A PROSPECTIVE OBSERVATIONAL COMPARATIVE STUDY OF MODERATELY HYPOFRACTIONATED VERSUS CONVENTIONAL FRACTIONATED ADJUVANT RADIOTHERAPY IN BREAST CANCER.

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ABSTRACT

BACKGROUND

Carcinoma Breast is potentially curable at early stages but is still the leading cause of cancer-related mortality among women living in a developing country like India

The conventional fractionation radiotherapy (CFRT) dose 2.0+/-0.2 Gy is delivered 50Gy/25 fractions for 5-6 weeks which causes a long hospital stay with physical and emotional burden and social isolation both for the patient and the family leading to poor compliance.

Hypofractionatedradiotherapy (HFRT) delivering more than 2.2 Gy per fraction needs only 3 weeks 40.05 Gy in 15 fractions or less duration of treatment only.

AIMS AND OBJECTIVES

To assess the feasibility and safety of hypo-fractionated radiotherapy in breast carcinoma cases compared with conventionally fractionated radiotherapy where adjuvant radiation is needed in breast cancer.Secondary objective to document acute toxicities in patients undergoing adjuvant radiotherapy

METHODOLOGY

We conducted prospective comparative study with 30 patients of breast cancer post op for adjuvant radiotherapy,with Arm A delivering 50 Gy in 25 fractions for 5 weeks and Arm B delivering 40.5 Gy in 16 fractions with 2.6 Gy per fraction and studied for feasibility and safety and toxicites

RESULTS

Mean age of the study is 49 yrs and tumor stage T2 correlating with START trials .most of the patients in our study underwent MRM and given PMRT and nodal irradiation that is 86 percent in Arm A and 60 percent in Arm B, which is contradictory to START trials with non inferior skin, cardiac and pulmonary toxicities

CONCLUSION

Hypo-fractionated Radiotherapy can reduce overall treatment time and hospital stay for patient and saves Machine time, manpower, and favors the economy for Institute.

Without decreasing the efficacy in terms of loco-regional control and relapse rates

Keywords: BREAST CANCER, CFRT, HFRT

INTRODUCTION

Carcinoma Breast is potentially curable at early stages but is still the leading cause of cancer-related mortality among women living in a developing country like India
The global incidence of female breast cancer in 2020 was 2.3 million, with a death rate of 6,85,000 (13%) Indian scenario1,78,361 new cases were contributing to 13.5% of the world cancer burden India[1]
The conventional fractionation radiotherapy (CFRT) dose 2.0+/-0.2 Gy is delivered 50Gy/25 fractions for 5-6 weeks which causes a long hospital stay with physical and emotional burden and social isolation both for the patient and the family leading to poor compliance.

Hypofractionatedradiotherapy (HFRT) delivering more than 2.2 Gy per fraction needs only 3 weeks 40.05 Gy in 15 fractions or less duration of treatment only.
Thus in turn in a tertiary hospital where extra work puts up a challenge invariably causing a huge workload on the health care system demanding manpower alongside a lot of economic burden with CFRT can be alleviated with HFRT
So, Breast cancer being the most common malignancy, need to study HFRT compared with CFRT regarding safety, tolerability, feasibility, efficacy, and post-radiation effects

AIMS AND OBJECTIVES

To assess the feasibility and safety of hypo-fractionated radiotherapy in breast carcinoma cases compared with conventionally fractionated radiotherapy where adjuvant radiation is needed in breast cancer.Secondary objective to document acute toxicities in patients undergoing adjuvant radiotherapy

REVIEW OF LITERATURE

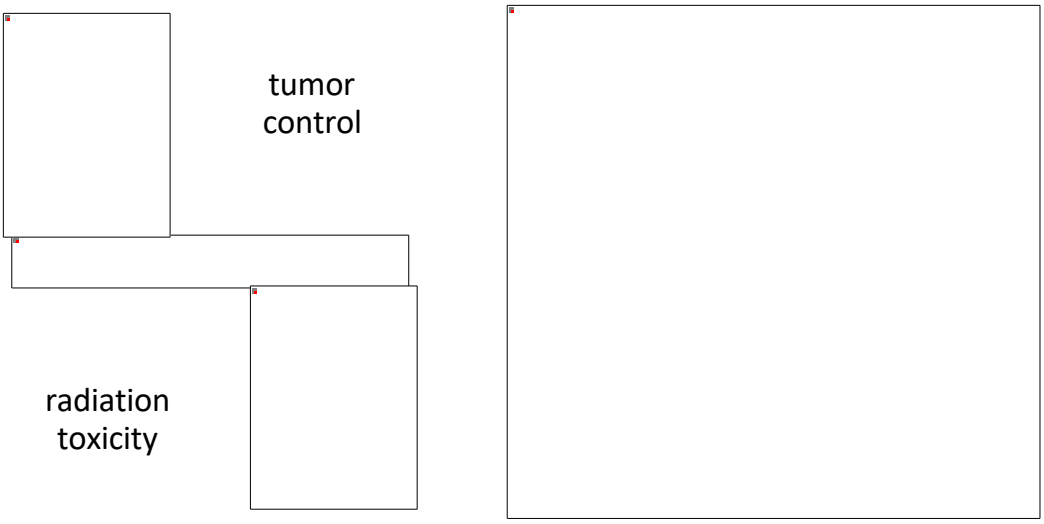
Radiobiology of hypo-fractionation

CFRT is defined as radiotherapy using doses of 2.0 ± 0.2 Gy per fraction. The historical conventional radiotherapy for breast cancer is based on a 50 Gy in 25 fractions over 5 weeks. HFRT is defined as radiotherapyof more than 2.2Gy daily with fewer and larger fractions.

Hypo-fractionation by Eric J Hall means a lesser number of divided high doseper

fraction (d) with a decrease in overall dose (D) with or without decreasing treatment time. (Equal iso effective dose value of Gy)
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[3] function in which directly proportional to $\boldsymbol{\alpha d + \beta d^2}$where'd' is the fraction size.
The effect of fraction size is measured by the degree of tissue damage on normal tissue and tumor recurrence rates for malignant tumors. The ratio of α and β is expressed in Grey, lower the ratio of α and β greater will be the effect of change in fraction size on normal tissue and malignant tumor
If the hypothesis is true, it means that breast carcinoma has α/β value of 3-5Grey. 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

HFRT (40Gy in 15 fractions) was found to have less damaging acute, sub-acute events [4]including brachial plexus injury under extreme assumptions regarding the sensitivity of the plexus. Regarding cardiac events, hypo-fractionation seems to protect the heart (apart from the Breath-holding technique/Respiratory phase gate even though ten years is not sufficient for assessing cardiac morbidity. Pulmonary fibrosis or acute dermatitis is also less likely.



Hypo fractionation gives a better probability of tumor control with a wide separation from adverse effects,increasing the therapeutic window

CANADIAN trial[5]

Though it was the first study in Hypofractionation, the caveats of the study made this a poor study design model for further studies.

TABLE :5

Timeline	1993-1996
Sample size	1234
Arm A	50Gy/5#/5weeks
Arm B	42.5Gy/16#/3.1w
Nodes%	0
MRM%	0
T size>/=T2	20%
Regional RT	0
Boost	0
Adj CT	11%

The pitfalls of this study were

All cases were N0
No Mastectomy cases
No tumor bed boost
No Nodal radiation

Results Table :2

	ARM A	ARM B
5y LRR	3.2	2.8
10Y LRR	6.7	6.2
COSMESIS	71.3	69.8

UK START TRAILS

START-UK STANDARDISATION OF BREAST RADIOTHERAPY TRAILS [6,7]

Table 3: START P and START A

	START P(RMH/GOC)	START A
Timeline	1986-1998	1998-2001
Sample size	1410	2326
Standard arm	50Gy/5# For 5weeks	50Gy/5# For 5weeks

Arm A	42.9Gy/13# for 5weeks	41.5Gy13# for 5weeks
Arm B	39Gy/13# In 5 weeks	39Gy/13# In 5 weeks
Mean age	54.5	57.2
MRM%	0	15
Nodal%	32.7(ONLY 1 NODE)	28.8
Tumor >/=T2	42.5	48.6
Regional RT%	20.6	14.2
Boost	74.5	60.6
Adj CT	13.9	35.5

Table 4: Results of START P and START A

	5y LRR **(95%cl)**	10YLRR **(95%cl)**	COSMESIS **(95%cl)**
START P			
Standard arm	7.9	1.1	63.8
Arm A	7.1	9.6	74.4
Arm B	9.1	14.8	58
START A			
Standard arm	3.4	6.7	34.2
Arm A	3.1	5.6	31.4
Arm B	4.4	8.1	30.0

START B TRIAL

Table :5

Timeline	1999-2001
Sample size	215
Standard arm	50Gy/5# / 5weeks
Arm B	40.05Gy/15# / 3weeks
Mean age	57.4
MRM%	8
Nodal%	22.8
Tumor >/=T2	35.9
Regional RT%	7.9
Boost	42
Adj CT	22.6

Table 6: Results

	Arm A	Arm B
5yLRR	3.3	1.9
10YLRR	5.2	6.2
COSMESIS	31.2	26.2

Retrospective studies on regional RT raise no evidence of increased long-term functional damage of the upper limb associated with HFRT (Havilland, in press).

Regarding the brachial plexus, no cases were recorded after 40 Gy in 15 fractions in the START-B trial; extrapolating the impact of this schedule assuming a very low value of α/β = 1.5 suggests that this regimen should be milder on the brachial plexus than CFRT.

ACCEPTANCE LEVELS OF HFRT IN INDIA

Goel et alconducted a phase III trial from 1989-1992,40Gy/17# @2.35Gy and 45Gy/0# @2.25Gy post MRM On cobalt-60 with equally efficacious outcomes of skin toxicity profiles and local relapse of 10%and 5.6%

TMH retrospective study published in 2010, with caution on node-positive, triple negative, high-grade histology tumors; with the most common schedule still CFRT.

HFRT in breast cancer-CMC experience-Favorable outcome in Indian scenario and relevant in terms of skin toxicity

RADIATION TOXICITY
The desired effect of LRRT and OS expected with PMRT is also affected with same Unwanted Radiation side effects. The main OAR in PMRT
Skin and Mucosa(esophagitis)
Lymphedema (subcutaneous tissue)
Lungs
Heart

INCLUSION CRITERIA:

Age above 18 years and less than 70 years
Female population.
ECOG score-0,1
Histological proven-all histology subtypes and molecular types of Breast carcinomas.
All patients requiring post-operative post-chemo radiotherapy

EXCLUSION CRITERIA

Pregnancy and lactating female
Male Gender.
Gross Residual,metastatic disease
Breast conservative surgery cases,and reconstrction
Double malignancies
Prior history of chest wall irradiation and contraindications for radiotherapy

MATERIALS AND METHODS

Type of study-prospective comparative study

Study design-Institute based Non-Randomized Double arm prospective observational comparative study
Place of study -Radiotherapy department, NATCO cancer Center, Guntur.

Period of study-2021February -August 2022

Patient recruitment and sample size. The study group consists of 30 patients. **Allocation into the study group**
Due to covid pandemic and the scarcity of hospital facilities with high patient /bed turnover

ratio, patients were allocated study arms based on nearby stay to the hospital(50km by road travel) into CFRT and who are at remote access from the hospital were allocated under HFRT is a reason for Non-randomization was discussed with the ethics committee and after approval, the study is started

Table:7 STUDY DESIGN

	Arm-A	Arm-B
Total dose	50	40.05
Dose per fraction	2	2.67
Fractions	25	15
Days per week	5	5
Total weeks	5	3
Allocation criteria	Local/50kmby road	Remote access to the hospital
On radiation assess for	Compliance, Acute toxicities	Compliance, Acute toxicities

Table 8:Organ at risk for breast cancer irradiation

Organ	**Serial/parallel**	**Early/late**	**A/β**	**Target**
Spinalcord	Serial	Late	0.87	Dmax</=44Gy
Skin	parallel	Early	10-12	Dmax</=P.D
Lung I/L	parallel	Late	<3.8	V20<30%
Heart	Seri /parallel	Late	3.6Gy	Dmean<5Gy
Brachial plexus	Serial	Late	1.2Gy	Dmax</=P.D
c/l breast	parallel	Late.	3.5Gy	Dmean<3Gy

Table: 9 Ipsilateral Lung dose

D mean	20Gy	
V20	<30%	<35%(upper limit)
V5(IMRT)	<50%	<60%

Table:10 Heart dose (EQD_2)

Mean Heart dose	3Gy(Right side) 5-8Gy (Left side)
V25	<10%

Patients were regularly monitored for loco-regional relapse Systemic metastatic symptoms of bone pain, Couch and Dyspnea
Chest x-ray once in 3 months, CT chest if symptomatic or by end of 1 year,

Clinical examination of mid-arm increase of more than 10% or increased2 cm circumference to assess Lymphedema, Radiation fibrosis.
Cardiac toxicity Assessed with any symptoms of Angina, congestive heart failure
Monitoring for chest pain or palpitations, or breathlessness ECGonce in 3 months.
2D ECHO EF 60% before radiation and by the end of the study period.

RESULTS
Age-.Mean age in this study was 49 years. The distribution of different Age intervals is tabulated below-
Table -11

Age	Total	Arm- A	Arm- B
20-29	1	------	1
30-39	3	1	2
40-49	13	6	7
50-59	7	4	3
60-69	7	5	2

Laterality
Left breast cancer were 9(60%) from Arm-A and 8(53%) from Arm-B) and Right breast cancer 6(40%) from Arm-A and 7 (46%) Arm-B

Table 12 T Staging

	Arm-A	Arm-B
T1	Nil	nil
T2	11	11
T3	2	1
T4	2	3

Table 13 Nodes

	Node Negative	Node positive
Arm-A	2	10
Arm-B	7	8

Table 14 Chemotherapy

	Arm-A	Arm- B
NACT	3	3
ACT	15	15
HT	4	8

Table 15 Anthracycline based chemotherapy

	Arm-A	Arm-B
FAC x 6	12	12
ACX4	3	3

Table 16 Adequate axillary nodal dissection

	Arm-A	Arm- B
Yes	12	15
No	3	NIL

Loco regional RT pattern

One of the reasons for including the axilla in the radiation field was inadequate nodal dissection/reporting 50% in ARM A due to the inadequacy of sampling/reporting.
Table 17 &18

	Arm A	Arm B
Chest wall only	2	6
Chest wall and SCF	7	6
Chest wall,SCF,axilla	6	3

Grade	Arm A	Arm B
0	14	15
1	1	0
2	0	0

.
Follow-up for Lymphedema PMRT Table 19

Month	Arm-A	Arm-B
3	0	0
6	0	0
9	0	0
12	0	0

None of the patients in the study experienced post radiation Limb edema in one year follow-up **Rib fractures** Table 20

	yes	No
Arm A	0	15
Arm B	0	15

Acute radiation dermatitis-table 21

	Arm A	Arm B
Week1	GR-0=15	GR-0=15
Week2	GR-1=8 GR-0=7	GR-1 =2 GR-0=13
Week3	GR-2=2 GR-1=8 GR-0=5	GR2=1GR-1=7 GR-0=7
Week4	GR2=3 GR1=11 GR0=1	
Week5	GR-3=1 GR-2=3 GR1=10 GR0=1	

Analysis by the end of treatment-acute dermatitis

Acute skin toxicity was observed with a slight variance in Arm–A and Arm B, FavoringArm-B, but the P value was not significant. Table_22

Grade	Arm-A	Arm-B	Chi sq test	P value
0	1(6.6%)	1(6.6%)	1.90	0.38
I	10(66%)	7(46%)		
II	3(22%)	7(46%)		
III	1(6.6%)	0		

Compliance-treatment breaks-table 23

Preference	HFRT	CFRT	BREAK
ARM-A	11	4	3
ARM-B	13	2	NIL

In Arm-A, 75%preferred HFRT As an option.

3 Patients had treatment breaks of more than three days gap for a period ranging from 3-7 days, out of which all were logistic, and none was due to radiation sickness.

Acute radiation pneumonitis-TABLE 24

week	ARM-A	ARM-B
I	GR-0=15	GR-0=15
II	GR-0=15	GR-0=15
III	GR-1=2 GR-0=13	GR-1=1 GR-0=14
IV	GR-1=3GR-0=12	
V	GR-1=3GR-0=12	

By the end of treatment, 20% of Arm-A experienced Grade-I Lung toxicity symptoms in group B it was6.6%

Chronic dermatitis-TABLE 25

Grade	Arm-A	Arm-B	Chi sq test	P value
O	12(82%)	13(86%)	0.38	0.82
1	2(14%)	1(6.6%)		

2	1(6.6%)	1(6.6%)		

The majority of the patients were normal, and two out of fifteen in Arm-A and one out of fifteen in Arm-B had grade 1 reactions.1 out of 15 In Arm-A had Grade-2 radiation dermatitis.

Follow-up for Radiation pneumonitis.-TABLE 26

Grade	Arm A	Arm B	Chi sq	P value
0	12(80%)	12(80%)	1.52	0.47
I	2(13.3%)	3(20%)		
2	1(6.6%)			

	Arm A	Arm B
Grade 0	12 (80%)	14(93.3%)
Grade 1	3(20%)	1(6.6%)
Grade 2	Nil	nil

3 out of 15 (20%) experienced grade -1 esophagitis in Group A, whereas 1 out of 15 in Group B

Cardiac functioning

Noticed ECG changes –TABLE 27

	ARM-A	ARM-B
On radiation	0	0
Follow-up	0	0

Ejection fraction pre-treatment and post-one-year follow-up A drop of 5% or less than 55%

	ARM-A	ARM-B
Pre radiation	0	0
Post radiation 1 year.	0	0

Follow-up for disease control-table 29

Status	**ARM A**	**ARM B**	**overall**	**Λ^2**	**P**
LC	13(86.7%)	13(86.7.%)	28(93.4%)	0.54	0.46
LF	1(6.6%)	0	1(6.6%)	1.01	0.31
RF	0	1(6.6%)	1(6.6%)	1.01	0.31
DM	1(6.6%)	1(6.6%)	2(6.6%)	0.71	0.40
DEAD	0	0	0	---	---

Out of 15 Arm -A patients, one had a local failure, and 1 had metastasis. In Arm B, 1 had a regional nodal relapse, and 1 had metastasis; all were statistically not significant as the p-value is Not significant.

DISCUSSION

Breast cancer is the most common cancer incidence wise globally as well as in India also. Several trials were conducted in various countries to explore the α/β for breast cancer and tried to standardize the best tolerable and efficacious regimen

Of all the landmark trials from Canadian START to the recent FAST FORWARD, most of the cases are post Breast conservative surgery with axillary clearance/Sentinel biopsy cases. These trials are extrapolated to PMRT in this study.

Salient features of different trials were tried to be extrapolated to our institute study.

AGE –Mean age in the study is 49 years, correlating with the postmenopausal age group in START trials. As per a recent ASCO 2018 analysis, younger female less than 40 years can also be given HFRT.4out of 30 patients were less than 40 years in this study. **TUMOR SIZE-** Most of the landmark trails included more cases falling under T2-4. In our study3/15-

(20%) in ARM-A and 4/15(23.3%) in arm B were more than T2.Canadian Trial recruited all T1-2 cases only. START Trials included T1-3 only, most were within T2 statistically supporting early cases.

REGIONAL NODE STATUS- 7(43.5%)in Arm-B and2(16%)in Arm-B (a total of 9 cases were node negative when compared to START trials and UK FAST/FAST FORWARD trials, HFRT arm of the START A received radiotherapy over five weeks rather than three weeks. The initial CANADIAN study did not include PMRT.

	Nodal status
Canadian	N0
START-P	N1
START-A	N1
START-B	N1
China, Beijing	N2-3
US Trial	N1-2
Denmark	N1-2
FAST/FOWEARD	N0

TABLE 46

SURGERY DONE- 30 Cases (100%) Were MRM cases while in Canadian 0% where MRM,START trials more than 80%. BCS cases China Beijing US included MRM Cases..

RADIATION VOLUMES PATTERN-post BCS whole breast radiation followed by lumpectomy boost was the mainstay of treatmentand regional RT was less in START trials. In our study nodal radiation was given in 13/15(86%) subjects in Arm-A and 9/15(60%) in ARM-B.

Studies that analyzed the PMRT subgroup in a limited manner in the START A trial, PMRT patients receiving Hypo fractionated treatment to Regional nodes did not get more normal tissue side effects (based on a patient assessment - about chest wall appearance, chest pain/ swelling, shoulder/arm function, and lymphedema) compared with CFRT. Similar findingsalso werenoted inSTART B PMRT patients when comparing hypo fractionation and standard fractionation..

ADDRESSING THE AXILLA Average number of nodes- 17 dissected in our study. Levels of nodal dissection mentioned clearly would help to define at risk of non- dissected axilla (Level-I, level-II, Level-III)

AddressingAXILLA after MRM with distorted lymphatics if needed adjuvant radiation, it will further compromise vascularity and precipitate limb edema due to fibrosis

START trials addressed AXILLA with BCS and axillary clearance. Regional RT was advised only in a few cases with 1- nodes positive were allowed .N2 disease was not in Study designs. If axilla is N2 positive it was addressed with Adjuvant RT, but Both Axilla dissection and axilla RT were not combined..

THE MEDIAN FOLLOWUP TIME- 10 years in START trials primary end point being

local control. China Beijing and U.S trials had a minimum of 5 years follow-up.

COMPLIANCE-TREATMENT BREAKS In Arm-A, 75%preferred HFRT As an option. HFRT decreases the DALY(Disability adjusted life years)

3 Patients Arm-A had treatment breaks of more than three days, out of which all were logistic, and none was due to radiation sickness.

ACUTE RADIATION DERMATITIS-it is proven from several series that HFRT is non inferior to CFRT in terms of skin toxicity. here in group-a 6.6% were in grade-0 4.6% in arm-b,66% and 46% in grade-1,22% and 46% in grade-2 only 6.6% in arm-a only in grade-3 toxicity where HFRT is well Tolerated without treatment breaks. In this study the follow-up period was 1 year post radiation to know the efficacy of radiation.

CARDIAC EVALUATION AND EVENTS.

The treatment plan was done with tangent fields, and the patient was under follow-up

None of the patients developed Angina related symptoms or abnormal ECG findings, and the 2D echo compared to the baseline was unchanged.

Dosimetric evaluation of both Arms yielded nearly the same radiation. Left chest wall radiation CFRT Heart received 4.33 Gy and HFRT received4.12 Gy. Right chest wall RT Heart received 1.8 Gy in CFRT and 0.72 Gy in HFRT.

LYMPHEDEMAFOLLOWINGLOCO-REGIONAL RADIATION

Early onset asymptomatic lymphedema was observed in 1 Patient of Arms A, which was transient and relieved with conservative measures.

The literature review depicts the Extent of axillary dissection and the number of involved diseases nodes as the main risk factor for limb edema, apart from BMI and Add on Axillary radiation

RADIATION AND PULMONARY SEQUENCE

Treated side lung Dmean is the most correlating effectors for radiation induced lung injury.

ARM-A was-18Gy and ARM-B was-12GY,V20-ARM A was-29.5% and ARM B was-24.6% V5 –IMRT cases-57 %(< 59%)

Partially favored better tolerability with HFRT.

None of the patients developed Symptomatic radiation lung injury or fibrosis in 1 Year follow-up.

POST RADIATION FOLLOW-UP Out of 15 Patients in Arm A, one patient had a local failure, and 1 had metastasis. In Arm B, one had a regional nodal relapse, and 1 had metastasis. All were statistically insignificant as the p-value is Not significant, implying that HFRT is non-inferior in terms of disease control which was supported by all the landmark trials in Hypo fractionation.

Limitations of the study.

Single institute study with diverse demographic recruitment.

Long-term analysis for loco-regional control and late tissue toxicities needs to be analyzed.

CONCLUSION

While conventional fractionated regimen of Adjuvant radiotherapy remains as the most commonly used still date in many centers

Hypo-fractionated Radiotherapy can reduce overall treatment time and hospital stay for patient and saves Machine time, manpower, and favors the economy for Institute.

Without decreasing the efficacy in terms of loco-regional control and relapse rates

Better/Equal safety or non inferior profile for normal tissue tolerance with equaling Oncological and acute toxicity outcomes

In our study Post-One-year follow-up with a good/similar toxicity profile and better

treatment compliance

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