analysed (Table 4.2). The chest wall expansion varied between 0.5 to 1.2 cms with a median of 0.5 cms and 75% quartile of 1 cm. 3 out of 10 patients had a

chest wall expansion of more than 1 cm (Figures 4.1 and 4.2). Korreman et al used RPM (Varian Real time Respiratory Position Management) system to show the mean chest wall excursion and found that at free breathing, the mean antero-posterior chest wall movement was 2.5 mm(52). Similary, Pederson et al also studied the antero-posterior excursion of chest wall in free breathing and found it to be 2.5 mm(53). Both these studies were done on patients with conserved breasts. They found that the mean heart dose could be reduced by using inspiratory gating or deep inspiratory breath-hold technique.

In the absence of respiratory management techniques which is propagated in the use of IMRT for breast cancer, we proposed this study to evaluate the correlation between the respiratory parameters and the target. Our study found that the mean tidal volume varied between 0.44 to 0.85 litres with a median of 0.68 L. 5 out of the 10 patients had a tidal volume of over 0.68 L. These are the patients who can be thought of as those with higher likelihood of changes with respiration. Peters et al has also documented that the lung volume changes by 10-25% with normal respiration.

5.2 THE IMPACT OF RESPIRATORY MOTION ON INTENSITY MODULATED RADIOTHERAPY PLAN

Target:

This study demonstrated that there is definite under coverage of target in inspiration and expiration with IMRT plan (Tables 4.3-4.6). Its magnitude was more than 5% in all the parameters assessed V90, V95, V100 and D95, reaching 10% variation in the parameter V95. A target under coverage of more than 5% in a clinical setting is significant. Even though it may be argued that the patient is not constantly in a respiratory phase in which target under dosage will occur, the fact is free breathing CT scan does not give the exact picture of target coverage or dose to organs at risk.

Keall et al has proven dosimetrically that respiratory motion causes considerable issue for IMRT delivery as beam intensity gradient is not confined solely to edges of the beams. Target while moves within this field in its own velocity different from that of the MLC leaves as well as deformation during its movement adversely affects the target coverage(35). Phantom studies which evaluated the effect of respiratory motion on target coverage with IMRT showed that difference in target doses between stationary and moving phantom ranged between -18.8% to 19.7%. Due to their random nature it was concluded that errors will average out during fractionated treatment and that IMRT treatments can be employed in targets which move with respiration(61)**.** However, the point to be noted is that stationary phantom or moving phantom can't be equalled to a patient whose breathing pattern is not regular.

Analysing the magnitude of hot spots we found that it crossed the limit of 10% in both inspiratory CT images as well as expiratory CT images (Tables 4.7 & 4.8). Hot spot of more than 10% in IMRT technique is significant and not acceptable. Especially in the setting of chest wall irradiation, where the hot spot may fall on organs at risk such as lungs, heart or brachial plexus (if nodal regions are being irradiated). This cannot be corrected by on board imaging and correction would require target tracking, which also is not likely to give 100% accuracy.

The magnitude of cold spots in an IMRT plan was assessed by the parameter D98 of target volume (dose received by 98% of target volume). Comparison of the D98 of target in the 2 phases of breathing (inspiration and expiration) with the free breathing CT scan showed that respiration results in production of cold spots within the target. The mean D98 in inspiration was less by 28.9% of the planned dose (Table 4.9).

Organs at risk:

The variation in dose received by organs at risk with respiration in post-mastectomy setting was analysed (Table 4.10). It was found that there was minimal change in mean combined lung volume receiving 20 Gy with respiration (1.21%)

Rudat et al compared tangential beam IMRT versus tangential 3D- CRT, Koshy et al tried a novel technique such as non- coplanar intensity modulated radiotherapy and Cavey et al analysed conventional versus forward planned IMRT (1,62,63) to spare normal tissue. From these studies it was concluded that IMRT results in increased conformity index in the target with sparing of lungs and heart especially in left sided breast irradiation. However, George et al showed in whole breast treatments that lung and heart doses increases with respiratory motion(60). Increase in dose to organs at risk with respiration was seen in this study as well, but it did not cross the tolerance limits (V20 < 20% for combined lung and V20 < 30% for ipsilateral lung).

We analysed the cardiac dose variation with respiration in the 10 study patients and found that mean heart volume (V25) receiving 25 Gy in free breathing, normal inspiration and expiration was as low as 2.53%, 3.91% and 2.15% respectively. They did not cross the tolerance limit of 10% with respiration (Table 4.11). However, in 1 of the 10 patients this criteria was not satisfied and the V25 was 12.8%. 4 of the 10 patients had left sided tumour, the mean cardiac dose of these patients in free breathing, normal inspiration and expiration was 5.37%, 7.95% and 3.65%. These means were also within the tolerance limit.

Ischemic heart disease, a late adverse effect of breast cancer irradiation has been evaluated at length and found to correlate with radiation dose. Though various methods of reducing the heart dose are available such as use of Non coplanar IMRT, we know that dose changes with respiration(26,28,54,59,62,64–66). A clinical trial by Tezcanli et al

analysed the cardiac dose variation with respiration in patients receiving IMRT for breast cancer (post breast conservation surgery or post mastectomy) and found that though the difference for whole heart, right and left ventricles, right and left atria, LAD+5 mm were not significant, the mean heart dose did cross the tolerance dose with inspiration in some patients (3 out of 10 patients). They concluded that radiotherapy planning for left sided breast cancer patient without breath control technique is not capable of compensating for whole intra fraction heart and its components' volumes and dose changes (67).

In this study the dose received by contralateral breast was higher with IMRT plan but it was limited to a tolerance dose of <5% of prescribed dose. Inspiration and expiration did not affect the dose received by contralateral breast. Van der Laan et al and others have also shown that the contralateral breast dose is higher with IMRT when compared to 3D-CRT(68).

We documented that dose received by non-target tissue by the parameter V2%, V5% and V10% of the total body volume and found that it was as high as 59.18%, 41.78% and 29.59% in free breathing, normal inspiration and normal expiration respectively. Study done by Palm and Johansson et al compared the out of field dose with conventional, IMRT and proton therapy and found that though IMRT results in increased dose to target tissue and reduced dose to nearby normal tissue, it also resulted in increased out of field dose and irradiated non-target volume(69).

5.3 THE IMPACT OF RESPIRATORY MOTION ON 3D CONFROMAL TANGENT RADIOTHERAPY PLAN

Respiratory motion affects all techniques of post- mastectomy radiotherapy but its magnitude changes with the technique. The need for normal tissue sparing has become of extreme importance with the growing use of chemotherapy. Thus, it is thought that

technologies which are capable of delivering high dose to tumour while sparing healthy tissue will balance the complication and cure rates. While advocating for respiratory motion management techniques in breast cancer radiotherapy, it is important to remember that these techniques are neither patient nor treatment team friendly. Thus it is not an easy solution to respiratory motion induced errors of radiotherapy(35).

It is also important to be aware that respiratory motion is just one potential source of error in radiotherapy. Smith et al showed that the magnitude of error caused by respiratory motion is less than that induced by set up issues(34). However, to ensure target coverage a large PTV margin should be given. Thus, during 3D planning of chest wall radiotherapy the MLCs are kept at-least 1 cm away from the skin and 0.5 cm into the lung. This increased treatment volume increases the likelihood of treatment related complications. At the same time, if margins are not adequate part of the CTV will not get covered. Since, all patients are given the same PTV margin it can be postulated that target under coverage is likely to happen in those with larger chest wall movement during respiration.

As the 3D treatment duration of 40 seconds consists of 14 breaths per fraction, it is postulated that the intra-fraction organ motion causes an averaging or blurring of dose distribution over the path of motion. This results in the deviation between intended and delivered dose distribution. Since in non IMRT treatments the dose gradient in the centre of the field is small, the blurring of dose distribution occurs only at the edge of the field thereby increasing penumbra(35). Thus target under coverage is likely to occur only at the beam edges in case of 3D treatment.

Target:

In this study we see that the overall target coverage with 3D conformal tangent technique was less than IMRT. Respiration also added to target under-coverage. Opp et al has also studied target coverage in various techniques of post- mastectomy radiotherapy and concluded that IMRT and Bolus electron conformal therapy had the best target coverage and least heart dose when compared to field in field or tangential radiotherapy(70).

Target coverage in various phases of respiration for 3D conformal tangents technique was analysed by comparing parameters such as V90, V95, V100 and D95 (Tables 4.12-4.15). It was found that there was mild under-coverage of target volume with respiration. The mean target under-coverage in terms of V95 with inspiration and expiration were 3.12% and 3.63% respectively.

Evaluating the magnitude of variation of hot spots with respiration, it was found that there was minimal/ no increase in hot spot (Tables 4.16 & 4.17).

There was an increase in cold spots within the target with respiration in 3D-CRT plans as well. However, the magnitude was less when compared to IMRT. The cold spot within the target was reduced by 14% with respiration (Table 4.18).

Organs at risk:

Documentation of the doses received by organs at risk in different phases of respiratory motion in 3D CRT plan was important to finally compare the effect of respiratory motion on the 2 techniques of radiation.

Our study (Table 4.19) showed that there was only a minimal increase in the volume of lungs receiving 20 Gy with normal inspiration and expiration. However it didn't cross the tolerance limits (V20 <20% for combined lungs and V20<30% for ipsilateral lung).

Similarly, there was only minimal variation of Heart dose with respiration (Table 4.20). Sub analysis of the 4 patients who had left sided radiotherapy showed that the cardiac dose was higher than IMRT and the mean cardiac dose crossed the limit of 10% with respiration.

Dose to contralateral breast with 3D conformal tangent technique was low and had no significant variation with respiration (range 1.37 to 1.56%), Table 4.28.

Integral dose was low and did not change with respiration (Table 4.29).

5.4 A COMPARISON BETWEEN THE IMPACT OF RESPIRATORY MOTION ON INTENSITY MODULATED RADIOTHERAPY PLAN VERSUS 3D CONFORMAL RADIOTHERAPY

There is no gold standard technique for the delivery of radiation for breast cancers, especially in post-mastectomy setting. The ideal radiotherapy plan for each patient differs according the patient anatomy and the regions that need to be treated. The main advantage of IMRT over 3D conformal tangent quoted in literature is the sparing of organs at risk and the improved conformity index, specifically when nodal regions need to be treated(1). Al-Rahbi et al did a dosimetric comparison between 3D CRT, forward planned IMRT and inverse planned IMRT (10 out of 20 patients evaluated were post- mastectomy). He concluded that all 3 techniques achieved comparable target coverage, inverse planned IMRT had better conformity index at the cost of homogeneity(71). These advantages were

clearly seen even in our study as well. However, the magnitude of impact of respiratory motion on IMRT and 3D CRT for chest wall needed to be evaluated.

Target:

Table 4.22 shows that when a bivariate analysis is done to compare 2 means, the difference in target under-coverage with normal inspiration and normal expiration are significant in an IMRT plan while that in 3D conformal tangents plan is not significant. This target under coverage is well depicted in Figure 4.3.

From Table 4.23 we can conclude that the increase in hot spots with inspiration in IMRT plan was significant while that with 3D conformal tangents was not. This increase in hot spots in IMRT plan is depicted clearly in Figure 4.4.

Table 4.24 showed that there was significant increase in cold spots in IMRT plan with inspiratory and expiratory phases while that with 3D conformal tangents was not significant. Figure 4.5 shows the difference in cold spots with respiration in IMRT versus 3D-CRT, favouring the latter.

Organs at risk:

In 8 out of the 10 study patients, lung dose with 3D CRT was more than that of IMRT. Similarly with the heart dose, 8 out of 10 patients had better whole heart sparing with IMRT than 3D CRT. However, the evaluation of the effect of respiratory motion on the dose to organs at risk needed comparison.

From Tables 4.25 and 4.26 we can conclude that increase in lung dose with respiration was significant with IMRT while that with 3D conformal tangents was not.

Table 4.27 showed that the increase in heart dose with respiration in IMRT and 3D conformal tangents are not significant. However, the volume of heart receiving 25 Gy crossed the limit of 10% with 3D-CRT in left sided tumour. Hence, it can be concluded that heart sparing is better with IMRT even in the presence of error caused by respiratory motion.

It was seen that the mean contralateral breast dose was higher with IMRT than 3D CRT. However, it did not change with respiration (Table 4.28).

This study also shows that integral dose is higher with IMRT than 3D CRT, though there was no change with respiration (Table 4.29).

Comparison of the duration of treatment with IMRT and 3D-CRT

IMRT treatment of chest wall takes 8 minutes while 3D CRT treatment of chest wall is completed in 40 seconds (beam on time). The mean respiratory rate of the 10 patients studied was 20.3 breaths/ minute. The predicted number of breathing cycles per treatment fraction will be 162 with IMRT and 14 with 3D conformal therapy. Thus we can infer that even small changes in target coverage and dose to organs at risk with respiration can adversely affect an IMRT plan when compared to a 3D CRT plan. The duration of beam on time is more with hypofractionated radiotherapy and hence this effect may be more pronounced if we use treatment regimens such as 4005 cGy in 15 fractions proposed by UK START trial(72) or the proposed 5 fraction regimen by FAST FORWARD trial(73)

5.5 CORRELATION BETWEEN THE MAGNITUDE OF RESPIRATORY MOTION AND ITS EFFECT ON RADIATION THERAPY TECHNIQUES

This study clearly demonstrates that there is definite under coverage with respiration in both techniques of post-mastectomy radiotherapy (IMRT and 3D CRT). The effect of respiratory motion on IMRT was more than that on 3D CRT plans. However, we wanted to further qualify this finding on the basis of patient's tidal volume (TV) and chest wall movement. The reason behind this was, our knowledge from literature shows that larger chest wall movement causes greater target under dosage and over dosage of organs at risk. We also did not want to totally negate the benefits of IMRT over 3D CRT in terms of organ sparing and dose homogeneity especially in patients who require nodal irradiation.

Thus, by categorising the 10 study patients according to their tidal volume (Category 1- TV $\leq$ 0.68L and Category 2- TV >0.68L, where 0.68 L was the median value of the 10 patients), we found that the effect of respiratory motion on IMRT plan was more in patients belonging to Category 2 (Figure 4.9). Because of the small sample size only a trend could be shown and significance of this finding could not be ascertained.

Similarly, the 10 study patients were also categorised according to their chest wall movement (Category 1- Expansion $\leq$ 0.5 cm, Category 2- Expansion > 0.5 cm, where 0.5 cm was the median value of the 10 patients). We found that there was a trend favouring 3D CRT plan when a patient's expansion on larger than 0.5 cm (Figure 4.11).

DVH bands seen in Figure 4.19 (the cumulative DVHs in free breathing, normal inspiration and normal expiration are plotted simultaneously) show the variation in target coverage and dose to organs at risk with respiration. When such bands were generated for a patient with high tidal volume and one with low tidal volume, it was noticed that the

width of the band was larger in patient with larger tidal volume than in one with low tidal volume indicating a higher influence of respiration on coverage in an IMRT plan.

5.6 RECOMMENDATIONS

IMRT to chest wall is recommended only for patients with chest wall deformities and in patients for whom heart sparing is of utmost importance (for eg. patients with cardiac comorbidities). This study showed that the heart doses with 3D CRT in left sided breast cancer patients crossed the tolerance limit of 10% with respiration.

Respiratory parameters have to be assessed prior to choosing the technique of post-mastectomy radiotherapy. For patients with high tidal volume or chest wall movement, 3D CRT technique might be more beneficial in terms of target coverage in a setting where respiratory management techniques are not practiced.

5.7 LIMITATIONS

The first 16 patients with breast cancer due for post-mastectomy radiotherapy who consented to take part in the study were randomly recruited. Though spirometry details and graphs of patients maintaining inspiratory breath hold and expiratory breath hold for the duration of a CT scan were documented, there was no on board verification of breath hold during the planning CT scans. IMRT and 3D planning of only 10 out of the 16 patients could be completed in the stipulated time. This sample size is small to predict the correlation between Tidal volume and chest wall expansion with target coverage/ dose to organs at risk.

5.8 AVENUES FOR FUTURE RESEARCH

In the Indian setting it is important to channel research towards cost effective as well as patient friendly treatment strategies. We have sparse knowledge on various areas of breast cancer radiotherapy which need future research:

- Similar study on larger sample size is required testing the significance of the trends seen in this study
- Changes in respiratory pattern between simulation and treatment.
- Does dosimetric research transform into information which is critical for clinical decision making?

6. CONCLUSIONS

6.1 MAGNITUDE OF RESPIRATORY MOTION AND ITS IMPACT ON BREAST CANCER RADIOTHERAPY

1. The magnitude of respiratory motion varies from person to person. Respiratory motion definitely affects target coverage in IMRT plans when compared to 3D CRT plans. Dose inhomogeneity increased within the target volume with respiration and its minimal dose was decreased by 28% in IMRT when compared to 14% in 3D-CRT.

2. There was a trend favouring 3D CRT technique for chest wall in patients with large tidal volume or chest wall expansion. However, it needs to be tested in a larger sample.

3. There was definite increase in lung dose with respiration in IMRT and 3D-CRT techniques, but being within the tolerance limits is unlikely to cause any clinical adverse effect. On the other hand, volume of heart receiving 25 Gy in patients with left sided breast cancer crossed the tolerance limit of 10% with respiration in 3D-CRT and might be predictive of higher long term cardiac complication rate. Contralateral breast dose and integral doses were much higher with IMRT technique when compared to 3D-CRT but respiration had no significant effect on its magnitude.

6.2 CONCLUDING REMARKS

Respiration induced errors form a significant component of the total error in post-mastectomy radiotherapy. Respiratory pattern varies greatly between individuals and hence it is important to consider the patient's respiratory pattern prior to choosing the technique of post mastectomy radiotherapy. Larger studies are required to confirm the finding of this work.

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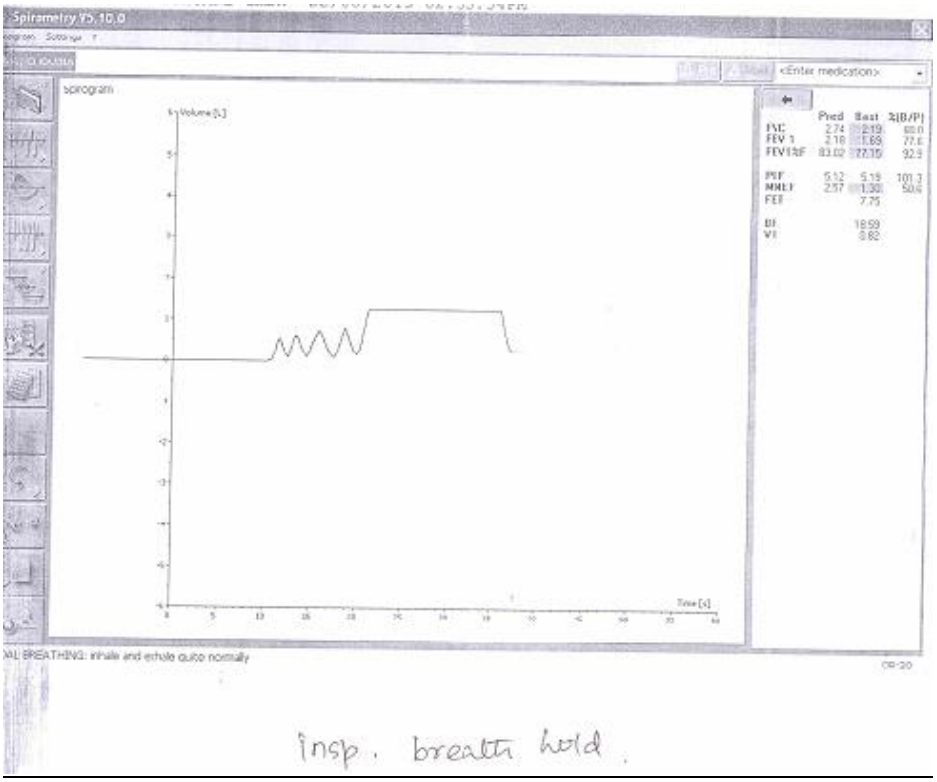
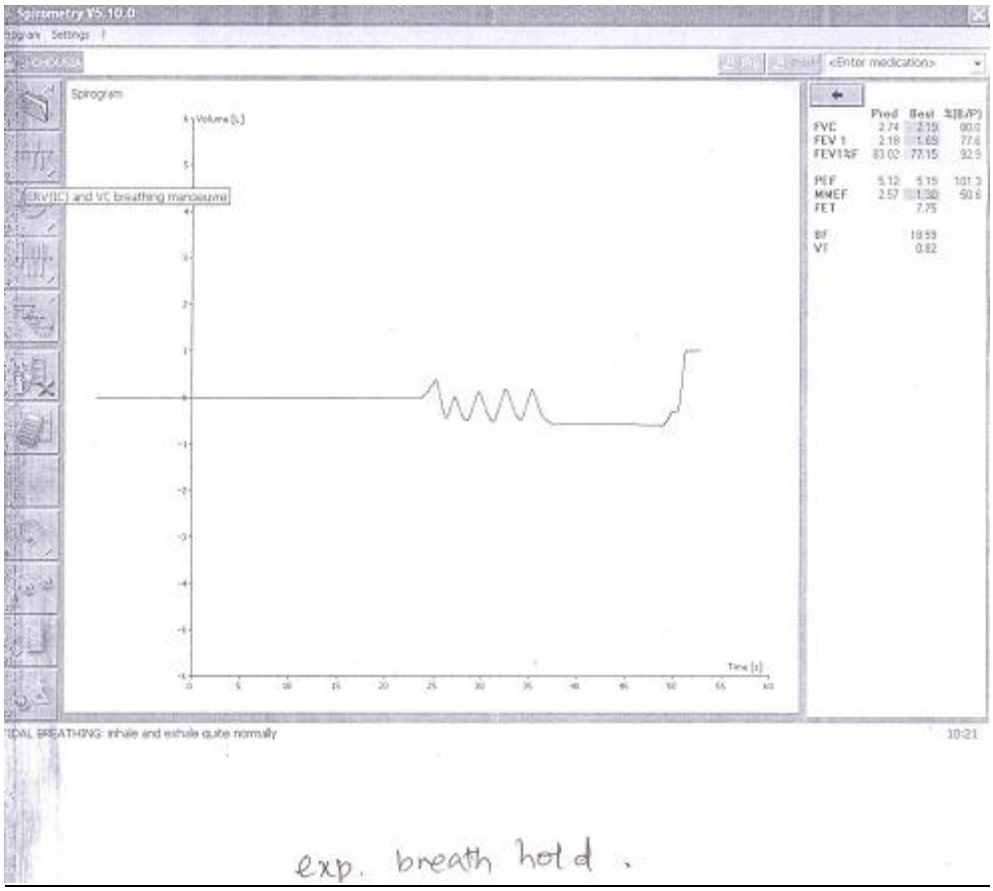
APPENDIX

Appendix 1

Spirometry documentation of breath hold in inspiration and expiration





Appendix II

RTOG contouring guidelines

	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Chest wall	Caudal border of the cavicle head	Clinical reference + loss of CT apparent contralateral breast	Skin	Rib-pleual interface (includes the pectoralis muscles, chest wall muscles and ribs	Clinical reference/ mid axillary line typically, excluses lattismus dorsi muscle	Sternal-rib junction
Supraclavicular	Caudal to cricoid cartilage	Junction of brachioceph-axillary veins/ caudal edge of clavicle head	Sternocleid omastod muscle	Anterior aspect of scalene muscle	Cranial-lateral edge of SCM Caudal-junction 1st rib- clavicle	Excludes thyroid and trachea

Appendix III

Information sheet

Department Of Radiation Oncology, Unit I

Christian Medical College & Hospital, Vellore

Study Title: To assess the impact of respiratory motion on intensity modulated radiation therapy to chest wall for breast cancer patients- A dosimetric analysis

Study No : **Subject's Name :**

Subject's Initial : **Date of Birth /Age :**

You are being requested to participate in this study to see whether respiratory motion significantly affects radiotherapy to chest wall

1. **What is this study about?**

   This study aims to generate criteria for selections of patients for the various techniques of radiation therapy (Intensity modulated radiotherapy and 3D conformal tangents).

2. **What is Intensity modulated radiotherapy?**

   It is a technique of radiation therapy which utilizes multiple beams of varying intensities to treat a particular target (which will be the chest wall in this particular case). The advantage of this technique is that it is capable of delivering required radiation dose to chest wall while reducing the radiation dose to underlying lungs and heart.

3. **What is 3D conformal tangent based radiotherapy?**

It is a technique of radiation which utilizes multiple tangent beams to treat the chest wall. This technique is also capable of reducing the dose to lungs and heart to a certain extent.

4. Why is this study being done?

The movement of chest wall during respiration can adversely affect the radiation dose to chest wall, lungs and heart. This dose variation is not significant in all patients. It is proposed that patients who have a heavy breathing pattern are likely to have dose variations which need adjustment. Thus this study aims to document the effect of respiration on radiotherapy to chest wall as well as identify the technique which is more suitable for each patient on the basis of their respiratory pattern.

5. What is done in the study?

In this study, patients will have to undergo baseline documentation of respiratory parameters such as Spirometry and Lung volumes. They will be trained to hold breath for short durations. They will then undergo simulation under fluoroscopy. Planning CT scan will be done at Free breathing, Inspiratory breath hold and Expiratory breath hold. Further analysis will be done with the use of these CT scans.

6. What is the adverse effect from taking part in this study?

A total of 3 CT scans will be done for radiation therapy planning. An effective dose of 7 mSv will be absorbed by the body during each CT scan.

7. What is the chance of you developing any study related injury?

The chance of developing study related injury is very low. Patients who will be recruited for this study are those who are planned for post mastectomy radiation therapy to chest wall. A dose of 50 Gy in 25 fractions will be delivered to chest wall. Thus an additional radiation exposure of 7 mSv is unlikely to have any adverse effect.

8. Will you have to pay for the study?

You will have to pay for the pre radiation therapy work up, IMRT planning and simulation as well as treatment charges. No additional cost will be incurred because study procedures are already included in the treatment cost.

9. **What happens after the study is over?**

   Once the CT scans are done, you are no more part of this study. You will receive treatment as per schedule.

10. **Will your personal details be kept confidential?**

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

PERSONS TO CONTACT FOR FURTHER INFORMATION AND IN IMMEDIATE NEED:

Dr Judith Aaron, Department of Radiation Oncology, Christian Medical College, Vellore; (Mobile No : 9894803915)

Dr Balukrishna S, Department of Radiation Oncology, Christian Medical College, Vellore

Dr Selvamani Backianathan, Department of Radiation Oncology, Christian Medical College, Vellore

Appendix IV

Informed consent:

Study Number:

Subject's Initials: _____ Subject's Name: _____

Date of Birth____/____/_____(DD/MM/YYYY) / Age: _____yrs

Study Title: To assess the impact of respiratory motion on intensity modulated radiation therapy to chest wall for breast cancer patients- A dosimetric analysis

(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 the Sponsor of the clinical trial, others working on the Sponsor's behalf, the 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. 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 Representative:_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____ Signature of the Witness: _____

Date: _____/_____/_____ Date: _____/_____/_____

Study Investigator's Name of the Witness:

Name: _____ _____

Appendix V

Data collection sheet

		IMRT FB	IMRT NI	IMRT NE	3D FB	3D NI	3D NE
TARGET	V90						
	V95						
	V100						
	V107						
	D95						
	D2						
	D98						
IPSILATERAL LUNG	V20						
	V10						
CONTRALATERAL LUNG	V20						
	V10						
COMBINED LUNGS	V20						
	V10						
HEART	V25						
OPPOSITE BREAST	D mean						
BODY	V2%						
	V5%						
	V10%						

Appendix VI

DATA

NAME	HOSP NO	AGE	BMI	STAGE	LATERALITY	RR	TV	CHEST EXPANSION
Devaki	124100c	55	29.4	II	LEFT	22	0.75	1.2
Preethal	340572f	72	28.1	II	RIGHT	30	0.84	0.5
Kamalamma	576064b	62	29	III	LEFT	15	0.47	1
Nasreen	433143f	44	29.3	II	RIGHT	21	0.85	0.5
Sabita	348507f	48	35.1	III	RIGHT	19	0.59	0.5
Thamayanthi	311522f	41	30.2	II	RIGHT	21	0.75	1
Shiny	385009f	35	22.5	II	RIGHT	22	0.49	0.5
Jesmin	432933f	53	20.9	II	LEFT	18	0.6	0.5
Ghousia	402630f	44	36.4	III	RIGHT	18	0.8	0.5
Shanthi	433413f	47	27	II	LEFT	17	0.44	0.5

Appendix VII

PLAGIARISM- Originality Report

Impact of respiratory motion on IMRT (Intensity modulated radiotherapy) of the chest wall in post-mastectomy breast cancer patients: A dosimetric comparison with 3D conformal radiotherapy

ORIGINALITY REPORT

9%	5%	5%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

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2	Frazier, R.C.. "Impact of breathing motion on… Publication	1%
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Assignment title	Medical
Author	Judith Aaron
E-mail	judithaaron3@gmail.com
Submission time	06-Dec-2013 09:29PM
Total words	15420

First 100 words of your submission

1. INTRODUCTION The field of oncology has expanded drastically in the past decade, in terms of both treatment options and expertise. Most of these options while improving overall survival and / or quality of life have increased the total expenditure of cancer treatment. Breast cancer, a common cancer among women is an example of this expansion that has occurred in the world of oncological treatments. We have moved from the era of radical surgeries to breast conservations, from CMF regimen of chemotherapy to anthracyclines and taxanes, various hormonal and targeted therapies, conventional radiation therapy and 3D conformal tangents to intensity modulated radiotherapy with image guidance,...

Appendix VIII

Institutional Review Board Approval

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002, INDIA

Dr.B.J. Prashantham, M.A.,M.A.,Dr.Min(Clinical)
Director, Christian Counseling Centre
Editor, Indian Journal of Psychological Counseling
Chairperson, Ethics Committee, IRB

Dr. Alfred Job Daniel, D (Ortho), MS Ortho, DNB (Ort
Chairperson, Research Committee &
Principal

Dr. Nihal Thomas
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

January 22, 2013

Dr. Judith Aaron
PG Registrar
Department of Department of Radiotherapy
Christian Medical College, Vellore 632 002

Sub: **FLUID Research grant project NEW PROPOSAL:**
Impact of respiratory motion on IMRT (Intensity modulated radiotherapy) of the chest wall in post-mastectomy breast cancer patients: A dosimetric comparison with 3D conformal radiotherapy. Dr. Judith Aaron, PG Registrar, Radiotherapy, Dr. Selvamani, Dr. Balukrishna Sasidharan, Mr. Ebenezer Suman Babu, Radiotherapy, Dr. Balamugesh, Pulmonary Medicine, Dr. Antonisamy, Biostatistics.

Ref: IRB Min. No. 8118 dated 05.12.2012

Dear Dr. Judith Aaron,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Impact of respiratory motion on IMRT (Intensity modulated radiotherapy) of the chest wall in post-mastectomy breast cancer patients: A dosimetric comparison with 3D conformal radiotherapy." on December 5, 2012.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Patient Information Sheet and Informed Consent Form (English, Tamil, Hindi and Malayalam)
3. Cvs of Drs. Balukrishna Sasidharan, Antonisamy, Selvamani Mr. Ebenezer Suman Babu, Balamugesh.
4. A CD containing documents 1 - 3

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002, INDIA

Dr.B.J. Prashantham, M.A.,M.A.,Dr.Min(Clinical)
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Chairperson, Research Committee &
Principal

Dr. Nihal Thomas
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

The following Institutional Review Board (Research & Ethics Committee) members were present at the meeting held on December 5, 2012 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. Susanne Abraham	MBBS, MD	Professor, Dermatology, Venerlogy & Leprosy, CMC.	Internal, Clinician
Dr. Benjamin Perakath	MBBS, MS, FRCS	Professor, Surgery (Colorectal), CMC.	Internal, Clinician
Dr. Priya Abraham	MBBS, MD, PhD	Professor, Virology, CMC	Internal, Clinician
Dr. Bobby John	MBBS, MD, DM, PHD, MAMS	Cardiology, CMC	Internal, Clinician
Dr. Denny Fleming	BSc (Hons), PhD	Honorary Professor, Clinical Pharmacology, CMC.	Internal, Pharmacologist
Dr. Simon Rajaratnam	MBBS, MD, DNB (Endo), MNAMS (Endo), PhD (Endo), FRACP	Professor, Endocrinology, CMC	Internal, Clinician
Dr. Anup Ramachandran	PhD	The Wellcome Trust Research Laboratory Gastrointestinal Sciences	Internal
Dr. Chandrasingh	MS, MCH, DMB	Urology, CMC	Internal, Clinician
Dr. Anil Kuruvilla	MBBS, MD, DCH	Professor, Neonatology, CMC.	Internal, Clinician
Dr. Paul Ravindran	PhD, Dip RP, FCCPM	Professor, Radiotherapy, CMC	Internal

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

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CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002, INDIA

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Dr. Nihal Thomas
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Mr. Sampath	BSc, BL	Advocate	External, Legal Expert
Mr. Harikrishnan	BL	Lawyer, Vellore	External, Legal Expert
Mrs. Mary Johnson	M.Sc	Professor, Child Health Nursing, CMC.	Internal, Nurse
Mr. Joseph Devaraj	BSc, BD	Chaplain, CMC	External, Social Scientist
Dr. B. J. Prashantham (Chairperson), IRB Blue Internal	MA (Counseling), MA (Theology), Dr Min(Clinical)	Chairperson(IRB)& Director, Christian Counselling Centre	External
Dr. Jayaprakash Muliyil	BSC, MBBS, MD, MPH, DrPH(Epid), DMHC	Retired Professor, Vellore	External
Dr. Nihal Thomas	MD MNAMS DNB(Endo) FRACP(Endo) FRCP(Edin)	Secretary IRB (EC)& Dy. Chairperson (IRB), Professor of Endocrinology & Addl. Vice Principal (Research), CMC.	Internal, Clinician

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent. And on completion of the study you are expected to submit a copy of the final report.

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

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MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

A sum Rs. 33,333/- (Rupees Three Thousand Three Hundred and Thirty Three only) will be granted for 10 months.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr Nihal Thomas
MBBS MD MNAMS DNB (Endo) FRACP(Endo) FRCP(Edin)
Secretary (Ethics Committee)
Institutional Review Board

CC: Dr. Selvamani, Department of Radiotherapy

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in