A prospective single arm study to assess the feasibility and tolerability of hypofractionated post mastectomy radiotherapy in patients with carcinoma breast

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF M.D

(RADIOTHERAPY)EXAMINATION OF THE

TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY

TO BE HELD IN APRIL 2014

Certificate

This is to certify that the dissertation entitled **"A prospective single arm study to assess the feasibility and tolerability of hypofractionated post mastectomy radiotherapy in patients with carcinoma breast"** is a bonafide record of the original work done by **Dr. Balu George** towards the partial fulfillment of M.D (Radiotherapy) Degree of The Tamil Nadu, Dr. M.G.R Medical University, Chennai to be conducted in April 2014.

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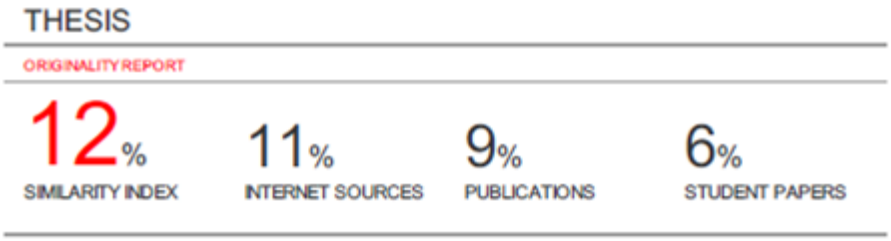

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1. INTRODUCTION

Breast cancer is one disease, the management of which keeps evolving and continues to baffle the clinician from ages. The surge for refinement in treatment modalities of breast cancer is ever growing and it is one of the most extensively studied diseases. Being the commonest cancer among women in the developed world, tremendous amount of research has gone into understanding the biology of this disease and novel treatment approaches are being investigated across the world.

Breast cancer is a disease with potential for systemic spread with high risk of local recurrence. Essentially, the treatment of invasive breast cancer has surgery and radiation therapy as the modes for local control of the disease and chemotherapy for addressing the systemic micrometastasis. Radiation therapy is inherent in the setting of breast conservation therapy. Modified radical mastectomy is followed up with radiation therapy to the chest wall, supraclavicular or the axillary region according to specific indications.

Treatment of breast cancer spans across six to eight months and radiation therapy contributes to about five weeks. Necessity is the mother of invention. The ever-growing number of breast cancer patients requiring either chest wall or whole breast irradiation in the United Kingdom, put many radiotherapy centres under pressure. To reduce the workload on machines, many centres started using shorter radiotherapy schedules with larger doses per fraction. Case series and cohort studies initially reported that these shorter schedules were acceptable in terms of both acute reactions and local control. Evolving radiobiological concepts has opened gates to research aimed at reducing the

treatment duration from five weeks to three weeks have proved that it is feasible in terms of tumour control and safety. The concept of hypofractionated radiotherapy was initially applied to breast cancer as early as 1986((1)) in the United Kingdom. Since then several randomized studies have been conducted on this shorter fractionation regimens, the landmark trials being the START A and START B trials.

The concept of hypofractionated radiotherapy has not become the standard of care in our country. The shorter treatment schedule is supposed to reduce the burden on treatment units and indirectly reduce the cost of treatment. Indian breast cancer scenario will definitely benefit from this well established treatment regimen.

2. REVIEW OF LITERATURE

2.1 INCIDENCE AND PREVALENCE

Cancer is one of the leading diseases in the world, both in the developed and the developing countries. Improved health system, the consequent increase in longevity and addictive habits like smoking, alcoholism, tobacco chewing and life style changes has contributed to the increased incidence of cancer. About 7.6 million cancer related deaths have been estimated to have occurred in 2008(**Figure 2.1**). The major proportion of these deaths (64%) occurred in the developing countries. Breast cancer contributes to 23% of the cancers diagnosed and is the second most common malignancy worldwide, lung cancer being the most common (2). Cancer breast continues to be the most common cause of cancer related deaths among women. It accounts for 14% of the cancer deaths. In the United States, it was found that after consistently rising for years, the incidence of breast cancer has started to decrease in the last decade which could partly be due to the decreasing trend of using hormone replacement therapy. Incidence of breast cancer in India shows a variable pattern within the country, with significant differences noted between metropolitan cities and rural India.

The incidence rates are 33, 24 and 7.5 per 100000 in metropolitan cities, urban areas and rural India respectively. Even though breast cancer is the second most common cancer (cancer cervix being the most common) in India as a whole, data from a nationwide study-Atlas of Cancer in India, shows that in metropolitan cities breast cancer is the most common cancer(3).

The Indian cancer registries have shown an increase 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(4). 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).

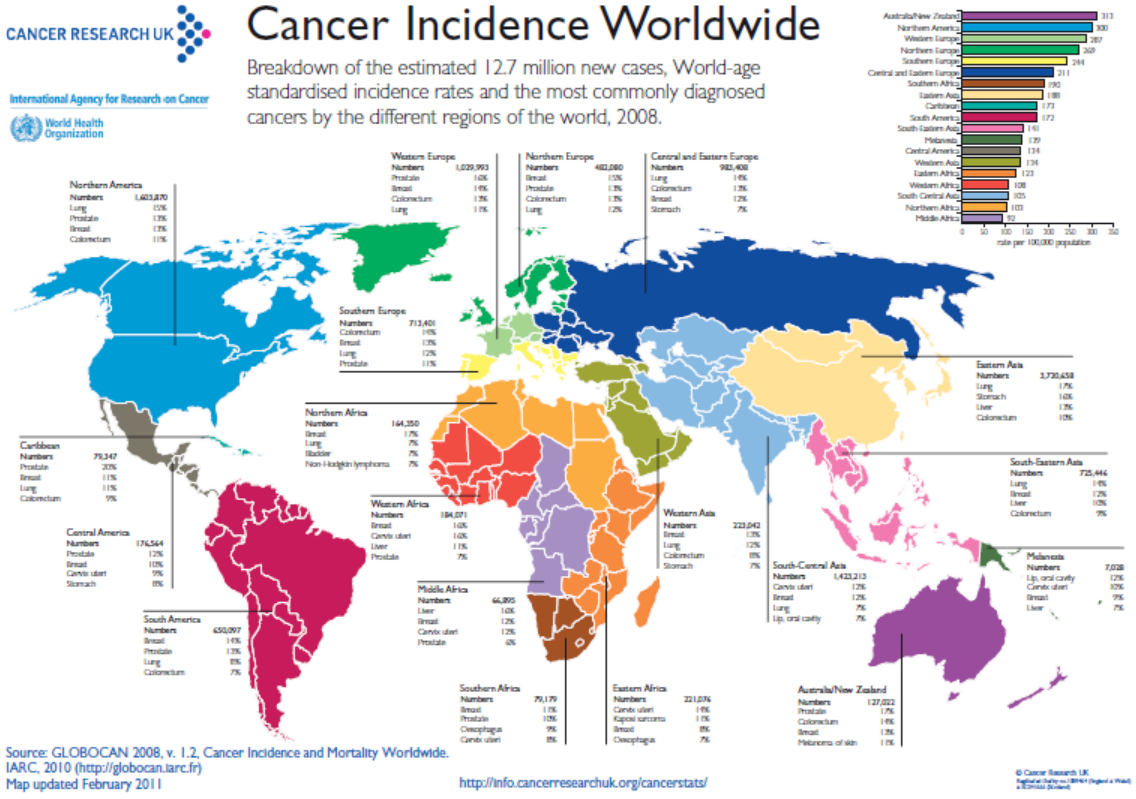


Figure 2.1: Worldwide Cancer Incidence

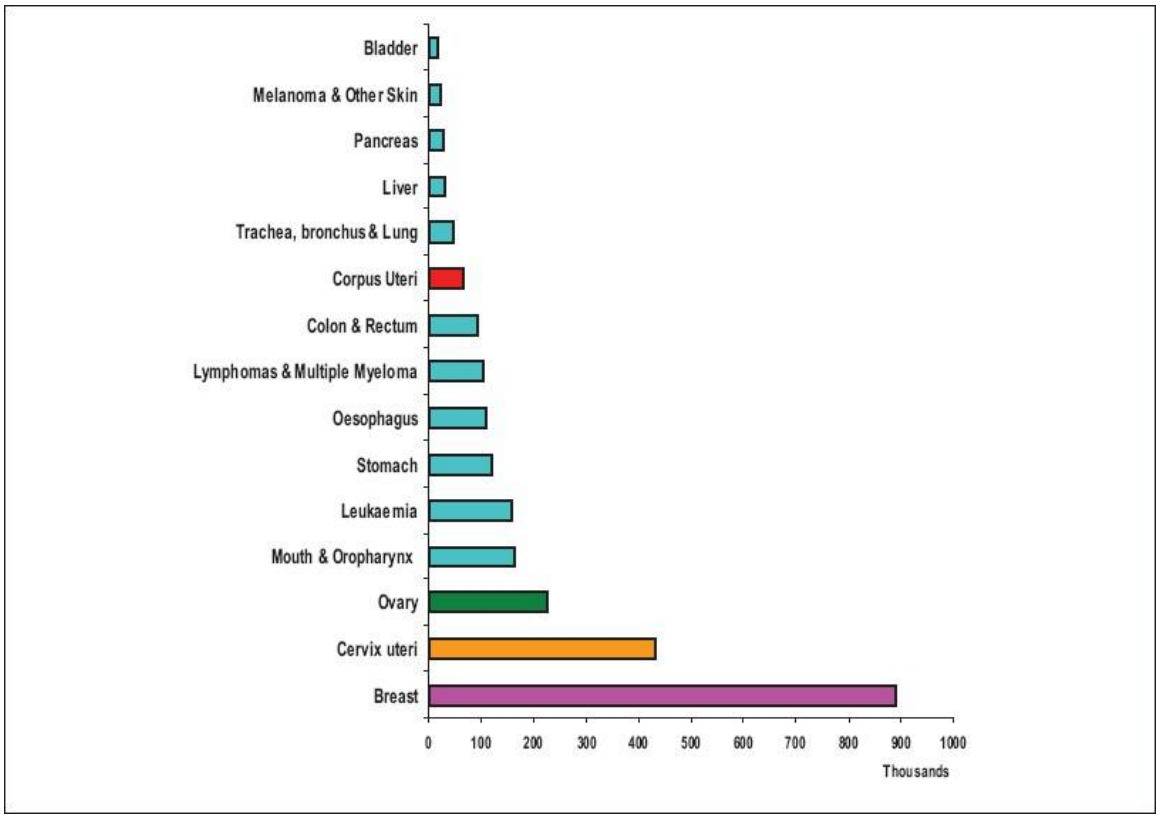


Figure 2.1: Common sites of cancers in female: Extrapolation to population of India, 2004 (ICMR)

2.2 ETIOLOGY

Breast cancer is a result of a series of events, both genetic and epigenetic, which finally culminates in dysregulation of cell growth, apoptosis and leads to development of invasive nature. The causes of these events are not clear, but studies have shown that lifestyle, environmental factors and germ line genetic factors predisposes one to breast cancer. Female sex is the strongest risk factor for developing breast cancer and only about 1% of all new breast cancer occur in men(5). The second most important risk factor is the age, as 95% of all new cases occur in women aged 40 years and above. Above 40 years, the annual risk of developing breast cancer increases exponentially until menopause, after which the risk lowers considerably(6). Estrogen exposure is a known risk factor for developing breast cancer. Situations where this excess estrogen exposure occurs are early menarche, late menopause, nulliparity and older age at the time of first child birth. Post menopausal hormone replacement therapy with Estrogen also has shown to increase the chances of one developing breast cancer. The annual relative risk of developing breast cancer increases by 2.3% per each year of hormonal therapy taken(7). Another recent study reported that combined estrogen and progesterone hormonal therapy is associated with an increase in relative risk by 8% when compared with non users, whereas the use of estrogen alone increases the relative risk only by 1%(8). A large Swedish study reported that the risk of breast cancer increases approximately by 13% for every 5 years increase in the age of first child birth(9). Alcohol consumption has been found to be associated with breast cancer risk(10). There is no strong evidence for any association between dietary fat and breast cancer risk(11). Regular exercise has been proved to reduce the risk of developing breast cancer(12,13).

Genetic events leading to breast cancer are more often sporadic than germ line mutations. Approximately 20 to 25% of patients with breast cancer have family history of breast cancer. The two most common tumor suppressor genes which undergo mutation are the BRCA 1 and BRCA 2. Female carriers of germ line BRCA1 mutation have a life time risk of breast cancer exceeding 80% and of ovarian cancer close to 60%(14). BRCA 2 mutant also carry a similar risk of development of breast cancer and a higher chance of developing ovarian cancer. Growth promoting proto oncogenes can become abnormal which is commonly seen in locally advanced breast cancer. Over expression of the proto oncogene Her2/neu has been associated with increased proliferative capacity and higher metastatic potential.

2.3 BIOLOGIC CHARACTERISTICS

Breast cancer has been grouped into several molecular subtypes based on DNA microarray expression profiles. These molecular subgroups correspond with different prognostic groups and predict the aggressiveness of the disease. The four molecular subtypes are luminal A, luminal B, Her2 tumors and basal-like type. Luminal A tumors include most ER positive, PR positive and Her2/ neu negative tumors. Luminal B tumors are ER positive, PR positive and Her 2 neu positive. Her2 tumors are ER negative, PR negative and Her2/neu negative. Basal-like subtype is triple negative disease. Luminal A type of tumors is generally associated with the best prognosis and predicts the response to hormonal therapy. Basilar type tends to be more chemoresponsive, but is associated with aggressive biology and poor prognosis.

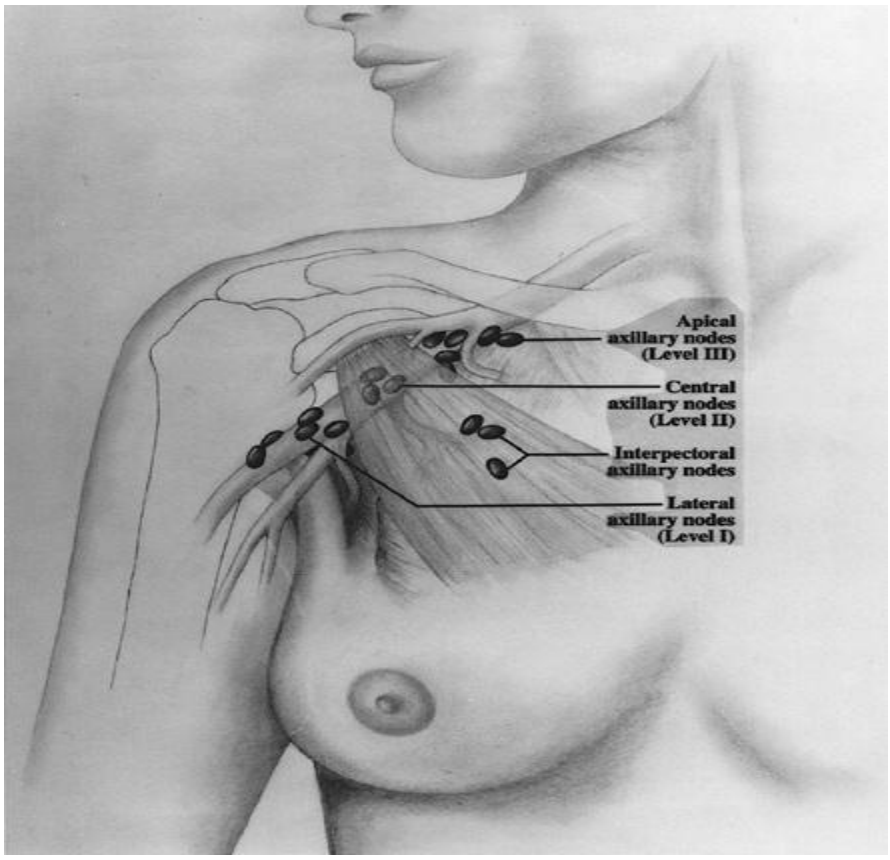


Figure 2.2: Levels of axillary nodes

2.4 ANATOMY

The breast is situated on the Pectoralis Major muscle and cranio-caudally extends between the second and the sixth ribs and between the sternal edge medially and the mid axillary line laterally. Skin, subcutaneous tissue and the breast tissue constitutes the breast. Breast tissue is composed of epithelial and stromal components. The breast tissue is supported by fibrous septae called Cooper's ligaments and connective tissue which harbours the blood vessels, lymphatics and nerves. The fascia of the Pectoralis fascia muscle forms the deep boundary of the breast. Lobules and ducts form the microscopic structural background of the breast. The interface between the lobule and duct is a common site where breast cancer develops(15). The rich lymphatic drainage of the breast primarily drains into the lymph nodes of axilla, internal mammary chain and the supraclavicular region.

Drainage can also occur into the intramammary nodes and the interpectoral Rotter's nodes. Axillary nodes are divided into three levels with respect to their anatomic location in relation to Pectoralis Minor muscle (**Figure 2. 3**). Those nodes which are inferolateral to the lateral border of the Pectoralis Minor are called the Level I axillary nodes. Level II nodes lie beneath the Pectoralis Minor muscle and those nodes which lie superomedial to the Pectoralis Minor muscle are called the Level III nodes. When the internal mammary chain gets involved usually the lymph nodes lie in the second, third and fourth intercostals spaces. The incidence of metastasis to the internal mammary nodes depends on the number of axillary nodes involved and the anatomic location of the tumour within the breast. Medial and central quadrant tumours with 4 or more positive axillary nodes had the highest rate (43%) of IMC involvement according to a study from China(16) . Risk of supraclavicular nodal involvement is dependent on the number of

positive axillary nodes. Around 15% of patients with four or more positive axillary nodes will develop supraclavicular recurrence if this region is left untreated(17).

2.5 DIAGNOSIS

In the Indian scenario, most of our patients present to the clinic many months after being aware of a breast lump, mostly due to the social stigma associated with it. The clinical diagnosis of breast cancer is straight forward in most cases when patients present with a hard lump in the breast. Routine screening mammogram may pick up micro-calcifications leading to the diagnosis of cancer. History and physical examination is the most important step towards diagnosis. Ultrasonogram of the breast and axilla is the preferred imaging in young premenopausal women. Mammogram is the recommended imaging for older women with dense parenchyma. These imaging modalities also provide information regarding the status of the axillary nodes and the contralateral breast. If any abnormality is picked up in the physical examination or imaging, then tissue needs to be obtained to rule out cancer. Per cutaneous core biopsy is the recommended procedure. Fine needle aspiration from the breast lump will aid in confirming the diagnosis without much delay, but further characterization and immunohistochemical tests will not be feasible. In a case where the patient is scheduled for an upfront mastectomy, FNAC would suffice as the surgical histopathology will be soon available. When a patient requires downstaging of the disease with neoadjuvant chemotherapy prior to surgery, a trucut biopsy is a must prior to initiation of the chemotherapy. Ultrasound guided biopsy might be needed when the breast lump is small and difficult to palpate. When the patient does not have a palpable lump and has suspicious microcalcifications, a stereotactic biopsy is recommended. Bone scan is recommended for all patients with locally

advanced disease. Upto 3 % of patients with clinical stage III disease has abnormal bone scans .Once the diagnosis is established, further evaluation aims at staging the disease. Routine tests included in the metastatic work up include, chest X ray and ultrasonogram of the abdomen and pelvis.

2.6 HISTOPATHOLOGICAL CLASSIFICATION OF BREAST TUMOURS(AJCC)

In situ Carcinomas

Not otherwise specified

Intraductal (insitu)

Paget's disease and intraductal

Invasive carcinomas

Not otherwise specified

Ductal, Inflammatory, Medullary, Medullary with lymphoid stroma, Mucinous, Papillary (predominantly micro papillary pattern), Tubular, Lobular, Paget's disease, Undifferentiated, Squamous cell, Adenoid cystic, Secretory, Cribriform

2.7 STAGING

American Joint Committee for Cancer staging seventh edition (2010) is used for staging purpose.

Primary Tumor (T)

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ

Tis (DCIS)	Ductal Carcinoma In Situ
Tis (LCIS)	Lobular Carcinoma In Situ
Tis (Paget's)	Paget's disease of the nipple with no tumor
T1	≤2cm in greatest dimension
T1mi	Microinvasion 0.1cm or less in greatest dimension
T1a	Tumor >0.1cm but not more than 0.5cm in greatest dimension
T1b	Tumor >0.5cm but not more than 1cm in greatest dimension
T1c	Tumor >1cm but not more than 2cm in greatest dimension
T2	Tumor >2cm but not more than 5cm in greatest dimension
T3	Tumor more than 5cm in greatest dimension
T4	Tumor of any size with direct extension to a)chest wall or b) skin, only as described below
T4a	Extension to the chest wall, not including only Pectoralis muscle invasion
T4b	Edema (including peau d'orange) or ulceration of skin of the breast or satellite skin nodules confined to the same breast
T4c	Both(T4a and T4b)
T4d	Inflammatory carcinoma

Regional Lymph Nodes (N)

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in movable ipsilateral Level I ,II axillary node(s)
N2	Metastasis in ipsilateral Level I, II node(s) that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary node in the absence of clinically evident axillary lymph node metastasis
N2a	Metastasis in axillary lymph node(s) fixed to one another(matted) or to other structures
N2b	Metastasis only in clinically detected internal mammary lymph node(s) and in the absence of clinically detected axillary lymph node metastasis
N3	Metastasis in ipsilateral infraclavicular lymph node(s) with or without level I ,II axillary lymph node involvement or in clinically detected internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastasis in infraclavicular lymph node(s)
N3b	Metastasis in internal mammary and axillary lymph nodes
N3c	Metastasis in supraclavicular lymph node(s)

M0	No metastasis
M1	Distant metastasis

STAGE GROUPING

Stage 0	Tis	N0	M0
Stage I A	T1*	N0	M0
Stage I B	T0, T1	N1mi	M0
Stage II A	T0, T1*	N1	M0
	T2	N0	M0
Stage II B	T2	N1	M0
	T3	N0	M0
Stage III A	T0, T1*, T2	N2	M0
	T3	N1, N2	M0
Stage III B	T4	N0, N1, N2	M0
Stage III C	Any T	N3	M0
Stage IV	Any T	Any N	M1

*T1 includes T1mi

The categories M1 and pM1 may be further specified according to the following notation:

Pulmonary	PUL	Osseous	OSS
Hepatic	HEP	Brain	BRA
Lymph nodes	LYM	Bone marrow	MAR
Pleura	PLE	Peritoneum	PER
Adrenals	ADR	Skin	SKI
Others	OTH		

pTNM Pathological Classification

pT –Primary Tumor

The pathological classification requires the examination of the primary carcinoma with no gross tumour at the margins of resection. A case can be classified pT if there is only microscopic tumour in a margin.

The pT categories correspond to the T categories.

When classifying p T the tumour size is a measurement of the invasive component. If there is a large in situ component (4cm) and a small invasive component (eg: 0.5 cm), the tumour is coded pT1a.

pN- Regional Lymph Nodes

The pathological classification requires the resection and examination of atleast the low axillary lymph nodes (Level I). Such a resection will ordinarily include 6 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

pNx	Regional lymph nodes cannot be assessed (e.g. previously removed, or not removed for pathological study)
pN0	No regional lymph node metastasis*

Note *Isolated tumour cell clusters (ITC) are single tumour cells or small clusters of cells not more than 0.2 mm in greatest extent that can be detected by routine H and E stains or

immunohistochemistry. An additional criterion has been proposed to include a cluster of fewer than 200 cells in a single histological cross-section. Nodes containing only ITCs are excluded from the total number of positive node count for purposes of N classification and should be included in the total number of nodes evaluated.

pN1	Micrometastasis; or metastasis in 1-3 axillary ipsilateral lymph nodes; and/or in internal mammary nodes with metastasis detected by sentinel lymph node biopsy but clinically not detected.
pN1mi	Micrometastasis (larger than 0.2 mm and/or more than 200 cells, but none larger than 2.0 mm)
pN1a	Metastasis in 1-3 axillary node(s), including at least 1 larger than 2 mm in greatest dimension.
pN1b	Internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected.
pN1c	Metastasis in 1-3 axillary lymph nodes and internal mammary lymph nodes with microscopic and macroscopic metastasis detected by sentinel lymph node biopsy but not detected clinically.

pN2	Metastasis in 4-9 ipsilateral axillary lymph nodes, or in clinically detected ipsilateral internal mammary lymph node(s) in the absence of axillary lymph node metastasis
pN2a	Metastasis in 4-9 axillary lymph nodes, including at least one that is larger than 2mm
pN2b	Metastasis in clinically detected internal mammary lymph node(s), in the absence of axillary lymph node metastasis
pN3a	Metastasis in 10 or more axillary lymph nodes (at least one larger than 2mm) or metastasis in infraclavicular lymph nodes.

pN3b	Metastasis in clinically detected internal ipsilateral lymph node(s) in the presence of positive axillary lymph node(s);or metastasis in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected.
pN3c	Metastasis in ipsilateral supraclavicular lymph node(s)

2.8 OVERVIEW OF CURRENT TREATMENT GUIDELINES IN BREAST CANCER

Breast cancer treatment is evolving constantly due to the alarmingly high incidence of this disease recently. Breast cancer can be broadly classified as early breast cancer (EBC), locally advanced (LABC) and metastatic breast cancer (MBC). Early breast cancer includes Stages I, II and III A. Stages III B and III C are grouped into the category of locally advanced breast cancer. Treatment of breast cancer is based on these broad categories. Surgery is the mainstay of treatment for early breast cancer. The trends in surgical management are also evolving and more and more patients who are eligible are opting to have breast conservation surgery. Modified Radical Mastectomy still continues to be widely used in India.

Modified radical mastectomy is removal of breast with level I/II axillary clearance.

2.9 SURGERY

Surgery is the principal loco regional treatment for any patient with early breast cancer. In case the disease is inoperable at presentation, the patient is re assessed for operability after a course of neoadjuvant chemotherapy which helps in downstaging the disease. Surgery addresses both the primary tumour and the axillary nodes. The primary

tumour is managed by either a mastectomy or lumpectomy and the axillary nodes are managed by a sentinel node biopsy or axillary dissection. The various surgical procedures do have an impact on the adjuvant oncological management.

Radical Mastectomy, Extended Radical Mastectomy, Modified Radical Mastectomy, Simple mastectomy, Skin sparing and Nipple sparing Mastectomy are all procedures that remove a considerable bulk of the breast parenchyma along with the primary tumour. The term Breast Conserving surgery can be collectively applied for procedures like lumpectomy, partial mastectomy, tylectomy and quadrantectomy. Simple mastectomy removes the breast tissue with the tumour alone and the axilla is not addressed. Radical mastectomy involves removal of the breast plus the Pectoralis major muscle and a level I/II axillary dissection. Modified radical mastectomy removes the breast with level I/II axillary clearance. When immediate re construction is considered, the preferred surgical procedure is Skin sparing mastectomy, which is nothing but a total or radical mastectomy where in the surgeon leaves a significant component of the native skin of the breast to optimize the aesthetic outcome of a reconstruction.

In general there is a trend towards less radical surgery from radical mastectomy to breast conservation surgery(18). There is no significant difference between breast conservation therapy and mastectomy in terms of overall survival rates, which is 45-90 % at five years(19).Breast conservation and mastectomy were recognized by the national institute of health to have equivalent medical outcome in a consensus development conference held in 1990 and recommended BCT for most of the women with early breast cancer(20–22). A study from the United States reported that even though breast conservation was an option for about 75% of patients with early breast cancer, only 20-50% of these patients

opted to conserve their breasts(23). Fear of recurrence of cancer was the most important factor which made these patients opt mastectomy(23). Patients who are eligible for surgery are assessed for suitability of breast conservation along with discussion with the patient regarding the options.

The following absolute contraindications need to be kept in mind while offering breast conservation therapy:

1. Pregnancy, especially first and second trimester.
2. Diffuse malignant appearing micro-calcifications
3. Multi-centric breast cancer
4. Previous history of irradiation of the breast region that would lead to an unacceptable high total dose delivered when post operative whole breast RT is given.
5. Persistent positive margins after multiple surgical attempts.

Relative contraindications include

1. History of collagen vascular disease
2. Tumour size large tumour in a small breast
3. Large or pendulous breast can be a relative contraindication as reproducibility and immobilization will be difficult.

Mastectomy is indicated in cases where breast conservation is contraindicated or when the patient opts to have the entire breast removed.

Following the surgery, further adjuvant treatment is based on the histopathological examination, the initial clinical stage of the disease and the hormone receptor status. Human epidermal growth factor receptor2 (Her2/neu) status is helpful in

predicting response to targeted therapy. Radiation therapy, chemotherapy, hormonal therapy and targeted therapy are the options for adjuvant treatment.

In India 30-35% of breast cancers are locally advanced at the time of diagnosis(24). Ignorance and fear of being diagnosed to have cancer, prevents many women from the rural areas, from seeking timely medical attention. This, along with poor screening strategies might be the explanation for such high number of locally advanced breast cancers in our country.

Patients, who present with locally advanced disease, have a course of neoadjuvant chemotherapy prior to surgery. Chemotherapy reduces the tumor size and makes it operable and at the same time provides systemic treatment.

2.10 POST MASTECTOMY RADIATION THERAPY

Results of several randomized studies showed that, in the absence of radiation therapy following mastectomy, there is a significant risk of locoregional failure(25,26). Approximately 25–40% of node positive patients and 15-40% of node negative patients may develop loco regional recurrence in the absence of radiotherapy. Locoregional recurrence most commonly develops in the chest wall, followed by axilla and the supraclavicular region. Recurrence on the chest wall can be distressing for the patients as it can ulcerate or fungate. Supraclavicular recurrence can cause neuropathy and significantly hamper the quality of life. Disease recurrence in axilla can lead to lymphoedema.

There is strong evidence to show that post mastectomy radiation therapy reduces the rate of loco regional failures in those patients who have a high risk of local failure. It

did not take much longer to prove that adjuvant radiotherapy not only improved locoregional control, but survival also. The British Columbia Cancer Agency(27) and the Danish Breast Cancer Cooperative group(28) conducted two randomized controlled trials, which were initially published in 1997 and was updated in 2005 and 2006. These were the first trials which demonstrated a survival advantage with radiation therapy over and above the locoregional control. Danish 82b trial compared radiation therapy plus CMF (Cyclophosphamide, Methotrexate and 5 Fluorouracil) with CMF alone in premenopausal women. At a median follow up of 10 years, the study reported statistically significant improvement in rates of local recurrence(32% vs. 9%), disease free survival(34% vs. 48 %) and overall survival(45% vs. 54%) in the combination group(29). Four or more positive axillary nodes, T3 tumours with positive axillary node and operable Stage III tumours are the indications for post mastectomy radiation therapy. Downstaging achieved by neoadjuvant chemotherapy will not alter the plan for adjuvant radiotherapy if it was indicated at presentation. Adequate coverage of the chest wall is mandatory in all these patients. Axillary irradiation is not routinely given to patients who have undergone a complete axillary dissection. The risk of lymphedema significantly rises when axillary dissection is combined with axillary irradiation. Only those patients who have evidence of extra nodal tumour deposits are treated with axillary irradiation. Supraclavicular failure rate is high in patients with four or more positive axillary nodes and supraclavicular region is included along with chest wall irradiation(30). There is insufficient data to offer supraclavicular radiation therapy to those patients with 1 to 3 positive axillary lymph nodes. Traditionally the dose prescribed for post mastectomy

radiation therapy is 50Gy in 25 fractions, 2Gy per fraction, five days a week. The total treatment duration was around five weeks.

2.10.1 THREE DIMENSIONAL CONFORMAL RADIOTHERAPY

The aim of radiotherapy is to deliver a homogenous dose to the target and at the same time keep the normal tissue complications to the minimum(31). Conventional radiotherapy with simple beam arrangements partially achieves this goal, but this may lead to unnecessary irradiation of large volumes of normal tissues. The shape of the chest wall can be highly variable and the close proximity to the lung and the heart, further warrants accurate dose delivery to the target. Two dimensional planning has the limitation that it cannot represent the prescribed dose delivered to a specified target volume and the volume of normal tissue irradiated is also ambiguous. Three dimensional conformal radiotherapy uses CT images to accurately delineate the target volume and the organs at risk. Dose Volume Histograms (DVH) are generated using three dimensional treatment planning system, which gives an estimate of the dose delivered to the target and the normal tissue. 3DCRT technique for chest wall when compared to two dimensional technique was found to reduce the ipsilateral mean lung dose by 24.6%. The V_{20} was also reduced using 3DCRT (22.2% vs. 30%). The mean dose delivered to the contralateral breast was also significantly lower in the conformal technique (8.2 % of the prescribed dose to target vs. 10.4%). For left sided breast cancer, it was seen that the mean dose to the heart could be reduced by 48.6 % using 3DCRT. The PTV coverage was also better with 3DCRT when compared to two dimensional treatment. Thus 3DCRT technique has the advantage that it is able to generate significantly better homogeneity index for the

PTV with a significant reduction in the mean doses to the ipsilateral lung and heart in left sided tumours(32).

2.10.2 RATIONALE FOR THE STANDARD FRACTIONATION

Fractionation of radiation dose provides better control of the tumor at a given level of normal tissue toxicity. The international standard 2Gy per fraction regimens are based on data from squamous cell carcinomas of the head and neck region, cervix and bronchi, which proved that these tumours are less sensitive to the dose per fraction than the late responding healthy tissues. Using doses more than 2Gy per fraction in these types of tumours would result in higher rate of late complications than tumour control. In post mastectomy radiation therapy the effective dose to be delivered is chosen in such a way that there is a balance between control of recurrence and side effects on the normal healthy tissue.

The standard fractionation in post mastectomy radiotherapy is based on the fact that the high total dose delivered in small fractions of 2Gy would offer maximum tumour control with minimum damage to normal tissue. This is based on the hypothesis that breast adenocarcinomas have similar sensitivity to fraction size as the squamous cell carcinomas.

2.11 EVOLUTION OF HYPOFRACTIONATION IN BREAST CANCER

Retrospective analysis of the enormous data available on breast cancer led to a hypothesis that breast cancer might be much more sensitive to fraction size than many other cancers. Sensitivity to fraction size in radiobiological terms can be quantified by the value α/β, which is a variable, derived from the commonly used LQ (Linear Quadratic)

model of fractionation. α and β are coefficients that are typical of the tissue under consideration. The response to fraction size is not linear but fits into the linear-quadratic function in which clinical response is proportional to $\alpha D + \beta D^2$, where D is the fraction size. Effect of fraction size is measured by the degree of tissue damage on normal tissue and tumour recurrence rates for malignant tumours. The ratio of α and β is expressed in Gy. The lower the ratio the greater will be the effect of change in fraction size on normal tissue and malignant tumour. Head and neck carcinomas have α/β value of 10Gy and they are less sensitive to the individual fraction size. This is the rationale behind treating them with small fractions of 2Gy each to a high total dose of 60-66Gy, keeping normal tissue late effects minimum and maximum tumour control. If the hypothesis is true it means that breast adenocarcinoma has α/β value of 3-5Gy (33), which in turn means that these tumours are very sensitive to change in fraction size. Hence increasing dose per fraction above 2Gy would provide better tumour control. Initial studies attempted to increase the dose per fraction above 2Gy, without reducing the total dose and had to confront unacceptable rates of late adverse effects.

The Oncologists in United Kingdom has been using the hypofractionated (three weeks) regimen for decades due to the ever increasing demand for radiotherapy in breast cancer patients. The only evidence based which these schedules were practiced came from small case series and cohorts. There was always a pressure on radiotherapy equipments and staff due to the high patient load. The centres empirically using the three weeks regimen were facing the pressure of considering the internationally popular five weeks regimen (50Gy in 25 fractions).

The two trials which provided data supporting the higher sensitivity of breast cancer are the UK Pilot trial which began in 1986 and the Canadian trial which began in 1993. The UK Pilot trial used three arms, 50Gy in 25 fractions, 39Gy in 13 fractions and 42.9Gy in 13 fractions all over a total duration of five weeks. The Canadian trial compared 42.5Gy in 16 fractions with the standard schedule. There was a wide range of variation in post mastectomy dose prescription within United Kingdom and hence to address this issue and the issue of workload, the UK Coordinating Committee on Cancer Research proposed a trial of standardization of breast radiotherapy. The aim was to study the effect of increasing the fraction size above 2Gy, on normal tissues, tumour control, quality of life and its financial implications.

The Standardisation of Breast Radiotherapy (START) trials (A and B) began in 1998. The trials recruited patients between 1999 and 2002 and the majority of patients were patients who had Breast conservation surgery (85%) and the rest were post mastectomy patients. START A compared the standard regimen with two other schedules, 41.6Gy and 39Gy in 13 fractions over five weeks. The START B trial compared the standard regimen with 40Gy in 15 fractions over three weeks. In 2010 Cochrane review concluded that hypo-fractionation in breast cancer does not compromise efficacy or safety, but suggested that a longer follow up analysis was warranted. The ten year results of these two randomized controlled trials have been published in the Lancet Oncology in 2013. START A enrolled 2236 women and 139 local regional relapses occurred after a median follow up of 9.3 years. The ten year rates of locoregional relapse did not vary significantly among the study groups (6.3%, 7.4% and 8.8% in the 41.6Gy, 50Gy and 39Gy groups respectively). The late effects like breast oedema, telangiectasia

and induration were significantly lower in the 39Gy group compared to the standard regimen. There was no significant difference in late effects between the 41.6Gy and 50Gy arms. START B enrolled 2215 and the median follow up was 9.9 years. The ten year recurrence rate was similar in the 40Gy and 50Gy groups (4.3% and 5.5% respectively). The breast related side effects were significantly lower in the hypo-fractionated arm compared to the standard 50Gy arm. The other late effects which were assessed were symptomatic rib fracture, ischemic heart disease, symptomatic lung fibrosis and brachial plexopathy. The aforementioned late effects were very rare across all the study groups. In the START B trial there was not even one case of brachial plexopathy. The hypofractionated schedule (40Gy in 15 fractions) was found to be less damaging to the brachial plexus even under extreme assumptions regarding the sensitivity of the plexus. With regards to cardiac events, hypofractionation seems to protect the heart, even though ten years is not sufficient for assessing the cardiac morbidity.

2.12 RADIATION TOXICITY

The benefits of local control and overall survival provided by post mastectomy radiotherapy are associated with certain side effects. The organs at risk in post mastectomy radiotherapy are the skin, subcutaneous tissue, ribs, lungs, heart, spinal cord and the opposite breast.

Radiation induced damage can be influenced by certain patient and treatment related factors. Patient related factors like obesity being associated with higher risk of skin toxicity, co morbidities like diabetes mellitus, connective tissue disorders, cardiac

diseases and previous history of smoking also could have a detrimental effect on the toxicity profile. The treatment related factors like the energy chosen, the technique applied, dose prescribed and the treatment plan also can have an impact on the radiation induced damage.

Toxicities can be classified as early and late effects. Early effects occur during the course of radiation therapy and upto six months post treatment. Late effects may occur from six months to years after the treatment. The acute side effect which is most commonly encountered is fatigue and irritation of skin. Fatigue is usually mild and does not affect the activities of daily living. Some form of radiation dermatitis occurs in most of the patients (90%) undergoing post mastectomy radiotherapy. Radiation induces injury in the basal stem cells that are responsible for replenishing the superficial cornified layer of the epidermis(**Figure 2.4**). As a result of insult to the basal stem cells, eventually there is shedding of the cornified layer, which is termed as dry desquamation.

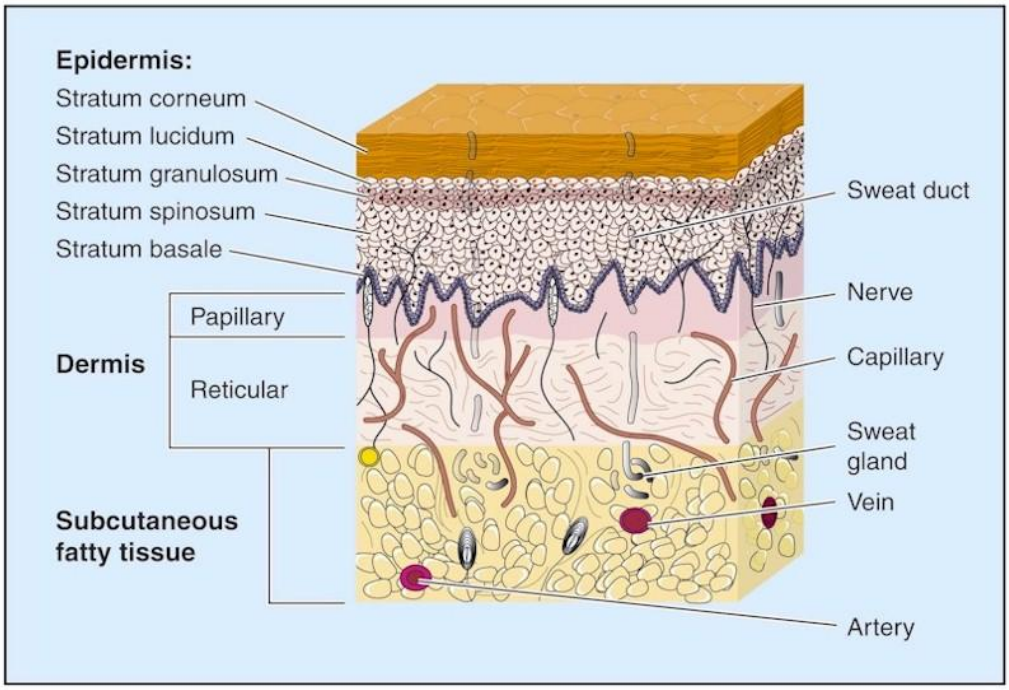


Figure 2.4: Layers of skin

Radiation also causes dilatation of capillaries, increased vascular permeability, enhanced inflammatory response leading to erythema and oedema. Hyperpigmentation, epilation, loss of sebaceous glands and sweat glands are all part of radiation dermatitis, resulting in dry and pruritic skin. Migration of the melanocytes from the basal layer to the superficial layers causes hyper-pigmentation. Moist desquamation occurs with continued loss of basal layer which exposes the dermis. Moist desquamation can lead to frank ulceration.

A study from Egypt, which looked into radiation dermatitis in conventional radiotherapy and hypo-fractionated radiotherapy in conserved breasts, reported that the peak incidence of severe skin reaction occurred during the fifth week of treatment in the conventional group and in the third week in the hypo-fractionated group. The study also reported that these reactions lasted for about three weeks in the conventional fractionation

group and for five weeks in the hypofractionated arm(34). The explanation for the early incidence of reactions in the hypofractionated group may be the dependence of timing and magnitude of inflammatory response on the rate of accumulation of dose. Inflammatory response does not clear up in hours like the sublethal damage does and hence the inflammatory response accumulates quickly(35). START B trial analysed patient self-assesments of five key normal tissue effects on the breast and chest. This analysis showed that rates of moderate/marked changes were lower in the hypofractionated radiotherapy group compared to the conventional arm(36). The various normal tissue effects like breast shrinkage, hardness, change in skin appearance, swelling in the area of affected breast, at five years were all consistently in favour of the 40Gy in 15 fractions regimen. An unusually marked acute skin reaction occurred in 16 (0.7 %) patients in the START B trial. Of these 16 patients, 13 (1.2%) were in the conventional fractionation group and 3 (0.3 %) were from the study arm. Radiation dermatitis is graded based on the RTOG Acute Radiation morbidity scoring criteria(37).

RTOG Acute Radiation Morbidity Scoring Criteria

GRADE	0	1	2	3	4
SKIN	No change over baseline	Follicular/faint /dull erythema epilation, dry desquamation decreased sweating	Tender/bright erythema, patchy moist desquamation, moderate edema	Confluent moist desquamation, other than in skin folds, pitting edema	Ulceration, hemorrhage, necrosis

Radiation pneumonitis typically occurs as a late effect and may present with low grade fever and dry cough. Interstitial inflammation is the hallmark of radiation

pneumonitis. Several patient and treatment related factors are associated with radiation pneumonitis. Some of these factors are age, body mass index (BMI), dose/volume and exposure to taxane based chemotherapy. Taghian and Burstein observed an association between concurrent or sequential use of taxanes and radiation pneumonitis(38). With the use of modern radiotherapy techniques like Three Dimensional Conformal Radiation Therapy (3DCRT) and Intensity Modulated Radiation Therapy (IMRT) the chance of radiation pneumonitis is low (1-7%). Treatment of radiation pneumonitis is with a short course of corticosteroids. Confirmed symptomatic lung fibrosis was very rare at ten years and 2 patients (0.2%) in the conventional fractionation arm and 8 patients (0.7%) in the hypofrationated arm developed it in the START B trial. Bronchiolitis Obliterans Organizing Pneumonia (BOOP) is another extremely rare pulmonary complication of radiation therapy. The condition is seen more commonly in the elderly patients with concurrent use of hormonal agents or taxanes. Treatment with long course of corticosteroids is the treatment for radiation pneumonitis.

The scoring of radiation pneumonitis based on RTOG Acute Radiation morbidity scoring criteria is given below:

GRADE	0	1	2	3	4
LUNG	No change	Mild symptoms of dry cough or dyspnea on exertion	Persistent cough, requiring narcotics/anti tussives, dyspnea with minimal effort, but not at rest	Severe cough unresponsive to narcotic/antitussive agents or dyspnea at rest/clinical/radiologic evidence of acute pneumonitis/intermittent oxygen orsteroids may be required	Severe respiratory insufficiency Continuous oxygen or assisted ventilation

Left chest wall irradiation is invariably associated with exposure of the heart. Retrospective analyses of studies have used outdated techniques of radiotherapy and have reported an increased incidence of cardiac events. It takes almost 15 years for these events to occur. But with modern radiotherapy techniques, the recent PMRT trials did not show any increase in cardiac side effects. The ten year results of START B trial was published recently and showed that the incidence of ischemic heart disease was similar in the standard fractionation arm and the hypofractionated arm (0.5 % and 0.4 % respectively). However the cardia needs to be protected in this era where the use of cardiotoxic agents like anthracyclines and Trastuzumab is on the rise.

Lymphoedema is the abnormal swelling of the arm which may occur after Modified Radical Mastectomy or more commonly as a sequel of both surgery and adjuvant radiotherapy to the axilla. Lymphoedema has various definitions in the literature, one of them being, more than 2cm difference in circumference between the affected and the contralateral arm measured at fixed points 10cm above and below the Olecranon.

The highest rate of lymphedema is seen in patients who undergo complete axillary dissection (levels I-III) followed by axillary irradiation. High BMI, age, hypertension, infection, dose prescribed, number of metastatic nodes, number of nodes removed are some of the factors associated with higher chance of lymphedema. The fact that there is no effective treatment for this condition makes it more distressing. The intent of any form of treatment will be palliation of symptoms and to prevent infections on the affected arm. Patients are advised to be cautious enough to avoid any trauma or even regular BP recording on the affected side.

Second non breast malignancy is another adverse effect of PMRT which is often not stressed while obtaining consent. This stochastic effect is not seen until ten years of radiation therapy. Approximately 7-8 % of women who undergo post mastectomy radiation therapy develop second non breast cancer. But it was also found that there was not a significant difference in the rate of malignancy in a similar non irradiated population. Reports say that the chance on developing lung cancer is higher in irradiated patients who underwent mastectomy than those who underwent breast conservation. Increased risk of second malignancy is not evident until about 15 years after the treatment.

Contralateral breast cancer is the most common second malignancy reported. Gao and colleagues reviewed more than one lakh diagnosed cases of breast cancer between 1973 and 1996 and reported an overall 4.2% incidence of contralateral breast cancer. There was no correlation noted when multivariate analysis was carried out. On subset analysis, the authors found an absolute 1.6% increase in contralateral breast cancer at 20 years post radiation therapy. On the whole there is lack of evidence to state that there is a definite correlation between radiation and contralateral breast cancer.

These side effects are not particular to hypofractionated radiation therapy and are seen in patients undergoing conventional fractionation also.

2.13 INDIRECT BENEFITS OF HYPOFRACTIONATION

The benefits of hypofractionated radiation therapy are multifaceted. Not all patients receiving radiation therapy live in the proximity of the treatment centre. In our country where radiotherapy centres are available only in tertiary hospitals, any given

centre would have a considerable proportion of patients coming from distant places to access the health care system. These patients usually make arrangements for staying in and around the hospital, be it in a lodge or a relative or friend's residence. Invariably each patient will be accompanied by a relative, who also needs to make arrangements for his or her absence from work or household. The patient is forced to be away from her family for the entire duration of treatment. The expenses include the direct medical cost and the indirect cost, for lodging and food. Loss of wages is also a financial burden to the family.

Breast cancer patients make up a substantial proportion of patients treated by any given treatment unit. When the number of fractions is reduced from 25 to 15, the reduction of 10 fractions per patient translates to saving 1000 treatment sessions per 100 patients treated. This corresponds to an additional 66 patients who could be treated with the same number of fractions. This reduces the workload for the treatment machines and for the staff.

Treatment is associated with both social and physical implications. The social costs are the time lost from normal family life, livelihood and the physical costs are the radiation induced injury to the skin, lungs and other organs at risk.

2.14 ACCEPTANCE OF HYPOFRACTIONATION IN INIDA

Indian literature on hypofractionated post mastectomy radiotherapy is limited. In a study conducted between 1989 to 1992 by Goel et al compared two radiotherapy schedules, 40Gy in 17 fractions (2.35Gy per fraction) over 3.2 weeks and 45Gy in 20 fractions (2.25Gy per fraction) over 4 weeks in patients who have undergone modified

radical mastectomy. Cobalt 60 unit was used for the treatment. Chest wall failure was noted in 10% and 5.6 % of patients in the first and second treatment groups respectively. Skin reactions, which were reversible, were the commonest side effect in both the groups. This study concluded that , both these shorter fractionation schedules are equally efficacious and tolerable for the Indian women(39).

Another retrospective study from Post Graduate Institute Chandigarh, published in 2007, assessed 688 patients who have undergone post mastectomy radiotherapy between 1995 and 2000. The schedule used was 40Gy in 15 fractions using Co 60. The five year local control was 94.4 % and frequency of loco regional recurrence was 8.5%.The incidence of WHO Grade III dermatitis was 7.1% and acute pneumonitis was seen in 3% of patients(40).

A recent practice survey which looked into patterns of locoregional treatment (2006 - 2008) in breast cancer conducted by Tata Memorial Hospital, published in 2010, reported that 67% of Radiation Oncologists approved the standard 50Gy in 25 fractions schedule for patients with early breast cancer, after breast conservation surgery. Another 23% of doctors preferred 45Gy in 25 fractions and surprisingly none of them approved hypofractionated radiotherapy. The questionnaire in that survey gave five different schedules and the most common schedule (82 %) was 50Gy/25 fractions(41).

These studies suggest that even though hypofractionated radiotherapy was being practiced in our country from as early as 1989; there is still paucity in whole hearted acceptance of this shorter radiotherapy schedule. One of the reasons might be the lack of availability of Three Dimensional Conformal Radiotherapy facilities across the country,

which is safer in delivering this higher dose per fraction. Another hurdle in applying this regimen in our country is the limited finances of our patients which precludes 3DCRT for them. Then, among the affordable patients, there is a tendency to assume that the longer treatment schedule would benefit them more in terms of recurrence of cancer. When informed about the higher dose per fraction, there is a fear among some patients regarding higher chance of side effects.

Breast cancer patients form a major proportion of patients being treated in our institution and a many of them are able to afford 3DCRT. Even though there is robust evidence for safety and efficacy of hypofractionated radiotherapy, our institution was continuing the longer (46-50Gy in 23-25 fractions) schedule. With the increase in breast cancer patients, the load on the Linear accelerator also increased and hence we proposed this study to look into the feasibility of changing over to the shorter regimen for eligible patients.

3. MATERIALS AND METHODS

3.1 HYPOTHESIS: Hypofractionated radiotherapy is a safe, tolerable and effective alternative to the conventional radiotherapy in patients with carcinoma breast who have undergone Modified Radical Mastectomy (MRM).

3.2 AIM: To conduct a single arm prospective trial to assess the feasibility and tolerability of hypofractionated post mastectomy radiotherapy.

3.3 OBJECTIVES:

To document the incidence of acute toxicities in patients treated with hypofractionated radiotherapy.

Period of study: One year, from January 2013 to November 2013

Setting:

The study was conducted in the Department of Radiation therapy in Christian Medical College. The proposal of the study was approved by the Institutional Review Board (IRB) and the Ethics Committee (EC). All post mastectomy patients who were seen in the dept. of Radiotherapy were screened for the study according to the preset inclusion and exclusion criteria.

The inclusion and exclusion criteria were the following:

Inclusion Criteria:

1. Age above 18 years and less than 70 years
2. Any patient requiring post mastectomy radiotherapy.
3. Enrollment possible within 42 days of surgery or last cycle of Chemotherapy

Exclusion Criteria:

1. Patients who had Breast Conservation surgery
2. Collagen Vascular disease
3. Poor performance status (ECOG >3)
4. Pregnancy and breastfeeding.
5. Patients who had immediate reconstruction after mastectomy.
6. Close or positive surgical margin 1 mm or less
7. Axillary nodal involvement with extranodal extension
8. Metastatic breast cancer
9. Prior history of radiation therapy to the chest.
10. Transmural myocardial infarction within last 6 months
11. Medical, psychiatric or other condition that may prevent the patient from receiving the protocol therapy or informed consent.
12. Unstable angina or congestive heart failure requiring hospitalization within the last six months.
13. History of interstitial lung disease or active lung infection

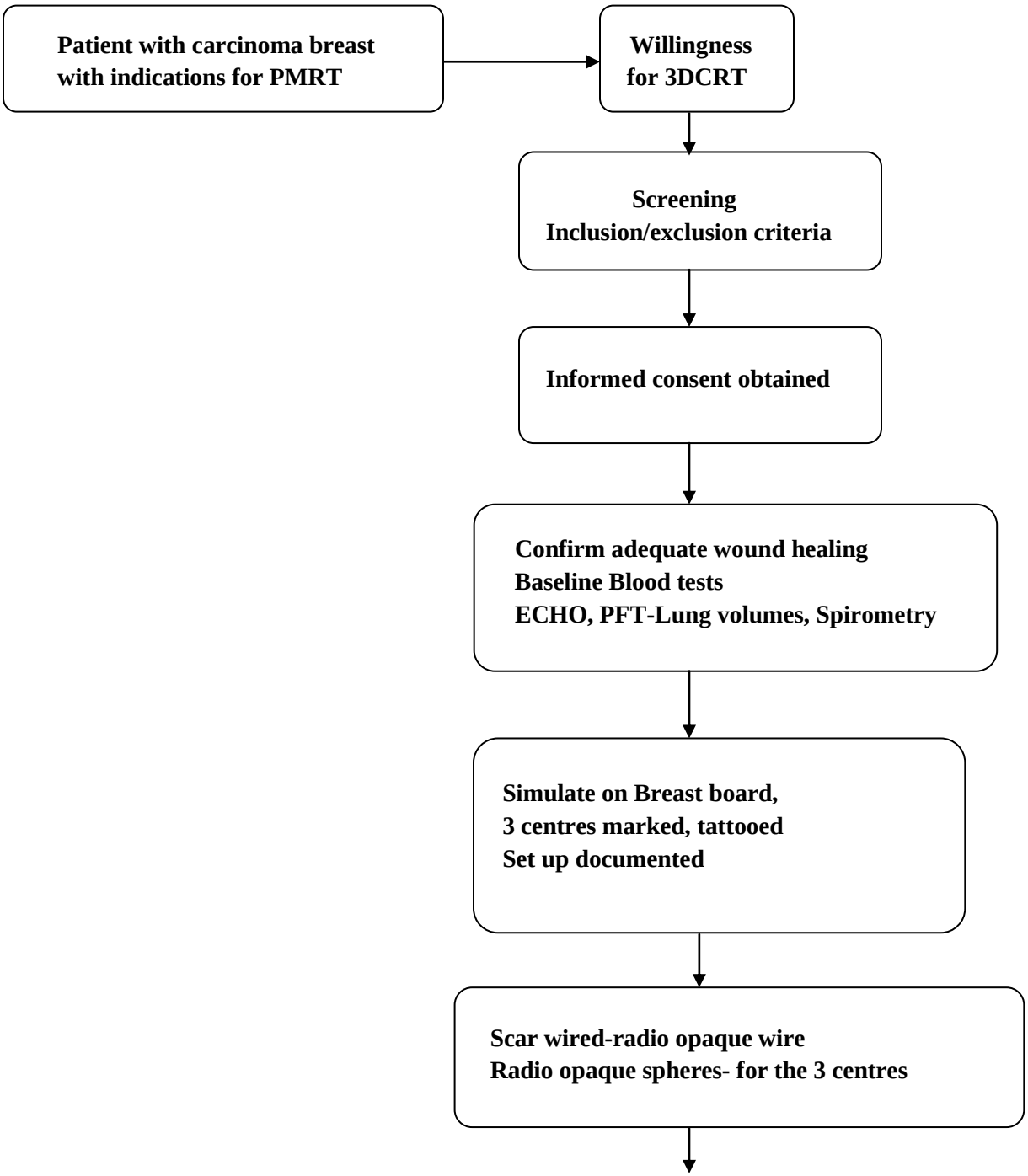
3.4 SAMPLE SIZE

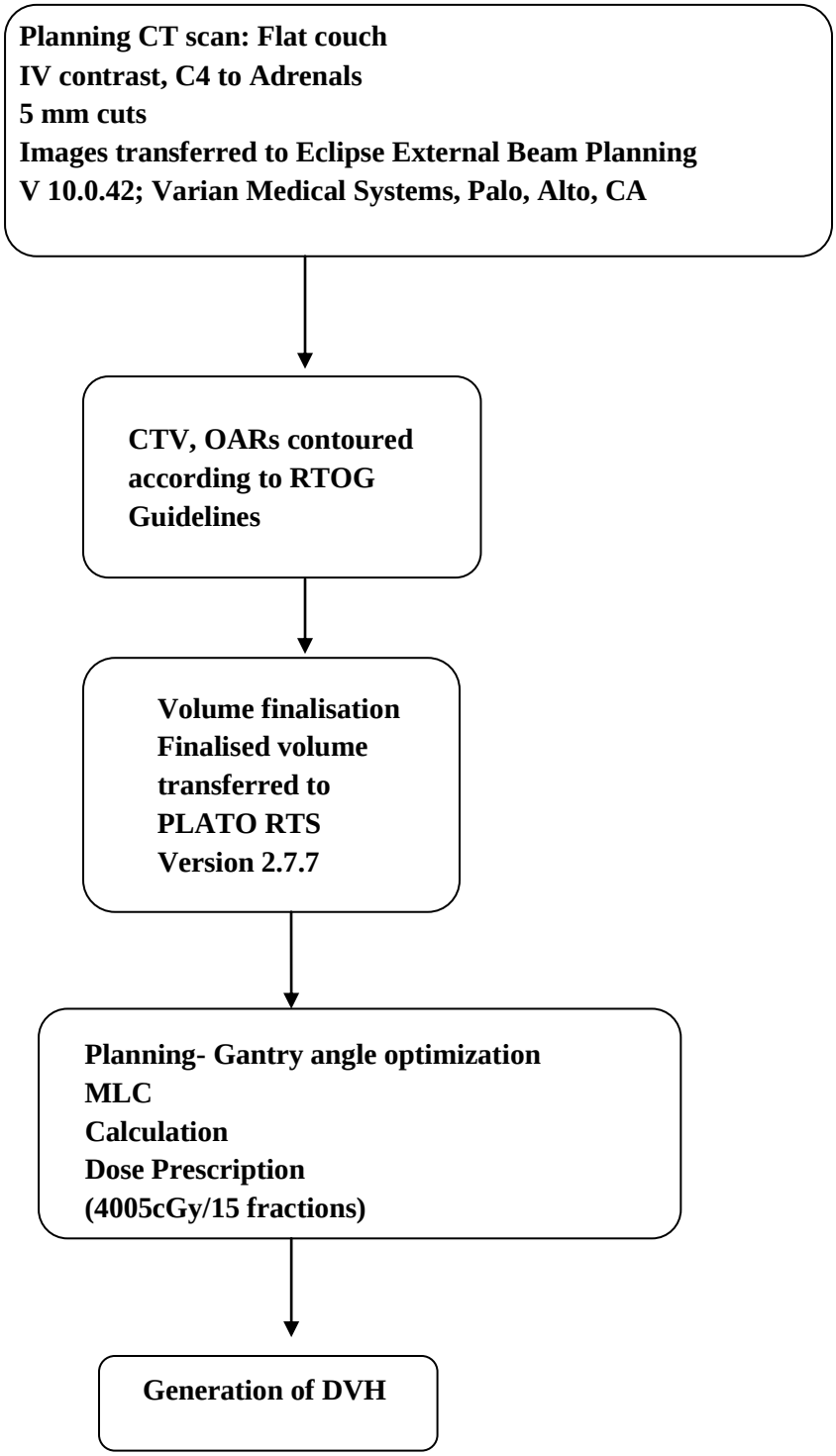
This is a pilot study to assess the feasibility of hypofractionated radiotherapy in patients with carcinoma breast. It was decided to study 20 patients for assessing the tolerability.

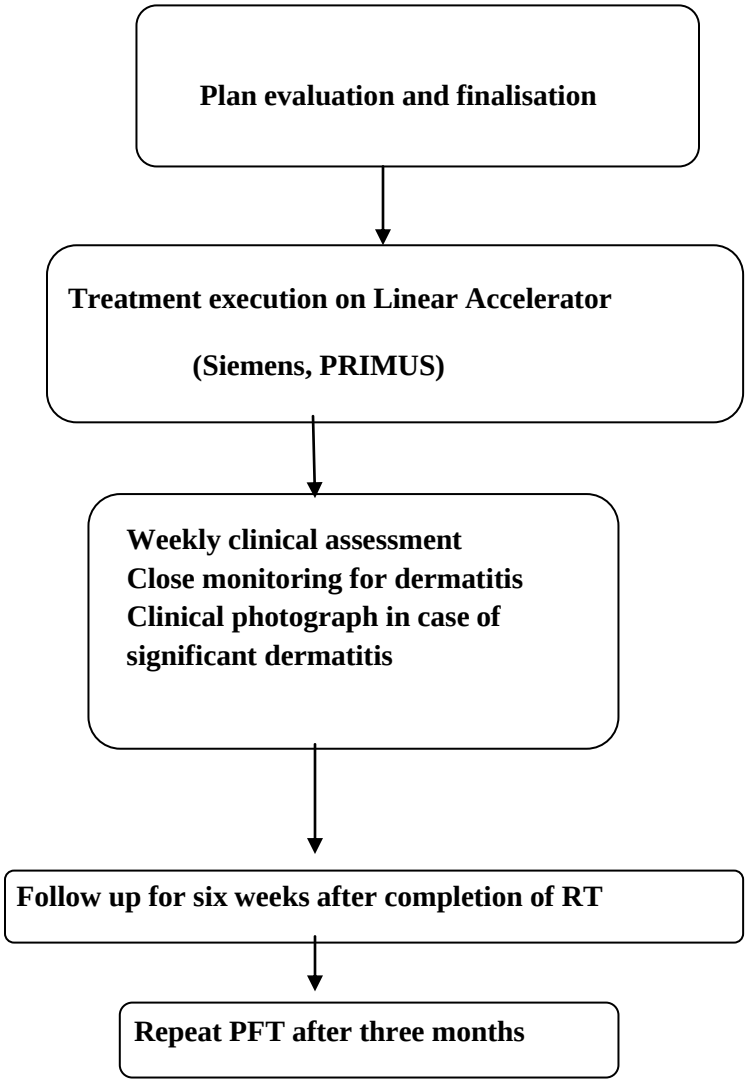
3.5 METHOD

All female patients diagnosed to have carcinoma breast, who required adjuvant radiation therapy were screened using the inclusion and exclusion criteria. Eligible patients were explained about the study, its purpose, benefits and side effects in detail. An information

sheet was given to the patient which provided details of the study. Patients who were willing to participate in the study gave their consent in a prefilled consent form in writing.




Planning CT scan: Flat couch
IV contrast, C4 to Adrenals
5 mm cuts
Images transferred to Eclipse External Beam Planning
V 10.0.42; Varian Medical Systems, Palo, Alto, CA
CTV, OARs contoured according to RTOG Guidelines
Volume finalisation
Finalised volume transferred to PLATO RTS Version 2.7.7
Planning- Gantry angle optimization
MLC
Calculation
Dose Prescription
(4005cGy/15 fractions)
Generation of DVH



Radiotherapy was scheduled as soon as the surgical wound has healed or after three weeks of prior chemotherapy. Routine blood tests were done to rule out neutropenia. Patient immobilization was done in the simulator using a breast board. CT centres were marked and tattooed. The clinical boundaries of chest wall were marked on the body. The details of the patient setup were documented. On the day of the scan, the CT centres and clinical boundaries of the chest wall, scar and the drain sites were marked with radiopaque markers. Contrast enhanced CT scan from C4 to the level of adrenals was obtained in the treatment position with a slice thickness of 5 mm.

The CT images were imported to the planning system (Eclipse External Beam Planning V10.0.42; Varian Medical Systems, Palo, Alto, CA). The RTOG contouring guidelines were followed in delineating the Clinical Target Volume and the Organs at Risk.

Regions treated

Chest wall

Supraclavicular region: Supraclavicular field was added if there were four or more positive axillary nodes.

RTOG guidelines

The RTOG contouring guidelines were used to contour the chest wall, supraclavicular regions and the organs at risk.

Chest wall- Clinical Target Volume (CTV)

The chest wall craniocaudally extends between the caudal border of head of clavicle and the level where there is loss of CT apparent contralateral breast. Antero-posteriorly the contour extends between the skin and the rib-pleural interface (includes Pectoralis muscle, chest wall muscles and ribs). The chest wall contour extends between the rib-sternal junction to the mid axillary line (excludes Latissmus dorsi muscle)

Supraclavicular region- Clinical Target Volume (CTV)

The supraclavicular region was contoured craniocaudally between the caudal edge of Cricoid cartilage to the caudal edge of the Clavicular head and antero-posteriorly between the Sternocleidomastoid muscle and the anterior Scalene muscle. Medially the volume excludes the trachea and thyroid gland and the lateral edge of the Sternocleidomastoid muscle forms the lateral boundary cranially and the junction of first rib and clavicle caudally.

Organs at Risk (OAR)

Lungs: Bilateral lungs were contoured separately and combined lung volume is also generated.

Heart: The superior aspect (or base) begins at the level of the inferior aspect of the pulmonary artery passing the midline and extend inferiorly to the apex of the heart.

Dose Prescription

Total dose (Gy)	**Dose per fraction (Gy)**	**No of Fractions**	**Fractions per week**	**Treatment time (weeks)**
40.05	**2.67**	**15**	**5**	**3**

3.6 STEPS INVOLVED IN 3D-CRT

1. Patient immobilization was done on breast board and the clinical references and the centers were marked and tattooed. A planning CT scan of thorax was obtained with 5mm slice thickness.

2. Delineating the Clinical Target Volume (CTV) and the Organs at Risk (OAR) on the planning CT images at the contouring station was done.

3. Beam selection and planning was done to see dose distribution using Plato treatment planning system. Both 6MV and 15 MV beams were used. Bolus was applied whenever applicable.

4. Plan evaluation was done using Dose Volume Histogram (DVH) and isodose distribution after which the final plan was selected.

5. Digitally Reconstructed Radiographs (DRR) were developed for comparison with the electronic portal image.

6. Treatment execution

The following guidelines were considered for finalizing the plan:

Lower dose limit:

More than 95% of the Clinical Target Volume should receive more than 90 % of the prescribed dose.

Upper dose limit

Less than 2 % of the volume should receive more than or equal to 107 % of the prescribed dose.

Less than 7 % volume should receive more than or equal to 105 %

Global max should be less than 110 % of the prescribed dose.

Ipsilateral lung

The volume of ipsilateral lung receiving 12Gy ($V_{30\%)}$ or V_{12Gy}) should be less than 17 %.

Heart

The volume of heart receiving 2Gy should be less than 30%.

The volume of heart receiving 10Gy should be less than 5%.

Contralateral breast

Maximum dose to the contralateral breast is less than or equal to 330cGy.

3.7 DATA ON DOSE VOLUME PARAMETERS

The details regarding the dose-volume parameters were obtained from DVH and entered in a data sheet. For those patients with chest wall and supraclavicular region as clinical target, the DVH combining both the regions was used for obtaining the relevant dose-volume parameters.

3.8 WEEKLY ASSESMENT

The patients on hypofractionated post mastectomy radiation therapy were monitored on a weekly basis by one of the investigators. Clinical examination was done particularly looking for dermatitis over the chest wall. Dermatitis was graded according to the RTOG Acute Radiation Morbidity Scoring Criteria. Weekly follow up details were entered in an assessment form (Appendix No 2). Patient demographic data was entered in a data sheet (Appendix No 1). Clinical photographs were taken if any patient developed significant dermatitis. Treatment was interrupted in case of Grade 3 dermatitis. Radiation therapy was not resumed until the reactions subsided to Grade I.

3.9 POST TREATMENT FOLLOW UP

Patients were followed up for six weeks post radiation therapy to assess for radiation dermatitis. Pulmonary Function Test is advised three months after the completion of the treatment.

3.10 STATISTICAL ANALYSIS

Data entry was done in Micrsoft Excel and was analysed using SPSS 16.0 (Statistical Package for Social Sciences). Frequencies and percentages were calculated for discrete variables like grades of radiation dermatitis. Mean, median and standard deviation were calculated for continuous variables such as age, BMI etc. The association between the outcome variables was tested using Chi square test. The data was represented graphically using bar diagrams and histograms. Correlation between variables was studied.

4. RESULTS

The target sample size for this feasibility study was 20. Twelve patients were recruited by the end of November 2013.

4.1 OVERVIEW OF PATIENTS

The study group included 12 patients diagnosed to have carcinoma breast and had undergone Modified Radical Mastectomy. Six of them were local patients, five hailed from other parts of Tamil Nadu, Kerala, Andhra Pradesh and West Bengal. One of the patients was here for treatment from Bhutan. The majority (58%) of patients belonged to the age group 46-55 years and the mean age was 50 years **(Figure 4.1)**. The study group consisted of 42% healthy individuals, 42% overweight, 8% with Grade I and another 8% with Grade II obesity. Diabetes mellitus and hypertension was the most common co-morbidities noted. There were seven patients with left sided breast cancer and five with right sided disease. Two women had mastectomy elsewhere. There were six patients with Stage IIIA, four with IIA, one with IIIB and another patient who underwent surgery at a different centre was staged as TxNxM0. Four of the patients had upfront surgery, seven received neoadjuvant chemotherapy and one patient received neoadjuvant hormonal therapy. Five patients received treatment to the chest wall and supraclavicular region where as seven of them received only chest wall irradiation. The patient characteristics are given in **Table 4.1**.

Table 4.1. Demographic and clinical characteristics

Tamil Nadu Kerala Andhra Pradesh West Bengal Bhutan	7 2 1 1 1
Age <35 36 - 45 46 – 55 56 – 65 >65	 1 2 7 2 0
BMI Healthy Over weight Grade I obesity Grade II obesity	 5 5 1 1
Premenopausal Postmenopausal	7 5
Patients with no co-morbidities Patients with co-morbidities	5 7 Diabetes mellitus - 1 Hypertension- 2 Diabetes mellitus, Hypertension- 1

	Dyslipidemia- 1 Diabetes mellitus, Hypertension, Coronary artery disease- 1 Hypetension, Bronchial Asthma- 1
Laterality	
Left	7
Right	5
Stage	
II A	4
IIIA	6
IIIB	1
TxNxM0	1
Estrogen receptor	
Positive	8
Negative	4
Progesterone receptor	
Positive	6
Negative	6
Her 2 neu	
Positive	2
Negative	10

Triple negative	4
Had neoadjuvant chemotherapy Did not have neoadjuvant chemotherapy Had adjuvant chemotherapy Did not have adjuvant chemotherapy	7 Anthracycline - 4 Anthracycline and Taxane - 3 5 11 Anthracycline- 4 Taxane – 4 Anthracycline and Taxane – 3 1
Regions treated Chest wall Chest wall and supraclavicular region	 7 5

All the patients completed the prescribed treatment without any major complications. The patients were followed up for a period of six weeks to assess acute toxicity. One of the patients subsequently developed distant metastasis (pulmonary) and is currently on systemic therapy. Others are disease free at the time of last follow up.

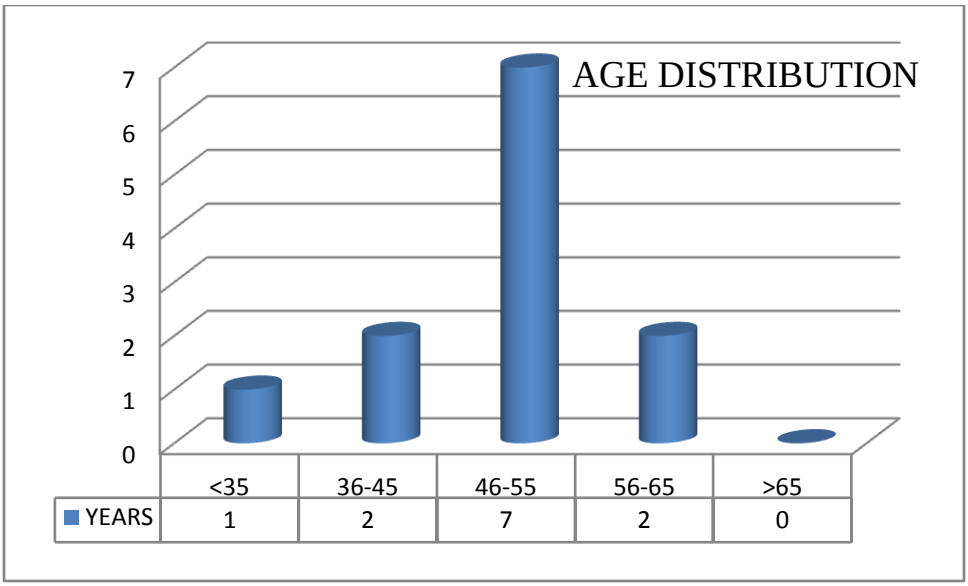


Figure 4.1: The majority of patients belonged to the 46-55 years age group

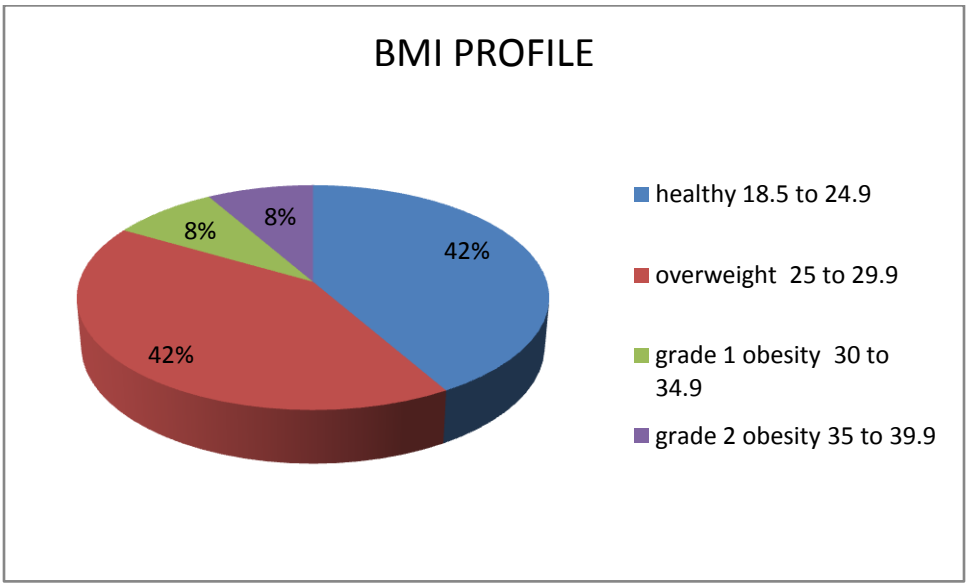


Figure 4.2: Obese patients formed only 16% of the study population

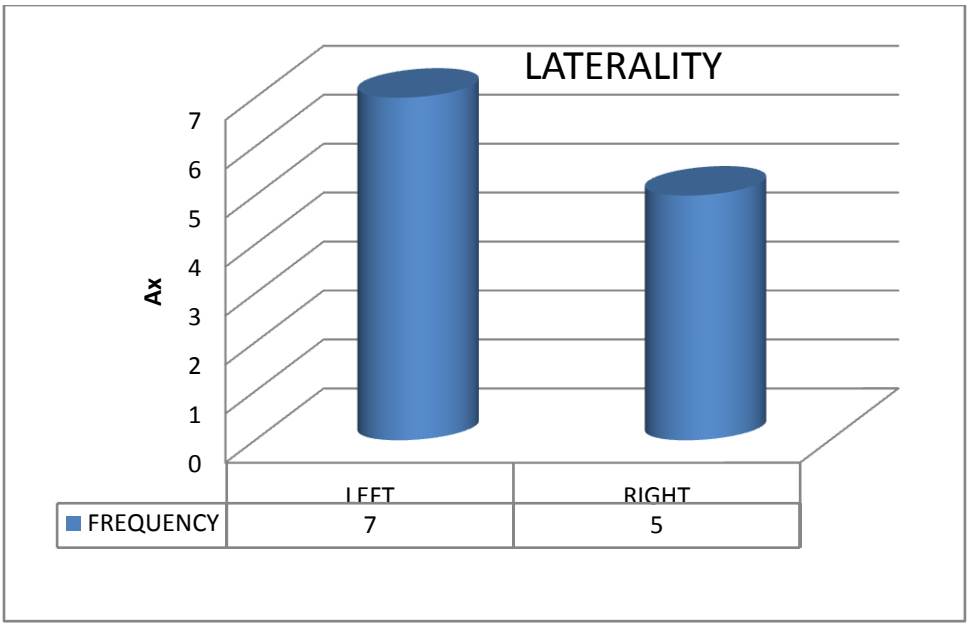


Figure 4.3: Seven out of 12 patients had left sided breast cancer

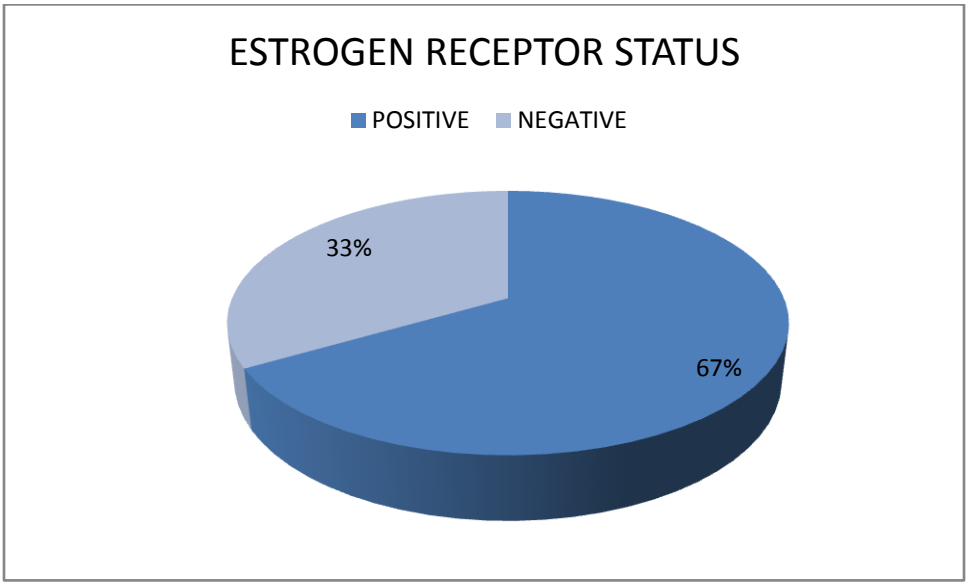


Figure 4.4: The majority of the patients were Estrogen receptor positive.

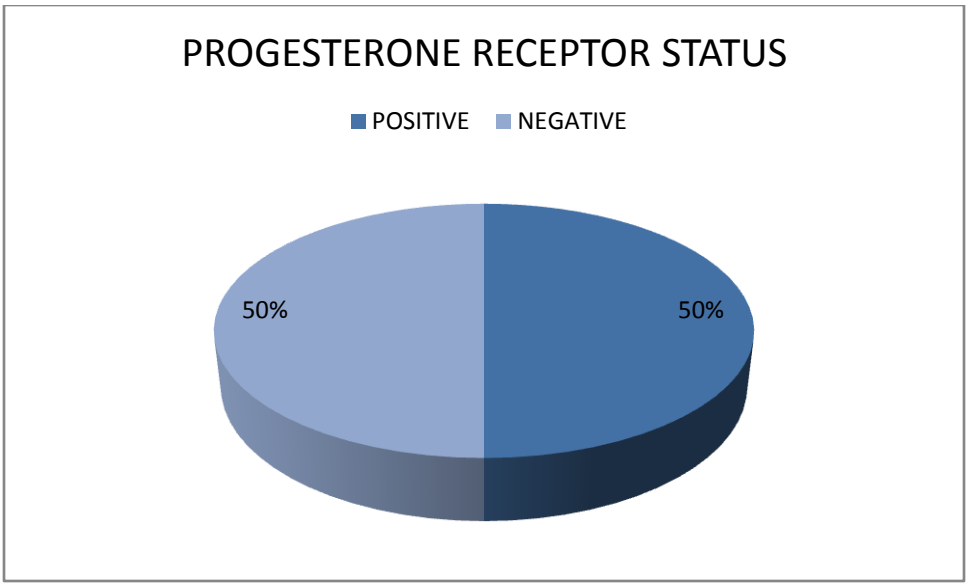


Figure 4.5: Equal distribution of Progesterone receptor status

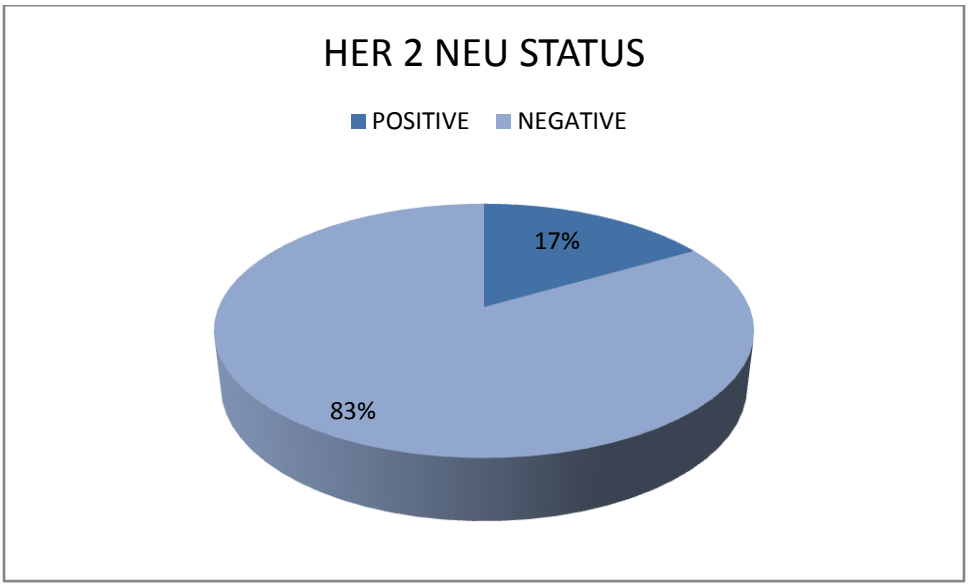


Figure 4.6: Most of the patients were her 2 neu positive

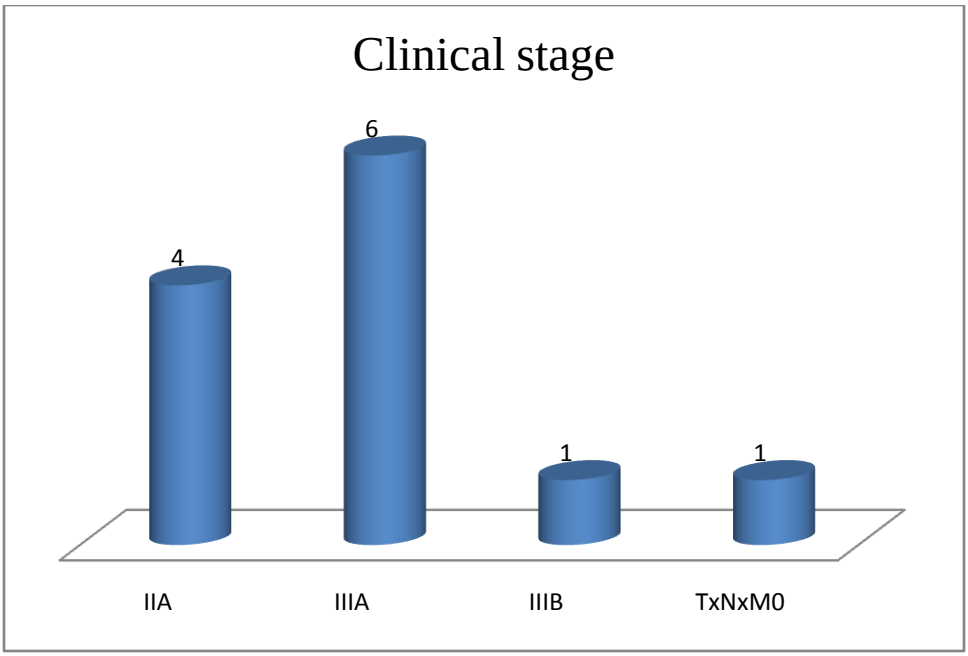


Figure 4.7: Stage wise incidence of breast cancer in the study group

4.2 DVH PARAMETERS

4.2.1 CLINICAL TARGET VOLUME

The lower dose limit applied for the CTV was that more than 90% of the CTV should receive 95% or more of the prescribed dose ($V_{95\%}$ > 95%). The upper dose limit constraints were, $V_{107\%}$ <2%, $V_{105\%}$ <7% and Global maximum <110%.

Table 4.2: CTV Coverage

PATIENT	V90%	V95%	V100%
1	95.54	91.55	53.2
2	97.38	87.98	28.18
3	99.04	96.02	71
4	99.37	95.23	47.99
5	94.05	86.33	4.3
6	98.63	95.66	60.44
7	98.17	92.06	45.07
8	98.8	96.8	58.5
9	96.4	91.6	69.1
10	98.1	94.2	71.8
11	98.34	92.52	47
12	97	91.1	60.6

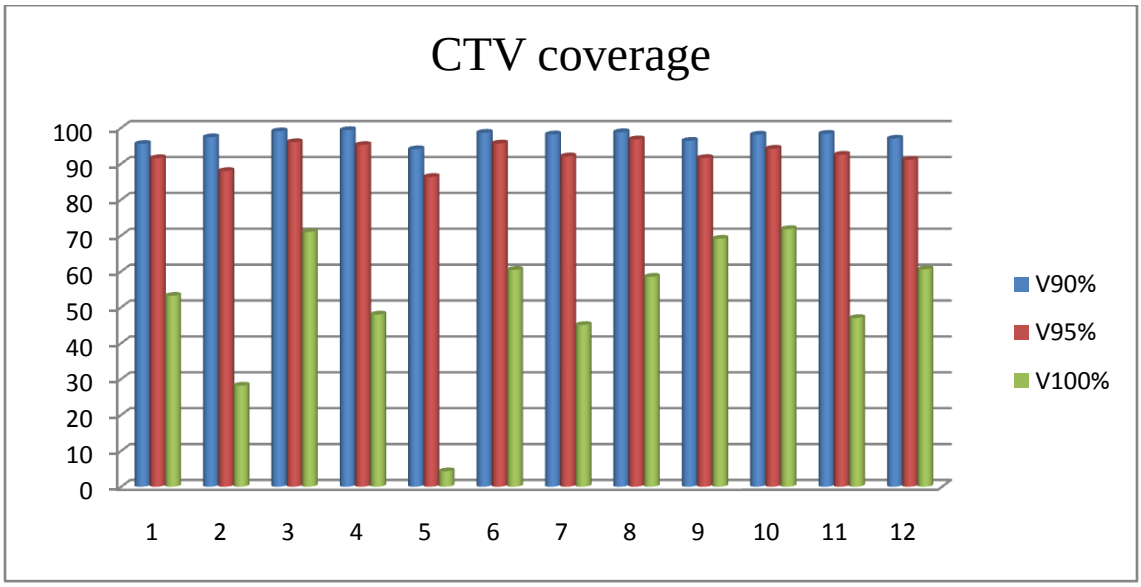


Figure 4.8: Bar diagram showing the CTV $V_{90\%}$, $V_{95\%}$ and $V_{100\%}$ on Y axis across patients on X axis.

CTV coverage was analyzed by dividing the cases into two groups according to the regions treated (**Table 4.3**).

Chest wall and Chest wall along with supraclavicular region

The median CTV $V_{95\%}$ was 92.52% when chest wall was treated alone and 91.60% when chest wall and supraclavicular regions were treated. Both CTV $V_{90\%}$ and $V_{95\%}$ were better when chest wall alone was treated, but this difference was not statistically significant.

Table 4.3: CTV coverage with respect to regions treated

CTV	Chest wall			Chest wall and supraclavicular regions			p value
	1st quartile	Median	3rd quartile	1st quartile	Median	3rd quartile	
$V_{90\%}$	95.54	**98.34**	99.04	96.70	**97.38**	98.45	0.530
$V_{95\%}$	91.55	**92.52**	95.66	89.54	**91.60**	95.50	0.755
$V_{100\%}$	45.07	**47.99**	60.44	43.34	**60.60**	70.45	0.343

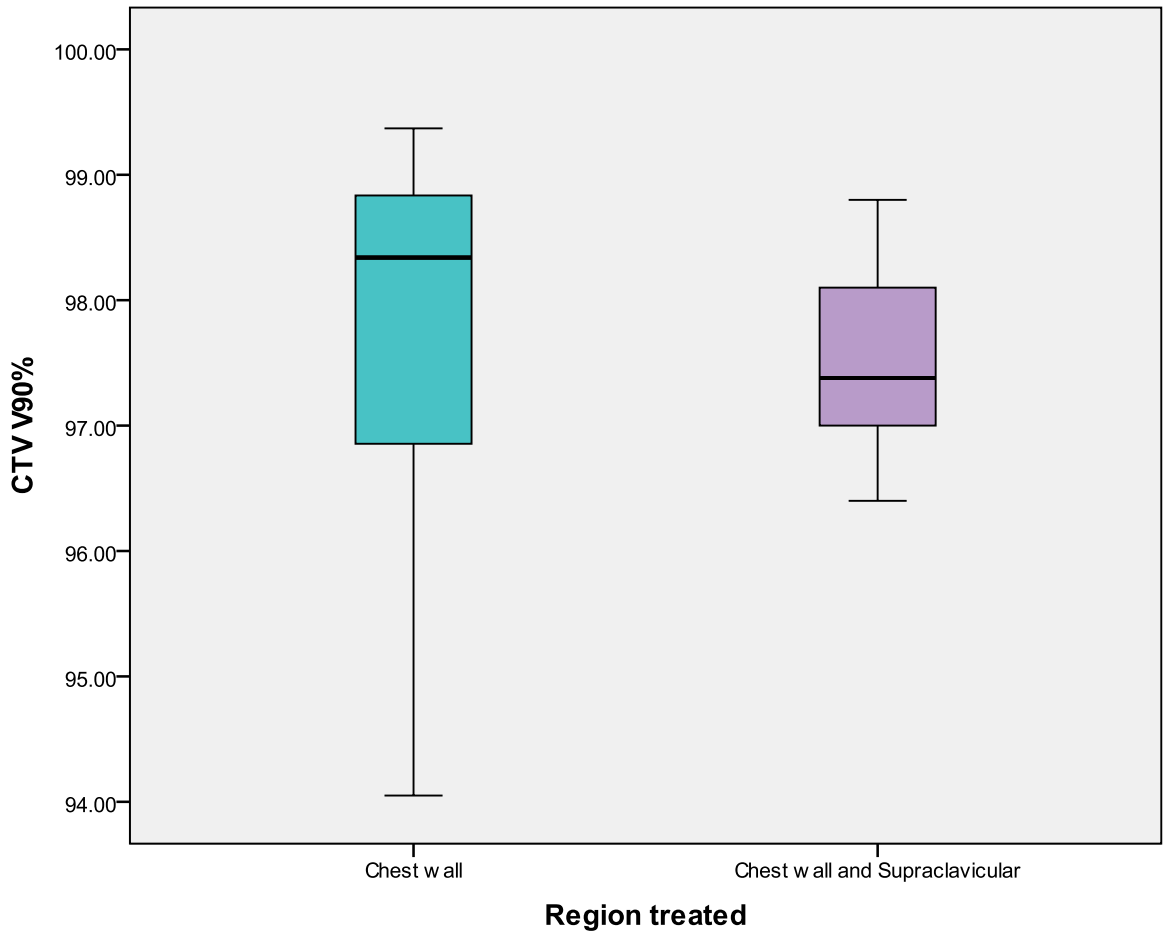


Figure 4.9: Comparison of $V_{90\%}$ among two groups – according to regions treated

The median $V_{90\%}$ was 98.34% in patients who received chest wall radiation alone compared to 97.38% in patients who received supraclavicular radiation in addition to the chest wall radiation (**Fig 4.9**). This variation in $V_{90\%}$ was not statistically significant (p value 0.530). The range of V90% values was broader when only chest wall was treated (**Table 4.3**)

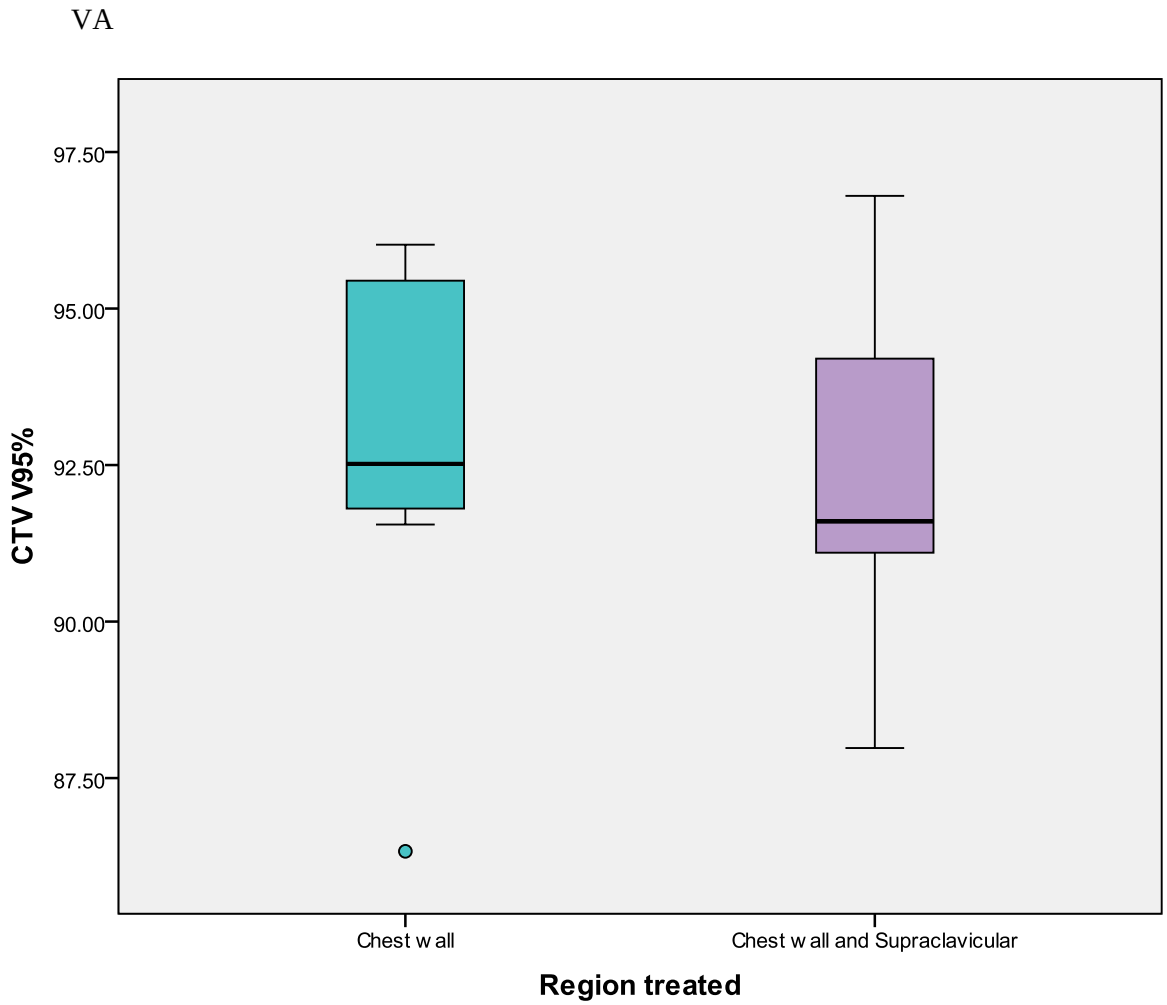


Figure 4.10: Comparison of $V_{95\%}$ among two groups –according to regions treated

The median $V_{95\%}$ values were 92.52% and 91.60% for chest wall irradiation alone and combined chest wall-supraclavicular irradiation respectively (**Table 4.3**). The range of $V_{95\%}$ was similar among the two groups and ranged between 86.33–96.02% and 87.98–96.80 (**Fig 4.10**). The first and third quartiles were 91.55% and 95.66% in the chest wall group (**Table 4.3**).

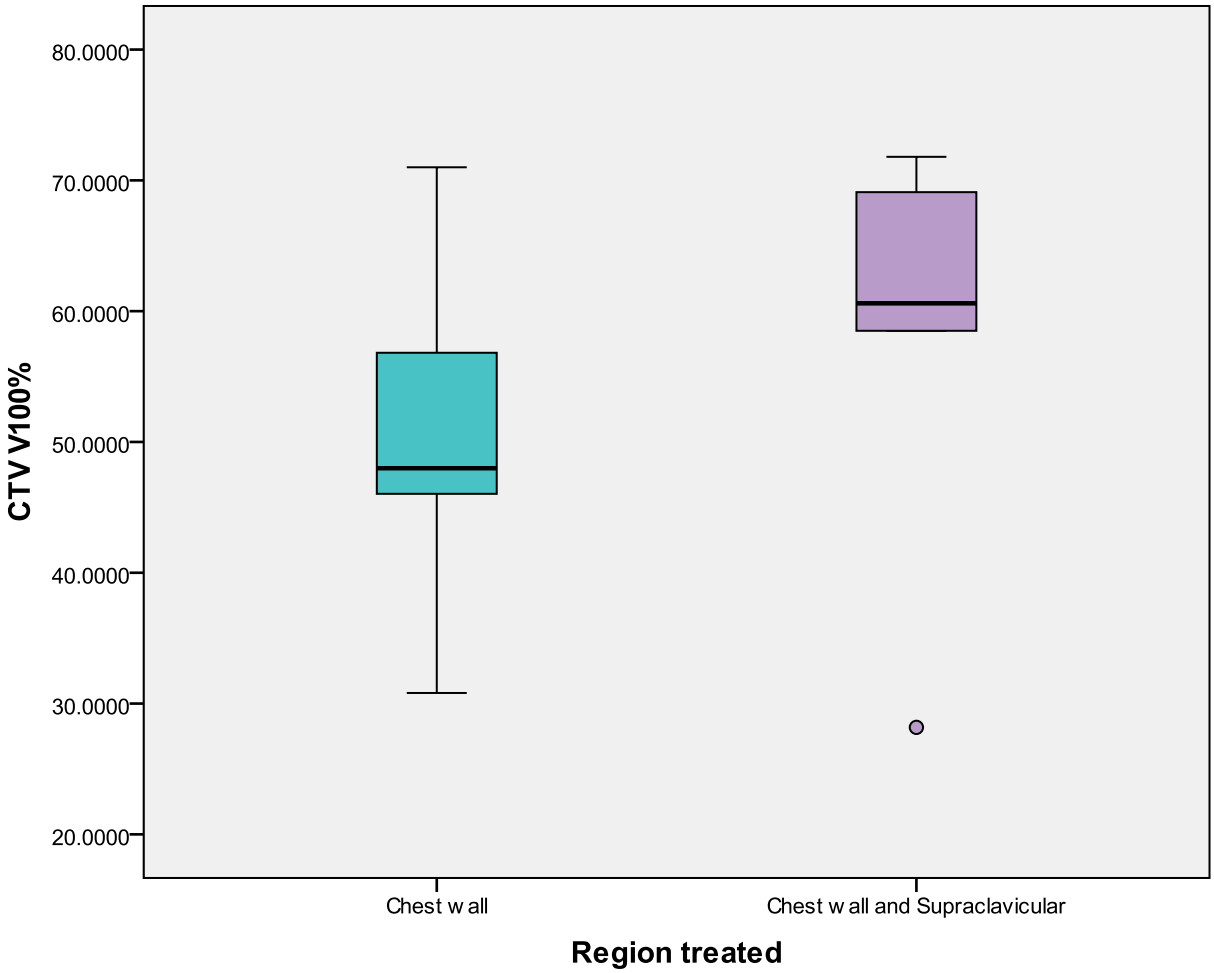


Figure 4.11: Comparison of $V_{100\%}$ among two groups – according to regions treated

The median V100% was 60.6% in the chest wall-supraclavicular group and 47.99% in the chest wall alone group (**Table 4.3, Fig 4.11**).

UPPER DOSE LIMITS

The hot spots, V105% and V107% were well within the tolerance limits (<7% and <2% respectively). The hot spots were analyzed by dividing the patients into two groups according to the regions treated:

Chest wall and Chest wall & supraclavicular region

Table 4.4: Upper dose limits with respect to regions treated

CTV	Chest wall			Chest wall – supraclavicular			p value
	1st quartile	Median	3rd quartile	1st quartile	Median	3rd quartile	
G max	106	106	107	104	106	106.50	0.343
$V_{105\%}$	1.96	3.43	5.50	0.45	3.10	7.05	0.876
$V_{107\%}$	0	0.14	0.49	0	0	0.35	0.639

The CTV Global maximum doses ranged between 104-108% in the group of patients who received chest wall radiation and 104-107% in the group of patients who received the supraclavicular irradiation in addition. The median Global maximum dose was same (106%) in both the groups (**Table 4.4, Fig 4.12**).

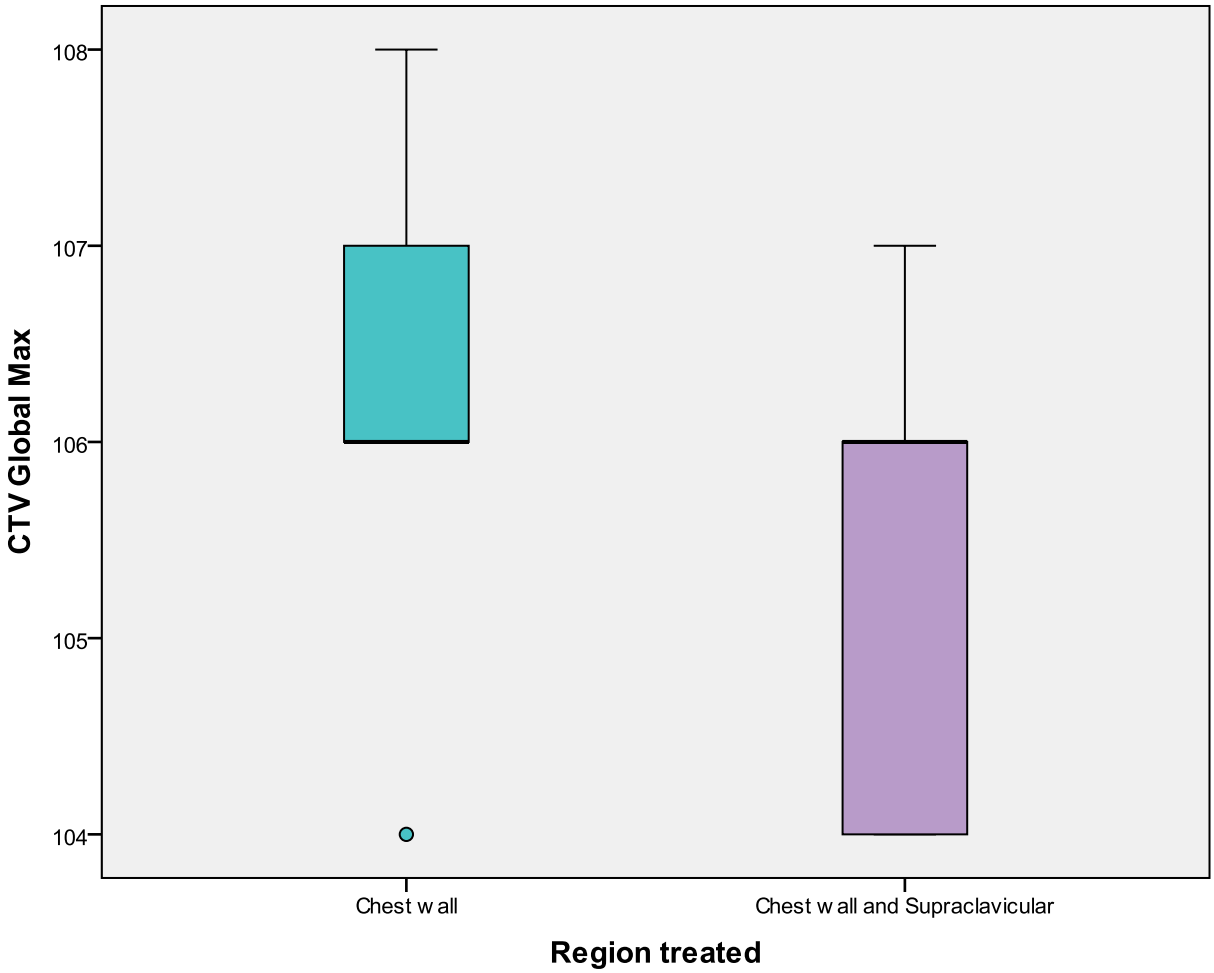


Figure 4.12: CTV global maximum according to regions treated

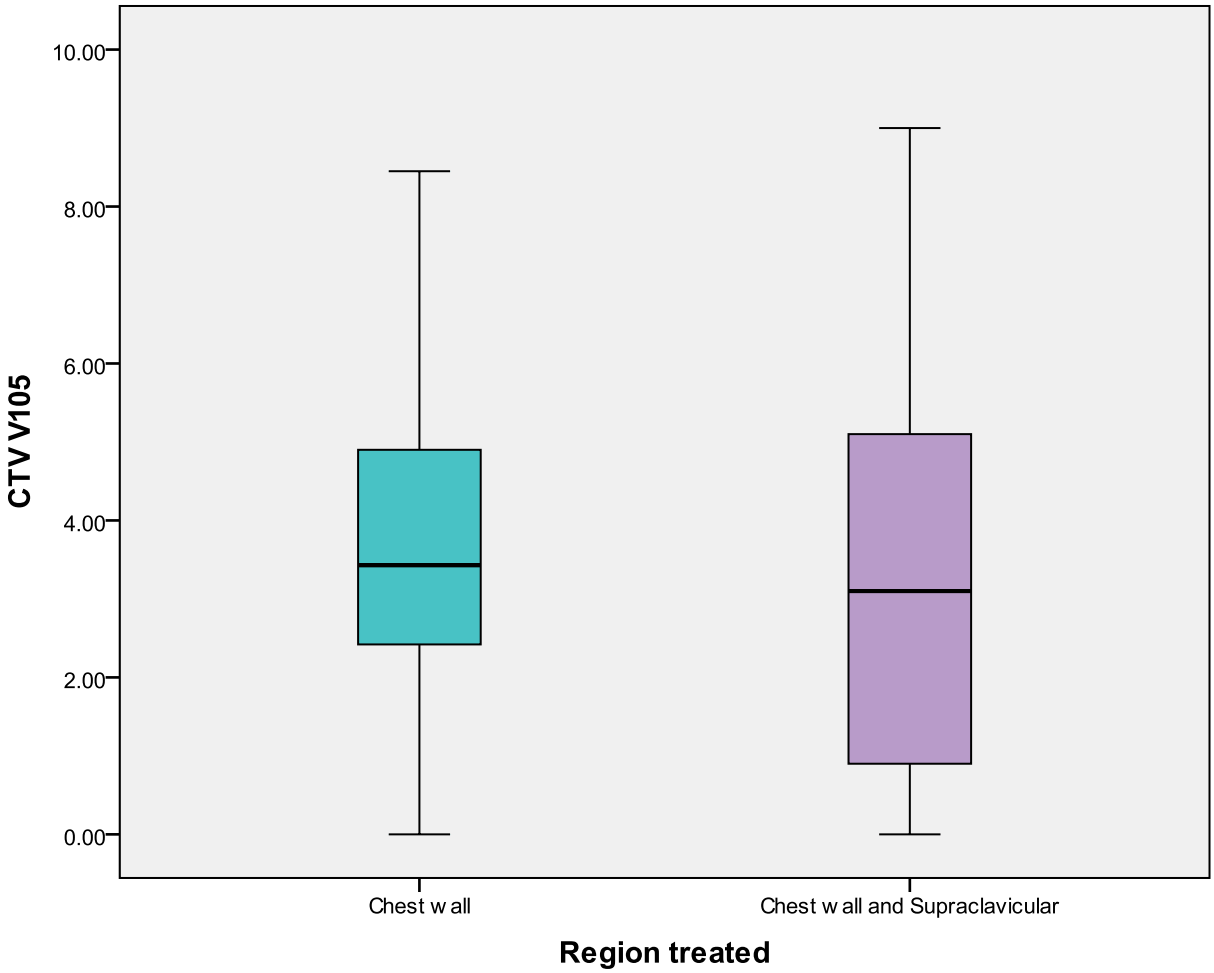


Figure 4.13: Comparison of CTV $V_{105\%}$ among the two groups based on regions treated.

The median V 105% was 3.43% and 3.10% respectively for chest wall alone and combination of supraclavicular and chest wall regions (**Table 4.4**). The values ranged between 0 and 9 % in both the groups (**Fig 4.13**).

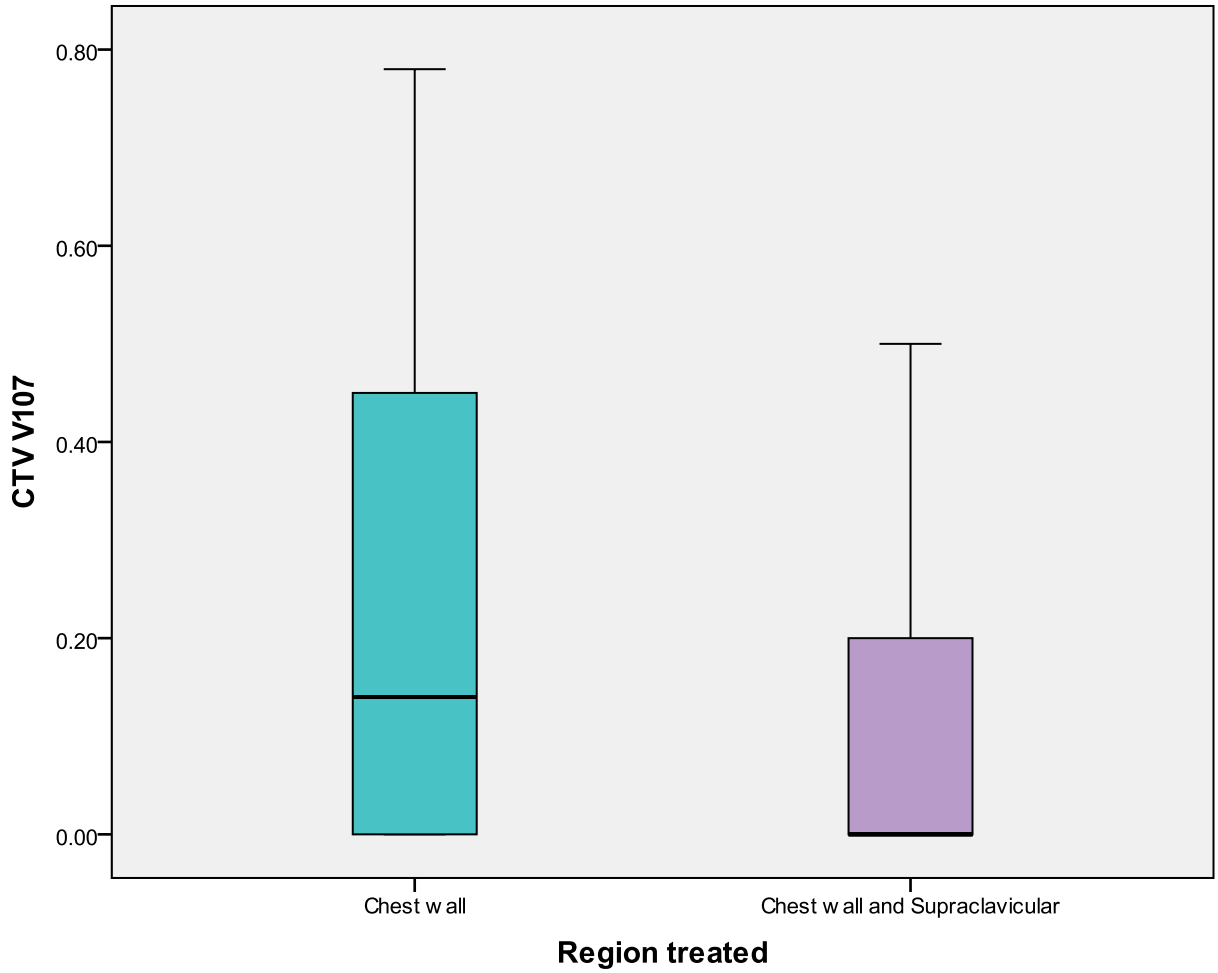


Figure 4.14: Comparison of V107% among the two groups based on regions irradiated.

Figure 4.14 shows that the range of V107% was 0 – 0.78% in the chest wall group and 0-0.50% in the chest wall-supraclavicular group. The median value was 0 in the two-regions group, where as median V107% was 0.14% in the single region group.

CTV COVERAGE AND BMI

There was a positive correlation between BMI and CTV 95%, which implied that higher the BMI, higher is the CTV V95%. But this was not statistically significant in view of the small sample size (**Figure 4.15**).

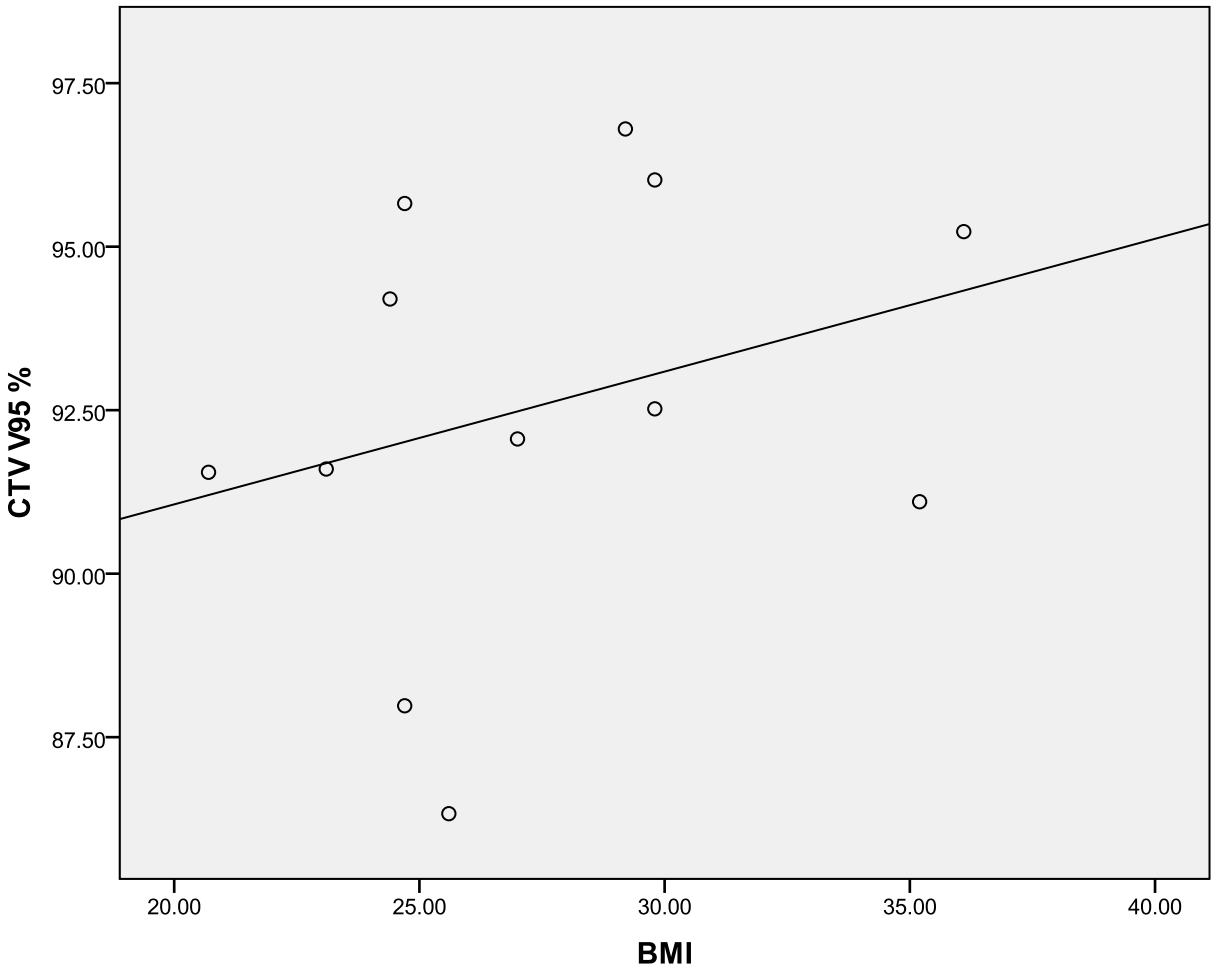


Figure 4.15: BMI and CTV $V_{95\%}$

4.2.2 ORGANS AT RISK

The organs at risks studied were ipsilateral lung, heart, contralateral lung, combined lung and contralateral breast. V_{10Gy}, V_{12Gy} and V_{20Gy} for the ipsilateral lung and V_{2Gy} and V_{10Gy} for the heart were documented. The dose constraint attempted to achieve was the volume of the ipsilateral lung receiving 12Gy to be less than 17%. The ipsilateral lung volume receiving ≥12Gy ranged from 7.43% to 35%. The contralateral lung V_{10Gy} and V_{20Gy} were found to be 0, which means that no part of the contralateral lung received 20Gy or 10Gy.

Table 4.5: Ipsilateral Lung volumes receiving 10Gy, 12Gy and 20Gy

Patients	V10Gy	V12Gy	V20Gy
1	20.99	20.2	18.12
2	21.61	20.85	18.36
3	20.06	19.42	17.43
4	14.99	14.19	11.75
5	19.06	18.18	15.51
6	15.62	14.93	12.91
7	7.94	7.43	5.83
8	22.4	21.1	17.3
9	37.6	35	32.1
10	30.8	29.5	25.7
11	16.96	16.23	13.97
12	26.1	25.2	21.5
Mean	21.17	20.18	17.54
SD	7.72	7.25	6.77

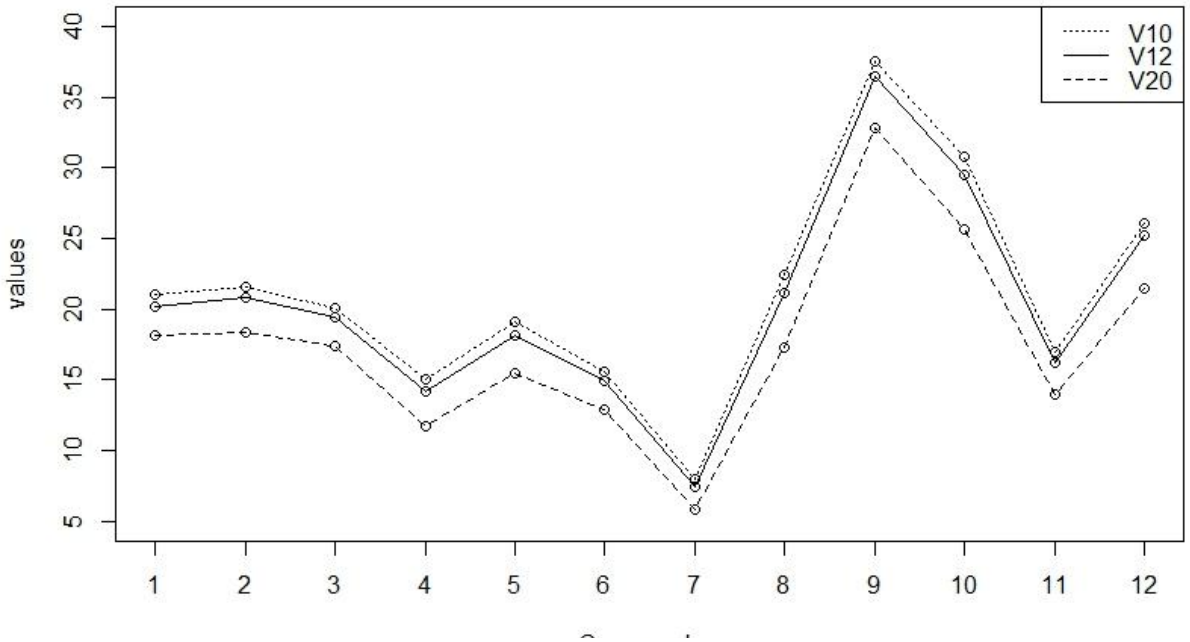


Figure 4.16: Plot showing the lung volumes receiving 10Gy, 12Gy and 20Gy in percentages

The dose constraint for ipsilateral lung could be met for only four patients (V12Gy <17%). The remaining 8 patients had >17% of their ipsilateral lung receiving 12Gy or more. Among these 8 patients, 3 of them had V12Gy ≤ 20% (**Table 4.5, Fig 4.16)**.

Volume of lung irradiated according to the regions treated

The V_{10Gy}, V_{12Gy} and V_{20Gy} which are the volumes of lung receiving 10Gy, 12Gy and 20Gy respectively was higher for those patients who had supraclavicular field in addition to the chest wall field. The Mann-Whitney test was applied and it was found that the V_{10Gy} and V_{12Gy} were significantly (p value 0.003) higher when both the regions were included as the target (**Table 4.6, Fig 4.17, 4.18, 4.19**).

Table 4.6: Ipsilateral lung dose volume data based on regions treated

Lung volume	Chest wall			Chest wall and supraclavicular			p value
	1st quartile	Median	3rd quartile	1st quartile	Median	3rd quartile	
V10Gy	14.99	16.9	20.06	22.34	26.10	34.20	0.003
V12Gy	14.19	16.23	19.42	20.98	25.2	33	0.003
V20Gy	11.75	13.97	17.3	17.83	21.5	29.25	0.010

V10Gy ranged between 7.94 % and 20.99 % in the group of patients who received chest wall

irradiation alone. The range of V10Gy was 21.61% to 37.6% in chest wall-supraclavicular group.

Figure 4.17 shows that the median V10Gy was higher in the chest wall-supraclavicular group than that of the chest wall alone group (26.10 % vs 16.9 % , p value 0.003).

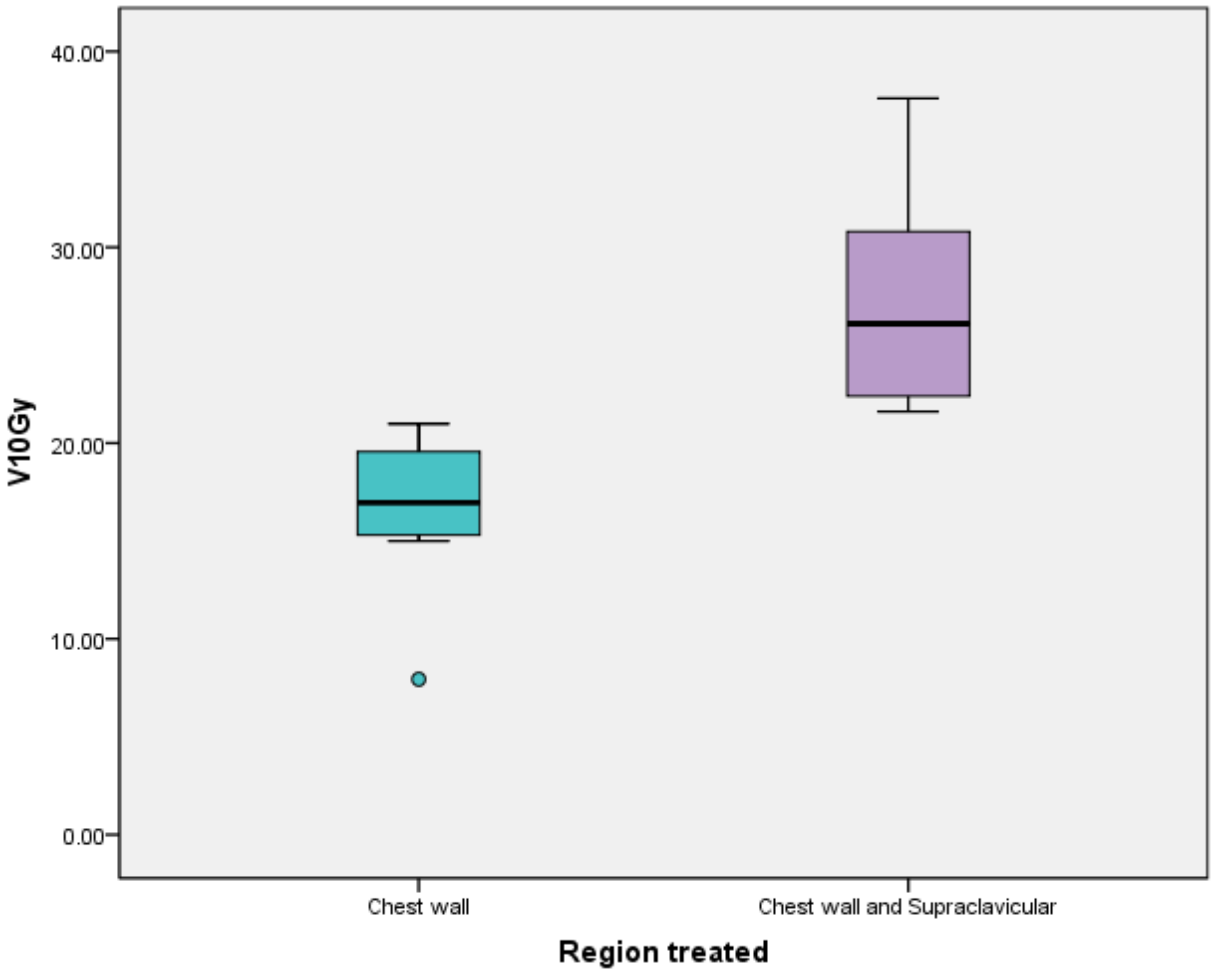


Figure 4.17: Comparison of V10Gy according to regions treated

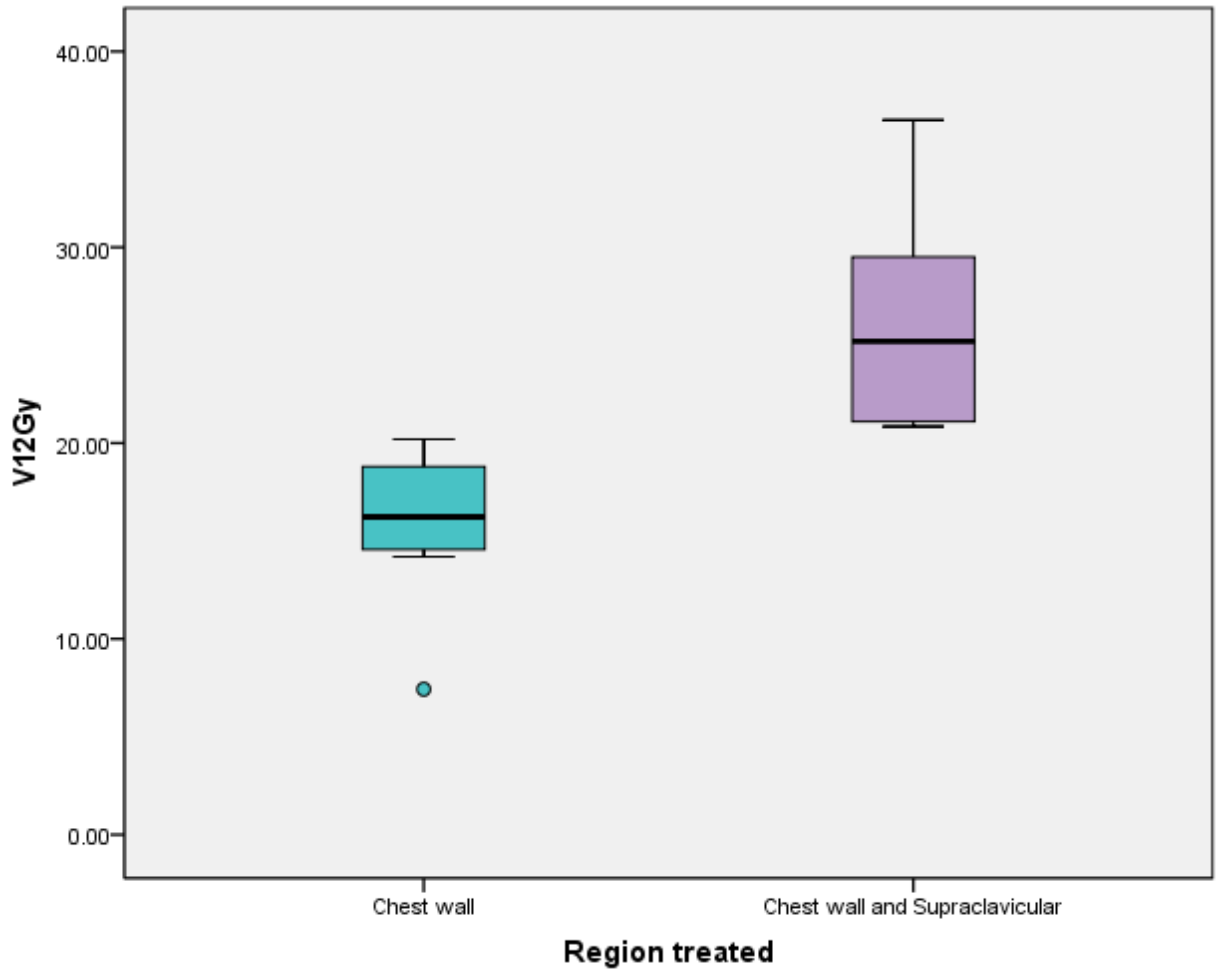


Figure 4.18: Comparison of V12Gy among groups of patients according to the regions treated

The median V_{12Gy} in the group of patients who had supraclavicular region in addition to the chest wall was 25.2% compared to the group of patients who received only chest wall irradiation 16.23% (p value 0.003). The first and the third quartiles values of V12Gy for chest wall irradiation was 14.19 % and 19.42%, which implies that 50 % of patients in this group had their V12Gy values in this range.

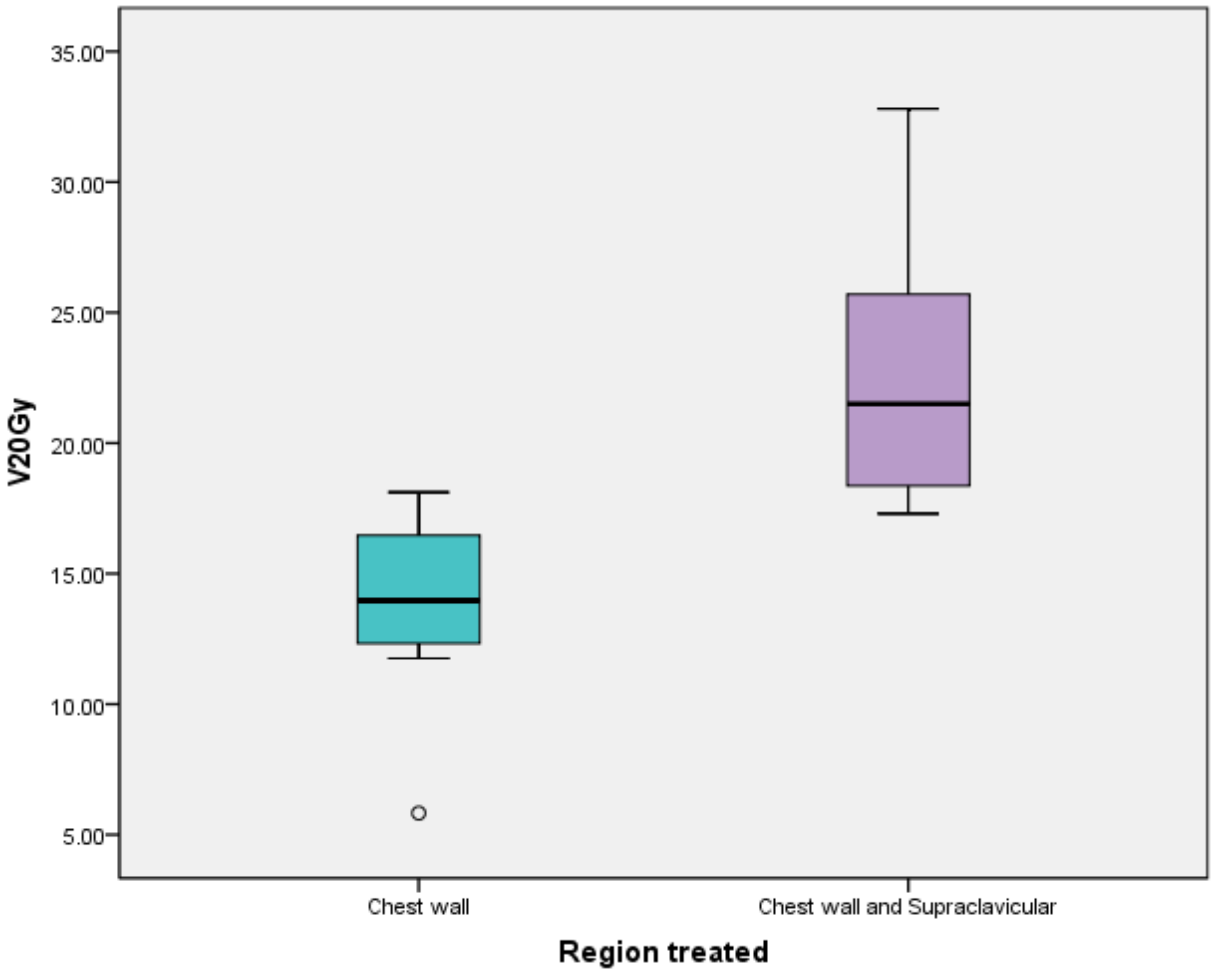


Figure 4.19: Comparison of V20Gy among two groups of patients according to the regions treated

The median values were 13.97 % and 29.25 % respectively for patients who received radiation to chest wall alone and supraclavicular-chest wall irradiation. Median V_{20Gy} was significantly higher in the patients who received supraclavicular treatment in addition to chest wall (p value 0.010).

Combined lung: Combined lung volume receiving 10Gy ($V10_{Gy}$) was less than 17% in eleven of the twelve patients. One patient had a V_{10Gy} of 19%.

HEART

The dose constraints we attempted to achieve was V10Gy ≤ 5% and V2Gy ≤ 30%. V2Gy ≤30 % could be achieved in 7 out of 12 patients and V10Gy ≤ 5 % was achieved in 6 out of 12 patients.

Volume of heart irradiated according to laterality of the disease:

The volume of heart receiving 2Gy and 10Gy were significantly (p value 0.003) higher in patients with left sided breast cancer (**Table 4.7, Fig 4.20, 4.21**).

Table 4.7: Heart dose-volume parameters according to laterality of the disease

Heart volume	**Left chest wall**			**Right chest wall**			**p value**
	1st quartile	Median	**3rd quartile**	**1st quartile**	Median	**3rd quartile**	
V2Gy	27.66	35.7	44.07	2.35	2.80	9.21	0.003
V10Gy	8.31	12.70	14.26	0	0	0.5	0.003

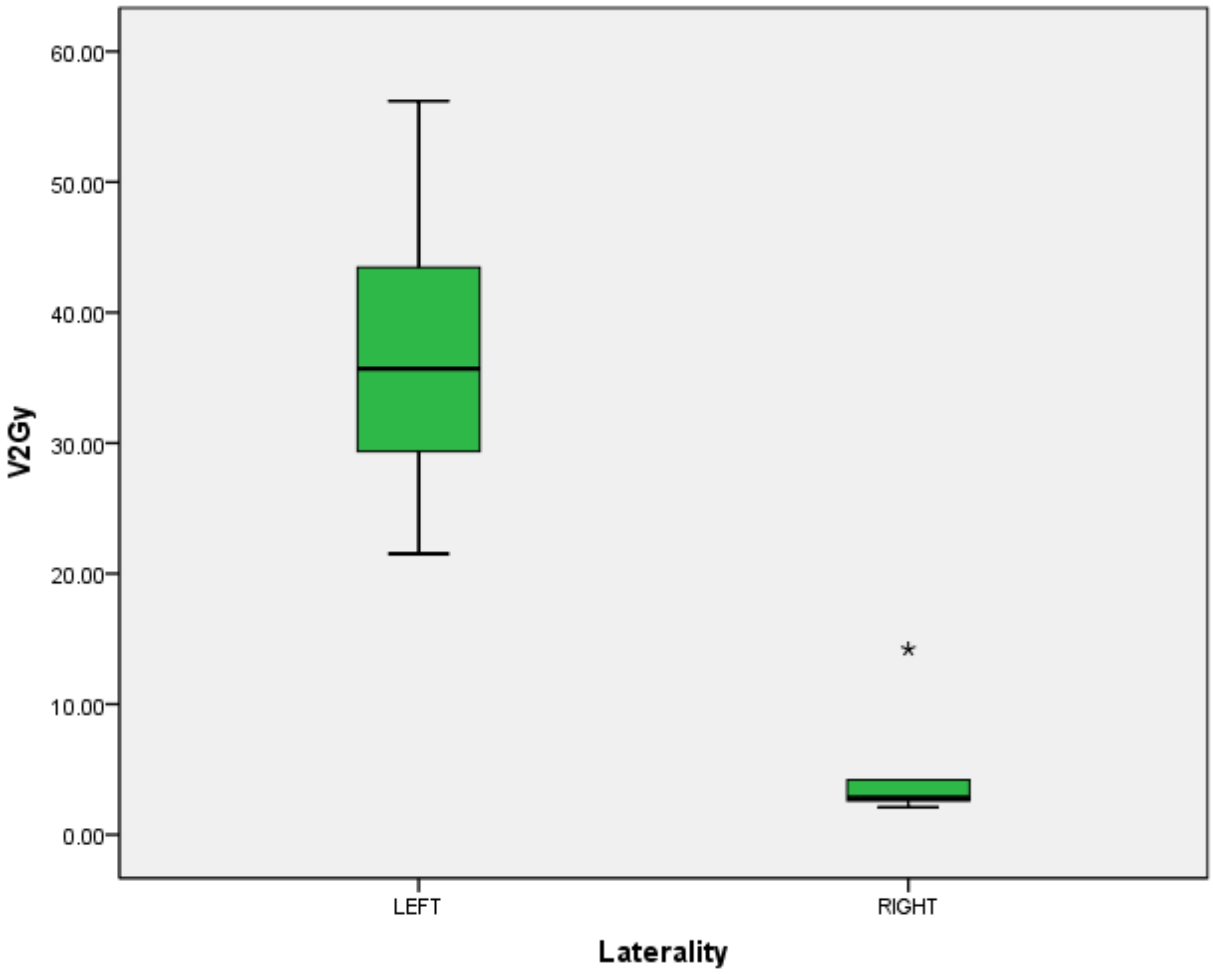


Figure 4.20: Comparison of V2Gy among left and right chest wall irradiation

The median V2Gy in patients with left sided disease was 35.7% and 2.8% in patients with right sided disease (**Table 4.7**). The difference in the volume of heart receiving 2Gy is depicted in Figure 4.20. The first and third quartiles for V2Gy in left side irradiation were 27.66 % and 44.07 %(**Table 4.7**).

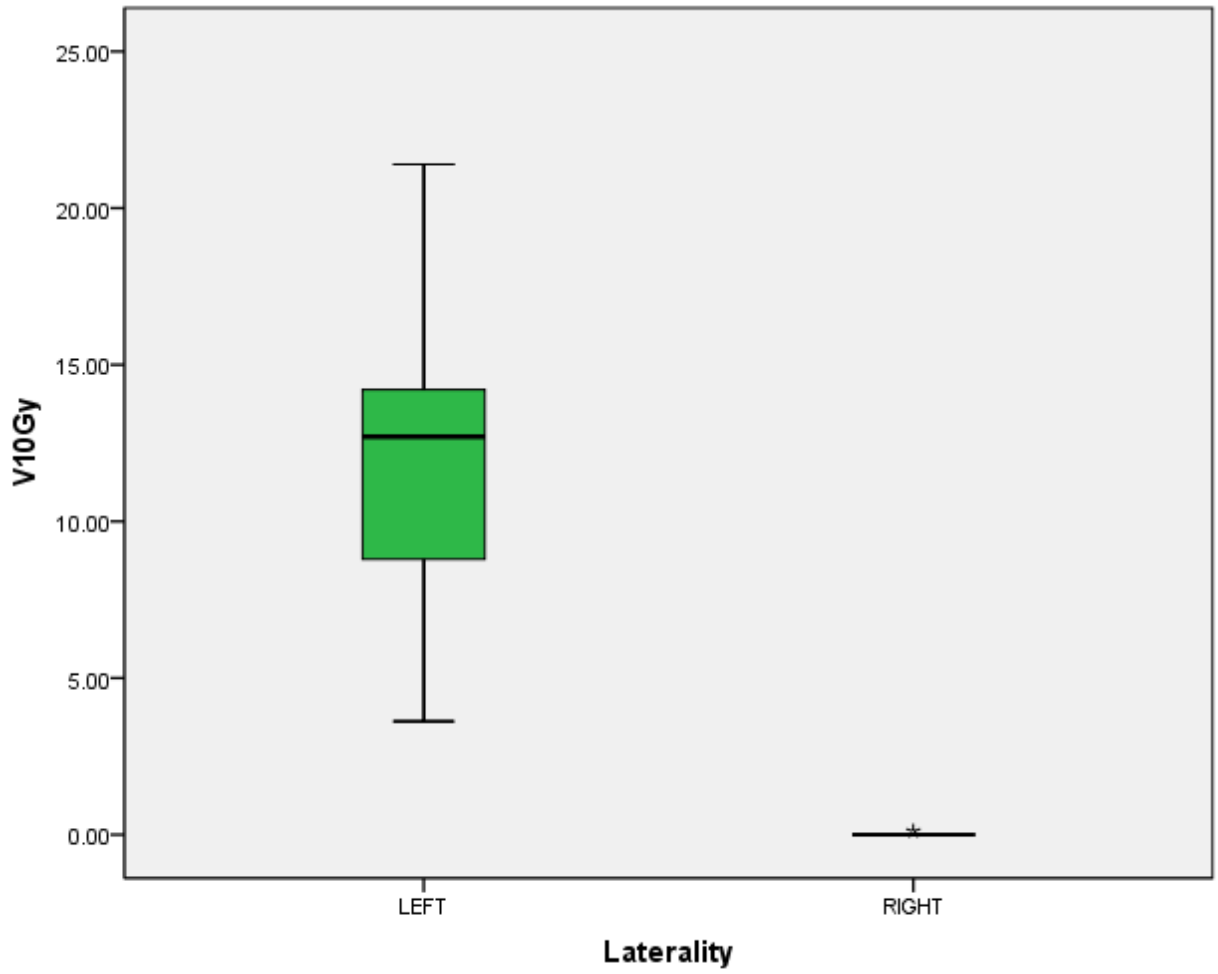


Figure 4.21: Comparison of V10Gy among left and right chest wall irradiation

Median V10Gy in the patients who received left chest wall irradiation was 12.7% where as the median value in right chest wall irradiation was 0%. Figure 4.21 depicts the range of V10Gy values among the two groups.

Contralateral breast: The dose constraint that we tried to achieve was to keep the mean dose to the contralateral breast ≤ 330cGy. The mean contralateral breast dose ranged between 38cGy and 126.5cGy. The mean of all the patients' contralateral breast mean

dose was 65.24cGy. All the patients had contralateral breast dose well within the tolerance limit.

4.3 ACUTE TOXICITIES

Patients tolerated the treatment well without any Grade IV toxicities. The acute toxicities that were noted in the study group were fatigue, dermatitis and mucositis (throat irritation).

Dermatitis and fatigue were the most common side effects noted (**Table 4.8, Fig 4.22**).

None of the patients developed features of acute radiation pneumonitis.

Table 4.8: Acute side effects

	week 1	week 2	week 3	week 4	week 5	week 6	week 7	week 8	week 9
Fatigue	1	5	3	1	0	0	0	0	0
Dermatitis	2	8	12	4	3	1	0	0	0
Cough	0	4	3	0	0	0	0	0	0
Throat irritation	0	2	1	0	0	0	0	0	0

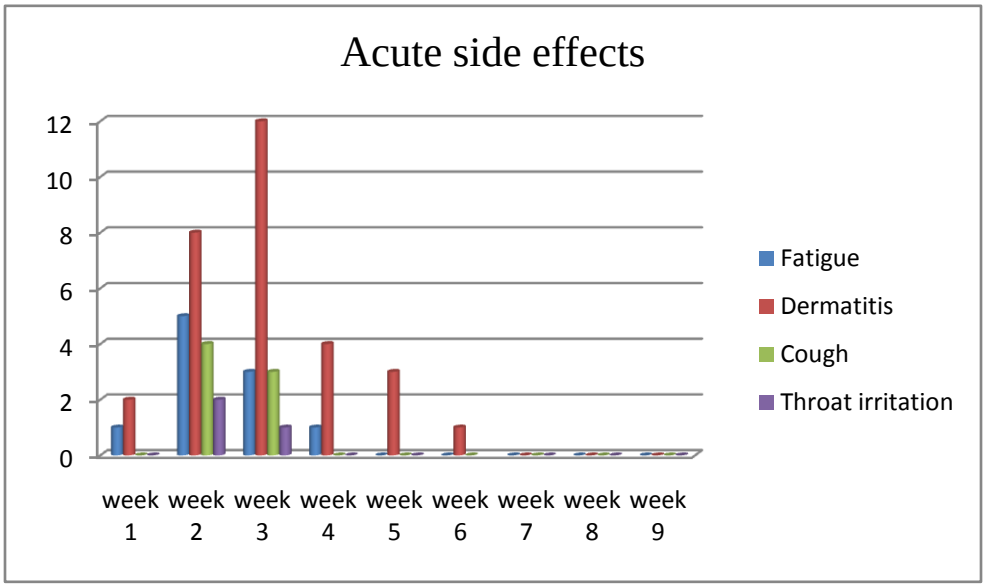


Figure 4.22: Acute side effects during and after treatment

DERMATITIS

None of the patients developed Grade IV dermatitis. One patient developed Grade III dermatitis by week 4 (the week after completion of radiotherapy). She completed treatment on 24.4.2013, Grade III reaction was documented on 1.5.2013, and by 8.5.2013 the reaction subsided **Colour plates 1,2,3**). Majority (10 out of 12) of the patients had only Grade I dermatitis and only one patient developed Grade II dermatitis (**Table 4.9, Fig 4.23**).

Table 4.9: Week wise incidence of dermatitis

DERMATITIS	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5
Grade I	2	8	11	2	2
Grade II	0	0	1	1	0
Grade III	0	0	0	1	0
Grade IV	0	0	0	0	0

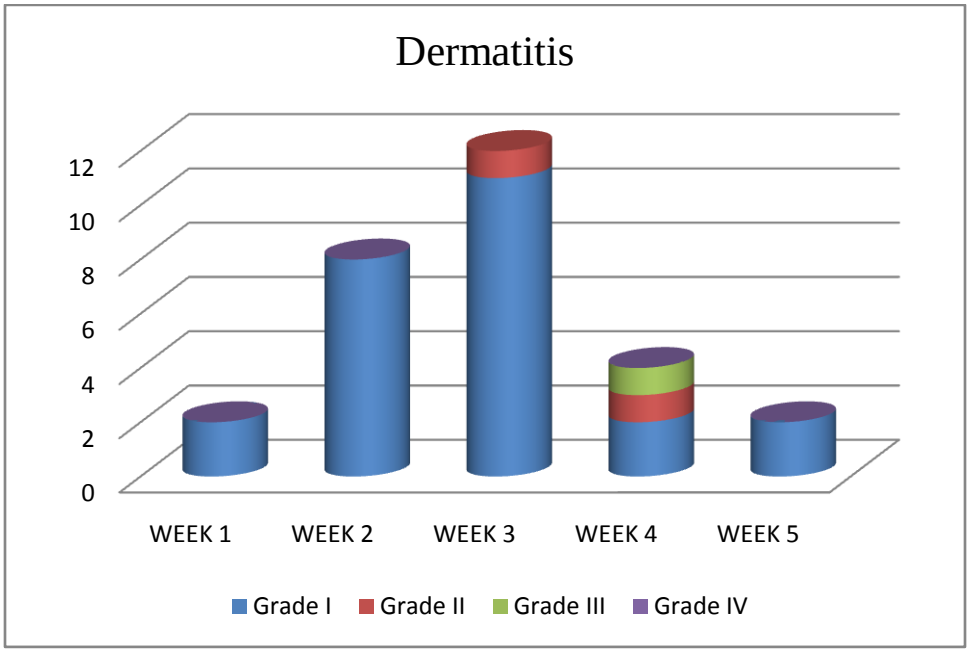


Fig 4.23: Week wise incidence of dermatitis

FATIGUE

Only 5 of the patients developed mild fatigue during the three week of treatment. They were able to continue the activities without any limitations.

OVERALL TREATMENT TIME

The overall treatment time varied between 18 to 24 days. The mean overall treatment time was 20.83 days.

TREATMENT BREAKS

There were no breaks in treatment due to patient related reasons. Three patients had 1 day each of break in treatment due to machine related issues.

FOLLOW UP

Patients have been followed up regularly and the longest follow up is 9 months. None of the patients had local recurrence within this short follow up period. Six out of the twelve patients had completed more than three months of follow up at the time of this analysis. Out of these six patients only three had pre and post radiotherapy Pulmonary Function Tests don**e.** Pre and post radiation therapy Forced Vital Capacity (FVC) was compared, the results of which are given in **Table 4.10**

Table 4.10 Pre and post radiotherapy FVC

	FVC in litres		**FVC in %** (Post bronchodilator/predicted)	
	Pre RT	Post RT	Pre RT	Post RT
1	2.92	2.52	95.4	83.6
2	1.61	1.69	62.5	71
3	1.79	1.76	66.9	64.8

FVC above 80 % is normal. There was no significant change in FVC values pre and post irradiation. One of the patients had low FVC at baseline and this was attributed to Bronchial asthma.

5. **DISCUSSION**

Hypofractionated radiotherapy for carcinoma breast is a safe and effective form of treatment in terms of toxicities, locoregional tumor control and survival. Our study focused on testing this hypothesis in our patients who are heterogeneous among themselves, but at the same time quite different from the population that were recruited in the landmark trials on hypofractionation for breast carcinoma. The UK Standardization of Breast Radiotherapy (START) trials are the landmark trials which forms the broad base for evidence for hypofractionated radiotherapy for patients with breast cancer. START B trial was a randomized controlled trial which compared the conventional standard schedule with the hypofractionated regimen (40Gy in 15 fractions, 3 weeks). The patients in the trial had breast conservation surgery predominantly and only about 8% had undergone mastectomy. We conducted a single arm, prospective study to assess the feasibility and tolerance of hypofractionated radiotherapy in patients who have undergone mastectomy.

The CTV coverage in patients who received supraclavicular regional irradiation in addition to the chest wall irradiation was as good as in patients whose chest wall only was treated (**Table 4.3**). In our study, it was noted that as the BMI of the patient increased, the CTV coverage (V95%) also increased (**Fig 4.15**). But, Koh et al has reported that in obese patients, the coverage for supraclavicular volume tends to be poor as the supraclavicular fossa will be deep. They recommend IMRT for better coverage of supraclavicular region,

especially for obese patients(42). Out of the twelve patients in our study, only five patients received supraclavicular radiation and hence it was not feasible to analyze correlation between BMI and CTV coverage in this subgroup as the numbers are small.

The dose constraints for ipsilateral lung dose could not be met for all patients especially in those who received supraclavicular irradiation (**Table 4.6**). Addition of supraclavicular irradiation has contributed significantly to the lung dose. This was consistent with the data from Yang et al, which also reports higher lung dose with supraclavicular irradiation(43). The constraint was extrapolated from the protocol of the Fast Forward trial which is set for hypofractionated whole breast irradiation, whereas our patients received post mastectomy radiotherapy(44). This could be the explanation for not being able to meet the dose constraint for lung in most of the patients in our study.

The volume of heart receiving 2Gy should be less than or equal to 30% - again a constraint followed in the Fast Forward trial. The median V2Gy in our study population was 35.7% in patients who received left chest wall irradiation (**Table 4.7**). The cardiac toxicities can take up to 15 years to develop and hence these patients need to be followed up on long term basis.

In our study, it was difficult to attain optimum balance between target coverage and dose constraints to organs at risk using 3DCRT in a subset of patients. These were patients with left sided tumour and those who required

supraclavicular irradiation. These patients may benefit from IMRT in terms of target coverage and dose to organs at risk.

There were 12 patients in the study and there were no incidence of any form of Grade IV acute toxicity in them, during the three weeks of treatment and six weeks of follow up (**Table 4.9**). This was in concordance with the results of a study by Hijal et al, which assessed dermatitis in patients undergoing hypofractionated radiotherapy following breast conservation. They reported that most of the patients developed Grade I dermatitis only(45). Among the 156 evaluable patients, five patients developed Grade III dermatitis and no patient developed Grade IV toxicity. Indication for axillary radiation was an exclusion criterion in our study. Axilla has abundant sweat glands and the presence of skin creases makes it the commonest region which develops moist desquamation(46).

The low incidence of serious dermatitis in our study might be due to the fact that patients who required axillary radiation were excluded from our study, which might be true for the study done by Hijal et al also. This means that, safety of hypofractionated radiotherapy needs validation in patients who requires axillary irradiation. One of the patients developed Grade III dermatitis, in the week following completion of treatment. The dermatitis subsided to Grade I, within a week with conservative measures. But Somaya et al has reported that dermatitis lasts longer (about 5 weeks) in patients who receive hypofractionated radiotherapy(47). The DVH of this particular patient was reviewed to find out if any hot spot was on the skin. There were no high

dose regions on the skin. The possible reasons for the occurrence of Grade III dermatitis could be that her BMI was high (29.8 kg/m^2 ,overweight) and the skin creases in the lateral aspect of chest wall, towards the axilla. Though she was a Diabetic, the skin reactions healed within a week without getting secondary infection. Long term cosmetic outcome was better in the hypofractionated arm of the START B trial. As our study included only post mastectomy cases, cosmesis was not an outcome variable.

Limitations

The number of patients included in the study was small. Due to the small sample, some of our results were not statistically significant. Patients who required axillary irradiation were not included in the study, thereby limiting our experience with hypofractionated radiotherapy in treating the axilla. The Left Anterior Descending (LAD) coronary artery is the structure that receives maximum dose when left chest wall is irradiated(48). In our study, dose to LAD was not studied. LAD coronary artery is the structure that is commonly affected by myocardial infarction.

The benefits of hypofractionated radiotherapy, in terms of financial benefits and Quality of Life of patients were not studied. Late effects on normal tissues require long term follow up. Locoregional control also requires minimum of five years of follow up. This was not feasible during the term of this study.

Recommendations

Randomized controlled trial comparing conventional and hypofractionated radiation therapy in Indian context in the treatment of whole breast and post mastectomy will help to answer the uncertainties prevailing now. Future studies need to address dose received by LAD coronary artery. Sub studies such as Cost effectiveness and Quality of life will address the additional benefits achieved by hypofractionated regimens. A large proportion of our patients still cannot afford 3DCRT, and so safety and effectiveness of hypofractionated radiotherapy needs to be investigated in patients treated with conventional radiotherapy with using either telecobalt megavoltage beam or megavoltage x-rays.

6.CONCLUSION

Hypofractionated post mastectomy irradiation was well tolerated by our patients in terms of acute toxicities. Patients completed treatment without any delay or treatment breaks. There were no significant toxicity upto six weeks post treatment. The rate and severity of acute side effects were comparable with conventional radiotherapy. Long term effects on the lung, heart and contralateral breast needs to be studied. Patients were very satisfied about the convenience of this shorter radiotherapy schedule. As far as feasibility was concerned, we conclude that Three Dimensional Radiotherapy based hypofractionation might not be feasible in all patients. There is a subset of patients who may benefit from IMRT. Obese patients, with left sided disease and who also require supraclavicular irradiation might benefit from IMRT. The fact that supraclavicular radiation has significantly contributed to the lung dose even in conformal radiotherapy, where in the volume is relatively small, further urges us to be cautious while planning the supraclavicular field conventionally.

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APPENDIX
I

IRB APPROVAL LETTER

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

Dr. B J Prashantham, M.A, M. A., Dr. Min (Clinical)
Director, Christian Counselling Centre
Chairperson, Ethics Committee

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

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

March 1, 2013

Dr. Balu George
PG Registrar
Department of Radiotherapy Unit I
Christian Medical College
Vellore 632 002

Sub: **FLUID Research grant project NEW PROPOSAL:**
Prospective single arm study to assess the feasibility and tolerability of hypo fractioned post mastectomy radiotherapy in patients with carcinoma breast.
Dr. Balu George, PG Registrar, Radiotherapy Unit I, Dr. Selvamani B, Radiation Therapy, Dr. Balukrishna S, Dr. Sunitha Susan Varghese, Radiotherapy Unit I.

Ref: IRB Min. No. 8074 dated 06.11.2012

Dear Dr. Balu George,

I enclose the following documents:-

1. Institutional Review Board approval
2. Agreement

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

With best wishes,

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

CC: Dr. Selvamani B, Department of Radiation Therapy

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. Balu George, PG Registrar, Radiotherapy Unit I, Dr. Selvamani B, Radiation Therapy, Dr. Balukrishna S, Dr. Sunitha Susan Varghese, Radiotherapy Unit I.

Ref: IRB Min. No. 8074 dated 06.11.2012

Dear Dr. Balu George,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Prospective single arm study to assess the feasibility and tolerability of hypo fractioned post mastectomy radiotherapy in patients with carcinoma breast." on November 6, 2012.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Information Sheet and Consent Form (English, Hindi , Tamil and Bengali)
3. Cvs of Drs. Balu George, Selvamani B, Balukrishna S , Sunitha Susan Varghese,
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
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Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

The following Institutional Review Board (Research & Ethics Committee) members were present at the meeting held on November 6, 2012 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. Priya Abraham	MBBS, MD, PhD	Professor, Virology, CMC	Internal, Clinician
Dr. Srinivasa Babu	M.Sc, M.Phil, PhD	Sr. Scientist, Neurological Sciences, CMC	Internal, Clinician
Dr. Susanne Abraham	MBBS, MD	Professor, Dermatology, Venerlogy & Leprosy, 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. Ranjith K Moorthy	MBBS MCh	Professor, Neurological Sciences, 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. Benjamin Perakath	MBBS, MS, FRCS	Professor, Surgery (Colorectal), CMC.	Internal, Clinician
Dr. Vinitha Ravindran	M.Sc Nursing, PhD	Professor, Child Health Nursing, CMC.	Internal, Nurse
Mrs. S. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person

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Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Mrs. Mary Johnson	M.Sc	Professor, Child Health Nursing, CMC.	Internal, Nurse
Mr. Harikrishnan	BL	Lawyer, Vellore	External, Legal Expert
Mr. Sampath	BSc, BL	Advocate	External, Legal Expert
Mr. Joseph Devaraj	BSc, BD	Chaplain, CMC	Internal, Social Scientist
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.

A sum of Rs 40,000/- (Rupees Forty Thousand only) will be granted for One Year.

Yours sincerely

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

CC: Dr. Selvamani B, Department of Radiation Therapy

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II

INFORMATION SHEET

CHRISTIAN MEDICAL COLLEGE, VELLORE

DEPARTMENT OF RADIOTHERAPY

Prospective single arm study to assess the feasibility and tolerability of hypofractionated postmastectomy radiotherapy in patients with carcinoma breast.

INFORMATION SHEET

This is a type of research study. The entire procedure will be explained to you in detail. Only those patients who wish to participate in it will be included in the study. Please find time to think about it and make a decision about taking part in it. You may discuss this with your family and friends before you make up your mind.

You are being offered to take part in this study because you have breast cancer and you have undergone surgery, but require further treatment with radiation therapy to reduce the chances of disease coming back.

Why is this study being done?

Studies have shown that, in patients with breast cancer, giving radiation therapy to the chest, after removal of breast help to reduce the chance of cancer coming back. This is commonly given over five weeks -Monday to Friday, five days a week. Recent studies have shown that, the chance of cancer control is same, if radiation therapy is given in higher dose per day over three weeks instead of the five weeks treatment. This makes the treatment shorter, with equal efficacy. If you take part in this study, you will receive the new short treatment schedule which is well proven to be safe and effective.

How many patients will take part in this study?

We are planning to offer this short radiation therapy treatment to 20 patients.

If you take part in this study what will you have to do?

Once the wound after the surgery heals, you will be offered radiation therapy, if indicated in your case. If you take part in the study you will receive 15 days of treatment, Monday to Friday, every week. Each day, the treatment may take about 15 minutes. The total duration of your treatment will be three weeks. You can involve yourself in the normal daily activities of life while on treatment. You will need to attend clinical examination once a week while on treatment and for atleast six weeks after completing radiation therapy, to look for development of skin reaction over the chest wall.

Before starting the treatment: You will need to undergo some tests before starting the treatment with radiotherapy. It is mandatory to do these tests prior to treatment even if you are not taking part in the trial.These are the tests:

Blood tests
Chest X ray
Ultrasound scan of the abdomen
Lung Function Tests
ECHO

During the study

Once you complete the tests and agree to take part in the study , the treatment starts and weekly once you need to meet the doctor. This is usual practice even for patients who are not in any study. This weekly visit will include history and physical examination to document any skin reaction. The doctor will assess how you are tolerating the treatment. Clinical photographs of the irradiated area will be taken on alternate weeks while on treatment and during the six weeks of follow up.

After the treatment

After completion of the treatment, you will be asked to come for check up once a week for six weeks and then once in three months for one year and once in six months for the second year. At three months after the treatment the lung test will be done to assess any radiation induced changes in lung.

Can I withdraw from this study after it starts?

Your participation in the study is voluntary and you are free to withdraw from the study anytime. If you withdraw also, you will continue to receive further standard treatment. In case you decide to withdraw from the study you have to inform the doctor so that he can advise you regarding what other treatment can be continued for you.

What side effects should be expected?

You may develop side effects while on treatment or after completion of treatment. Everyone taking part in the study will be carefully watched for side effects. Side effects can be mild to moderate. You will be given appropriate medications and if required radiation treatment may be stopped for few days.

Likely side effects are

Reddening of skin over the chest.
Darkening of skin over the chest.
Generalized weakness and fatigue.
Peeling of superficial skin.
Mild pain at the irradiated area which requires simple pain killers.

Rare side effects are(occur in 3 % of patients):

Cough
Breathlesness

Inflammation of heart muscle.
Rib fracture
Slight increase in risk of heart disease for patients with left sided breast cancer.
Small chance of another cancer developing several years after the treatment.

What will happen if I develop any study related injury?
We will take maximum care to avoid any study related injury. In case you develop any study related injury, you will be treated at no cost. However there is no scope for financial compensation in case of study related injury occurs.

Can I become pregnant while in this study?
Pregnancy is to be avoided while on radiation therapy, be it while being in the study or otherwise. If you are in the reproductive age group it is advisable to use effective contraception.

What are the benefits of being in this study?
By being in this study, you have a chance to complete your treatment earlier. If this shorter treatment is found to be feasible, it will be very convenient for future cancer patients as it saves time and money.

Will you have to pay for the tests and treatment?
Yes, you will have to bear the cost of routine tests and treatment. One or two tests which are not routinely done, but, done as a part of this study will be done free of cost. The details of payment can be discussed with your doctor in detail.

What happens when the study is over?
Once the study is over, you will further receive the rest of your treatment- chemotherapy or hormonal therapy according to the individual disease status. After radiation therapy, you will be closely observed with weekly clinical examination for six weeks. If radiation therapy is the last part the entire cancer treatment for you, then you will be called for check up after six weeks, and three months, and once in three months for an year. You can come for check up earlier in case you develop any new symptoms.

Will my personal information be kept confidential?
The result of this study may be published, but your personal identification details will not be revealed in any publication or presentation. However, your medical records may be reviewed by the people associated with the study, without your additional pemission, even if you withdraw from the study.
If you have any further questions please feel free to ask Dr.Balu George or Dr Selvamani B .

III

CONSENT FORM

Study title: Prospective single arm study to assess the feasibility and tolerability of hypofractionated postmastectomy radiotherapy in patients with carcinoma breast.

Participant's name:
Date of birth/age in years:

I _____, daughter / wife of _____ declare that I have read the information sheet provided to me regarding this study and have clarified my doubts regarding this ( ).

I also understand that my participation in this study is entirely voluntary and that I am free to withdraw from this study at any time without affecting my usual treatment or my legal rights ( ).

I also understand that, I have to pay for my treatment ( ).

I understand that I will receive free treatment for any study related injury or adverse event, but I will not receive any financial compensation ( ).

I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the study. I agree to this access ( ).

I understand that my identity will not be revealed in any information released to third parties or published ( ).

I voluntarily agree to take part in this study ( ).

Name:
Signature:
Date:

Name of the witness:
Relation to participant:
Date:

IV

DATA COLLECTION FORM

HOSPITAL NO:

CASE NO:

1. Age:
2. Height:
3. Weight:
4. BMI:
5. Pre/Post menopausal :
6. Performance status:
7. Comorbidities
8. Laterality:
9. Clinical stage:
10. Date of 1st biopsy/FNAC:
11. Neoadjuvant chemotherapy: Yes / No
12. If Yes: Regimen:
13. Date of last cycle:
14. Date of surgery:
15. MRM/SM ,ANC
16. Pathological stage:
17. Margin status:
18. Hormone receptor status :ER:
19. Hormone receptor status: PR:
20. Her 2 neu
21. Grade:
22. Currently on endocrine therapy?
23. If yes: Tamoxifen / AI
24. Regions planned for irradiation:

PATIENT ASSESSMENT PROFORMA

HOSPITAL NUMBER: **CASE NUMBER:**

NAME:

	ON RT			ON FOLLOW UP					
	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6	WEEK 7	WEEK 8	WEEK 9
Date									
Dose									
Fatigue									
Throat irritation									
Itching									
Pain/burning sensation									
Cough									
Dermatitis									
Dysphagia									
Photograph									
Break in treatment									

VI

DVH PROFORMA

	PTV						IPSILATERAL LUNG			CNTRA LNG		CMB LNG		HEART			C.BREAST		
	G MX	V90	V95	V100	V105	V107	D98	D2	V12	V10	V20	V10	V20	V10	V2	V33	MN D	D2	MX D

VII

1	Column2		Column4	Column5	Column6	Column7	Column8
S.NO	H No:		Age	Ht	Wt	BMI	Menop
1	258367F		52	157	51	20.7	2
2	277009F		25	156	60	24.7	1
3	066598b		65	151	68	29.8	2
4	603308F		45	158	90	36.1	1
5	092524C		65	150	60	25.6	2
6	328555F		52	151	67	24.7	2
7	433413F		47	151	61.5	27	1
8	443544F		51	156	71	29.2	1
9	375026F		55	147	50	23.1	2
10	432933F		55	150	55	24.4	1
11	311522F		40	150	67	29.8	1
12	348507F		48	151	80.2	35.2	1

Column9	Column10	Column11	Column12	Column13	Column14	Column15	Column16
Perform	Comorb	Laterality	T	N	NACT_Surgery	NACT_if_yes	Date_last_cy
1	0	2	2	0	1	1	30.6.13
1	0	1	4	2	1	3	5.1.13
1	6	1	3	1	1	4	
1	2	1			2		
1	1,2,5	2	2	0	2		14.3.13
1	2,4	1	3	1	1	3	28.3.13
1	0	1	2	0	2		
1	0	2	3	1	1	1	3.7.13
1	0	1	3	1	1	1	7.3.13
1	1,2	1	3	1	1	3	24.7.13
1	1	2	2	0	2		
1	2	2	3	2	1	1	

Column17	Column18	Column19	Column20	Column21	Column22	Column23	Column24
Date_surgery	p_T	p_N	ER	PR	her_2	adj_chemo	adj_chemo_if yes
6.8.13	1	0	0	0	0	1	2
13.11.12	2	1	0	0	0	1	3
22.11.13	2	0	1	1	0	0	
15.5.13			1	0	0	1	1
3.12.12	3	0	1	1	1	1	1
29.113	0	0	0	0	0	1	3
1.4.13	2	0	1	1	0	1	1
23.7.13	1	0	0	0	0	1	2
17.4.13	1	0	1	0	1	1	2
28.5.13	1	1	1	1	0	1	3
24.8.12	2	0	1	1	0	1	1
12.2.13	2	2	1	1	0	1	2

Column25	Column26	Column27	Column28	Column29	Column30	Column31	Column32
Horm therapy	Horm_if_yes_	Regions Treated			CTV_G_Mx	CTV_V90	CTV_V95
		1	CW	RIGHT	106	95.54	91.5
		2	CW,SC	LEFT	104	97.38	87.9
1	2	1	CW	LEFT	108	99.04	96.0
0		1	CW	LEFT	107	99.37	95.2
1	2	1	CW	RIGHT	104	94.05	86.3
		1	CW	LEFT	107	98.63	95.6
1	1	1	CW	LEFT	106	98.17	92.0
		2	CW,SC	RIGHT	106	98.8	96
0		2	CW,SC	LEFT	107	96.4	91
0		2	CW,SC	LEFT	106	98.1	94
0			CW	RIGHT	106	98.34	92.5
1	1	2	CW,SC	RIGHT	104	97	91

Column33	Column34	Column35	Column36	Column37	Column38	Column39	Column40
CTV_V100	CTV_V105	CTV_V107	CTV_D98	CTV_D2	V12_IPSI_LNG	V10_IPS_LNG	V20_IPS_LNG
53.2	3.43	0	78	105	20.2	20.99	18.12
28.18	0	0	89	103	20.85	21.61	18.36
71	5.5	0.78	93	106	19.42	20.06	17.43
47.99	4.3	0.49	93	106	14.19	14.99	11.75
4.3	0	0	71	104	18.18	19.06	15.51
60.44	8.45	0.41	92	106	14.93	15.62	12.91
45.07	2.88	0	90	105	7.43	7.94	5.83
58.5	0.9	0	92	104	21.1	22.4	17.3
69.1	3.1	0	85	105	35	37.6	32.1
71.8	9	0.2	90	105	29.5	30.8	25.7
47	1.96	0.14	88	105	16.23	16.96	13.97
60.6	5.1	0.5	80	106	25.2	26.1	21.5

Column42	Column43	Column44	Column45	Column46	Column47	Column48
CNTRA_LNGV10	CNTRA_LNGV20	COMB_LNGV10	COMB_LNGV20	HEART_V10	HEART_V2	HEART_V33
0	0	11.16	9.65	0	2.8	0
0	0	9.63	8.1	14.26	42.86	7.21
0	0	9.2	7.8	9.27	31.07	5.3
0	0	7.08	5.49	3.62	21.53	1
0	0	19.06	15.5	0	2.6	0
0	0	6.58	5.45	8.31	27.66	3.33
0	0	2.76	2.02	14.15	44.07	6.09
0	0	13.3	10.3	0	4.2	0
0	0	16.1	13.9	21.4	56.2	9.3
0	0	13.4	11.5	12.7	35.7	4.5
0	0	8.56	6.84	0.11	14.22	0
0	0	16	13	0	2.1	0

C.BREAST_D2	C.BREAST_MX_D	GAP_CHEMO_RT	RT_START	RT_END	OTT	RT_FATIGUE
2.8	3.76	36	18.11.13	5.12.13	18	
3.2	7.95	22	28.1.13	20.2.13	24	
1.9	3.36		3.6.13	21.6.13	19	
3.7	19.96	28	6.11.13	29.11.13	24	
4.1	13.4	33	17.4.13	7.5.13	21	
3.2	8.44	33	1.5.13	23.5.13	23	
		30	20.8.13	9.9.13	21	
2.78	11.7	37	18.11.13	6.12.13	19	
6.46	33.68	47	29.8.13	18.9.13	21	
2.96	25.1	22	16.8.13	5.9.13	19	
11.3	34.63	68	4.4.13	24.4.13	21	
2.18	37.22	33	5.6.13	26.6.13	20	

F_DERM4	F_DERM5	F_DERM6	F_DERM7	F_DERM8	F_DERM9	PFT DUE	DONE/NOT	FEV1 PRE RT
						0	0	
2			1		1	1	1	90.5
1		1		1		1	0	
						0	0	
						1	0	
1	1		1		1	1	1	60.4
	0		0		0	0	0	
						0	0	
	1		0		0	0	0	
						0	0	
3	1	1	1		1	1	1	59.1
						1	0	

COLOUR PLATES

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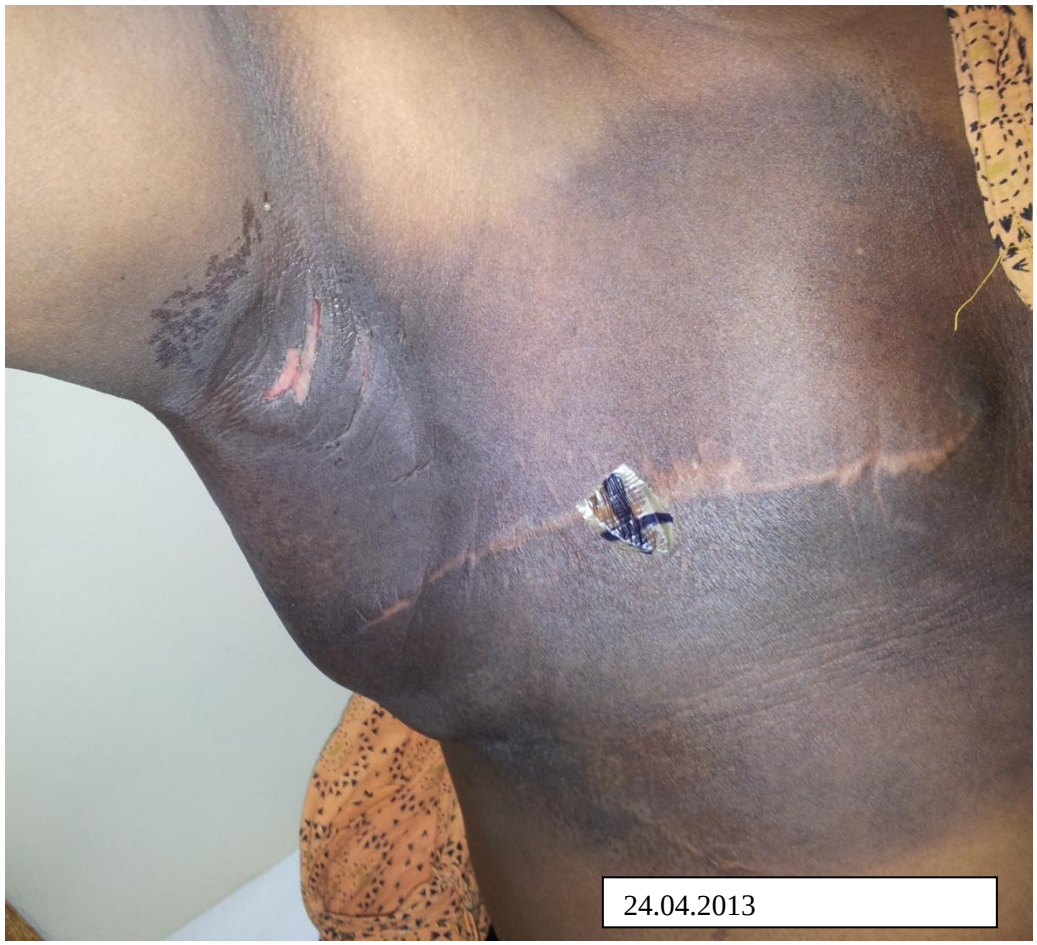

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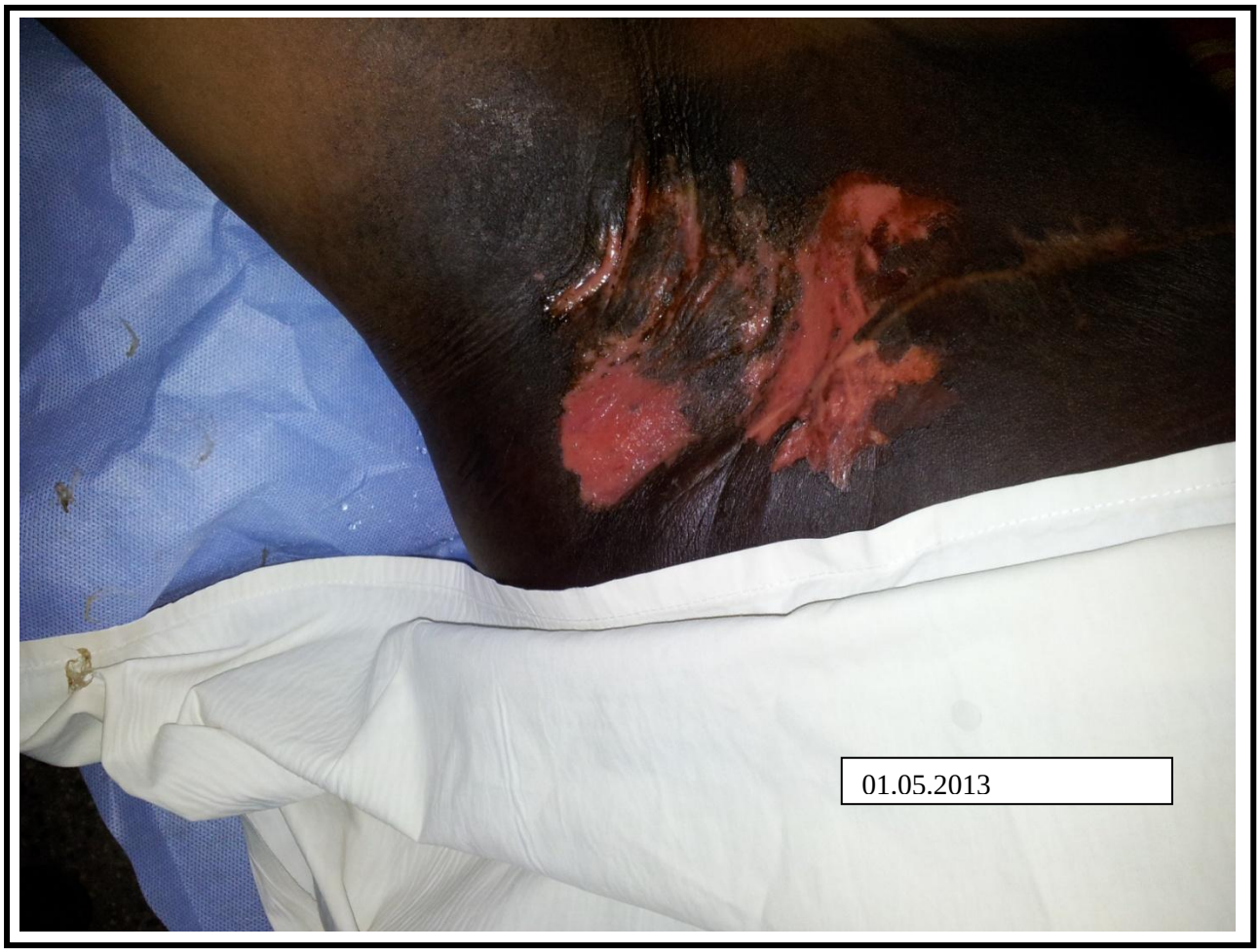

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