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Tafaul-Al-Ahsa Cancer Foundation Wins EXCELLENCE AWARD for Cancer Awareness Initiatives at Gulf Cancer Awareness Week 2024





The Gulf Oncology Society meeting resulted in fruitful outcomes, with young doctors showing keen enthusiasm for assuming leadership roles and implementing impactful initiatives.

The Official Journal of the Gulf Federation For Cancer Control

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Original Article

Assessment of Radiation Induced Pneumonitis and Pericarditis in Patients Undergoing Breast Conservative Treatment Using Hypofractionated Simultaneous Integrated Boost Technique

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Abstract

Introduction: To determine the proportion of radiation–induced pneumonitis and pericarditis in patients who have received Hypo–fractionated Radiation along with simultaneous integrated boost technique after breast conservative surgery using a prospective observational study from a tertiary hospital.

Materials & Methods: The incidence of radiation–induced pneumonitis and pericarditis was evaluated in all adult patients with biopsy–proven early–stage unilateral breast cancer who underwent breast–conserving surgery followed by hypo–fractionated radiation with a simultaneous integrated boost technique. Baseline assessments including a six–minute walk test, high–resolution computed tomography (HRCT), pulmonary function tests (PFTs), electrocardiography (ECG) and echocardiography (ECHO) were performed. At three months post–radiation treatment, patients underwent follow–up assessments with a six–minute walk test, ECG and ECHO. At six months post–radiation treatment, patients underwent further assessments with a six–minute walk test, ECG, ECHO, PFTs, and HRCT of the thorax. Data analysis was performed using SPSS version 19.

Results: Our study investigated the incidence of acute radiation–induced pneumonitis and pericarditis in patients treated with hypofractionated VMAT–SIB technique in 20 eligible early breast cancer patients. The study found that the technique is feasible and achieves encouraging dosimetric parameters, including well–achieved ipsilateral lung and heart doses. The reduced treatment time of 3–4 weeks compared to the previous 6–7 weeks with sequential boost was also found to be desirable in resource–constrained settings. The incidence of acute radiation pneumonitis and pericarditis was acceptable and comparable to existing data, with 90% of patients experiencing grade 1 radiation pneumonitis according to CTCAE v5.0. Post–treatment pulmonary function tests showed significant changes, particularly in patients who had received neoadjuvant chemotherapy and nodal irradiation. The six–minute walk test and Borg scale also showed a significant positive correlation with pulmonary function tests. There was no significant pericarditis during the follow–up. The study proposes that the hypofractionated radiotherapy using VMAT–SIB is a suitable alternative to conventional fractionation, with acceptable acute toxicities, but longer follow–up is required to assess the impact on late toxicities.

Conclusion: Our research has shown that hypo–fractionated adjuvant radiotherapy with SIB is a safe and feasible treatment for patients with early breast cancer. This treatment method doesn't pose any significant short–term risks to the lungs or heart, and the SIB technique provides better coverage, conformity and sparing of organs at risk. Additionally, patients have reported positive cosmetic outcomes with this treatment. However, to make more accurate conclusions, we need

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to conduct further studies with larger sample sizes and longer follow–up periods to evaluate the potential long–term side effects of this treatment using VMAT in whole breast radiation.

Keywords: Breast cancer, Breast conservation therapy, Hypo–fractionated RT, Pneumonitis, Pericarditis, VMAT–SIB.

Introduction

Breast cancer is a global health concern, with more than two million cases diagnosed annually and is the leading cause of cancer–related deaths among women[1]. However, there is limited research on the impact of Whole breast hypofractionated simultaneous integrated boost using VMAT on the development of radiation–induced pneumonitis and pericarditis, particularly in the Asian subcontinent. This is significant because racial differences may impact how patients react to this treatment. To address this knowledge gap, a study was conducted in the Asian subcontinent to investigate the incidence of radiation–induced pneumonitis and pericarditis in patients undergoing breast conservative treatment using the hypofractionated simultaneous integrated boost technique. The study utilized various tests such as the six–minute walk test, ECG, ECHO, HRCT and PFT to assess the occurrence of these conditions.

Patients and Methods

This prospective observational study was conducted from August 2020 to June 2022 in a tertiary care hospital.

Eligibility criteria: The study included adult female patients aged 18 or above with biopsy–proven unilateral early breast cancer who had undergone breast conservation surgery and planned for whole breast irradiation with hypofractionated simultaneous integrated boost using VMAT technique.

Exclusion criteria: The study excluded patients who were over 70 years old, had a history of previous surgical treatment of breast or axilla, had a second malignancy or recurrence of tumor, had prior history of chest wall/ breast RT, were treated with conventional radiotherapy techniques, had a history suggestive of ischemic heart disease or other cardiac ailments, had distant metastasis, had an ECOG performance status ≥3, or were diagnosed with or on treatment for chronic obstructive pulmonary disease and old Tuberculosis.

The study obtained ethical clearance [JIP/ IEC/2020/051] from the Institute Ethics Committee (Human studies), JIPMER, and followed the Helsinki declaration.

Following completion of breast conservation surgery, patients were followed up in accordance with the institute departmental protocol. To minimize setup error, patients were simulated on a supine position on a breast board with raised arms and used a customized thermoplastic mask. A headrest was placed with the head turned towards the untreated breast. Large bore CT scans with a slice thickness of 3mm were taken from C3 to L3 using a Siemens Somatom Spirit. The planning system was used to optimize the dose delivered to target organs while minimizing dose to organs at risk (OAR), such as the heart, lungs, spinal cord, liver, and thyroid. Varian treatment planning systems were employed in this process, and radiation therapy was administered in accordance with the plan.

Enrolled patients who met the inclusion criteria received approval from the Institute Ethics Committee. Clinical examinations and grading of radiation–induced pneumonitis and pericarditis were performed at baseline, 3 months, and 6 months post–treatment. Prior to radiation therapy, patients underwent a six–minute walk test, HRCT thorax, PFT, ECG, and ECHO. During radiation therapy, patients were clinically reviewed as per departmental protocol. At 3 months post–treatment, patients underwent a six–minute walk test, ECG, and ECHO. At 6 months post–treatment, patients underwent a six–minute walk test, ECG, ECHO, PFT, and HRCT thorax.

The following methods were used for assessing radiation–induced pneumonitis:

- Common Terminology Criteria for Adverse Events v. 5.0 (CTCAE v 5.0)[2]
- Six–minute walk test[3]
- High Resolution Computed tomography of Chest using Nishioka et al grading system[4]
- Pulmonary Function Test[3]

The following methods were used for assessing radiation–induced pericarditis:

- Common Terminology Criteria for Adverse Events v. 5.0 (CTCAE v 5.0)[2]
- Electrocardiogram (ECG)[5–7]
- Echocardiogram (ECHO)[8–9]

Grade 0	No change
Grade 1	Asymptomatic, only radiological or tomographic findings
Grade 2	Symptomatic does not interfere with daily activities
Grade 3	Symptomatic interferes with daily activities requires supplemental O2
Grade 4	Threatens life, requires mechanical ventilation support
Grade 5	Death–related severe pneumonitis

Tabel 1. Common Terminology Criteria for Adverse Events Version 5.0

STEP 1 – At the beginning of the 6–minute exercise, show the scale to the patient and ask the patient this: "Please grade your level of shortness of breath using this scale."

↓

STEP 2 – Then ask this: "Please grade your level of fatigue using this scale."

↓

STEP 3 – At the end of the exercise, remind the patient of the breathing number that they chose before the exercise and ask the patient to grade their breathing level again.

↓

STEP 4 –Then ask the patient to grade their level of fatigue, after reminding them of their grade before the exercise.

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	–
7	Very severe
8	–
9	–
10	Very, very severe (maximal)

Tabel 2. BORG SCALE

GRADE	HRCT FINDINGS
Grade 0	no significant changes in the radiation fields
Grade 1	only pleural thickening is seen in the radiation fields
Grade 2	pulmonary changes (plaque–like or heterogeneous density) are seen in less than 50% area of the radiation fields
Grade 3	pulmonary changes are seen in more than 50% area of the radiation fields.

Tabel 3. HRCT thorax – grading of radiation induced pneumonitis using Nishioka et al:

SIX–MINUTE WALK TEST:

1. Within 60 minutes of the pulmonary function test, a six–minute walk test was performed for a distance of 30 meters (according to the ATS guideline) as follows:
2. Patients were asked to take rest for 10 minutes before the test.
3. Baseline heart rate, Systemic blood pressure, oxygen saturation, and dyspnea status were recorded. These parameters were again recorded at the end of the test.
4. Distance covered in 6 minutes was recorded in meters.
5. Post–test the patients were observed for 15 minutes for any adverse events. (The test was discontinued if any of the following occurred: chest pain, severe dyspnea–, spasm of lower extremity muscles, or if the patient wanted to quit).

Grade 1	Asymptomatic; ECG or physical findings (e.g., rub) consistent with pericarditis
Grade 2	Symptomatic; pericarditis (e.g., Chest pain)
Grade 3	Pericarditis with physiologic consequences (e.g., pericardial constriction)
Grade 4	Life–threatening consequences, urgent intervention indicated
Grade 5	Death

Tabel 4. CTCAE Version 5 grading of pericarditis was used for clinical assessment

Pericardial changes in ECG were assessed by analyzing the following parameters diffuse ST segment elevation, PR segment elevation in aVR lead, PR segment depression inV5V6 lead, diffuse T wave inversion and poor R wave progression[5–7].

Pericardial changes in ECHO were assessed by analyzing the following parameters cardiac tamponade, dilatation

of Inferior Vena Cava > 20mm, pericardial thickening, calcification, increased echogenicity, a bulge of the interventricular system during diastole, restrictive diastolic filling, diastolic flattening of the left ventricular posterior wall, expiratory flow reversal in the hepatic veins, regional wall motion abnormality, left ventricular systolic dysfunction, ejection fraction < 60%, vegetations, clot, pulmonary embolism, abnormal valves, and abnormal chambers[8–9].

The study data was analyzed using SPSS version 19. The normality of the data was assessed using the Kolmogorov–Smirnov test. Mean and standard deviation were used for normally distributed continuous data, while median and interquartile range were used for non–normally distributed continuous data. Categorical variables were presented as numbers and percentages with a 95% confidence interval, and continuous variables were described using mean with standard deviation or median with interquartile range. Different statistical tests such as Wilcoxon tests, Mann–Whitney U tests, Pearson's correlation, ANOVA tests, student T–tests, and Fischer's exact test were used to compare and assess the relationships between different variables and outcomes.

Results

Characteristic	Number (n)	Percentage (%)
MENOPAUSAL STATUS		
Premenopausal	7	35
Postmenopausal	13	75
LATERALITY		
Left	10	50
Right	10	50
QUADRANTS DISTRIBUTION		
Upper Outer	9	45
Upper Inner	7	35
Lower Outer	1	5
Lower Inner	1	5
Central Quadrant	1	5
Axillary tail	1	5
STAGE (T)		
T1	3	15
T2	15	75
T3	2	10
STAGOE (N)		
N0	13	65
N+	7	35
HORMONAL STATUS		
Luminal A	8	40
Luminal B	6	30
Her 2 Enriched	0	0
Basal	6	30
ADEQUACY OF LYMPH NODE DISSECTION		
Adequate (>/=10 LN dissected)	6	30
Inadequate (<10 LN dissected)	14	60

Table 5. Patient & Treatment Characteristics

All of our patients were compliant and received complete dose of Adjuvant Radiotherapy

VOLUME	PARAMETER	MEAN ± SD	MEDIAN (IQR)
PTV Boost	D98	98.315 ±0.909	
	D2	108.013 ±0.898	
	D90	101.064 ±0.742	
	D95	99.605 ±0.341	
	Dmax	53.0295 ±0.557	
	Dmin	43.611 ±0.804	
	Dmean	50.176 ±0.385	
	Dmedian	50.3815 ±0.402	
	V90		100 (99.99–100)
	V95		99.85 (99.55–100)
	V100	92.0185 ±4.108	
	V107	22.2525 ±8.172	
	Conformity Index	0.9785 ±0.0499	
	Homogeneity index		0.091 (0.078–0.116)
PTV WB	D98	97.21 ±0.82	
	D2	111.324 ±3.242	
	D90	101.4325 ±0.66	
	D95	99.6365 ±0.727	
	Dmax	48.8355 ±1.276	
	Dmin	31.4865 ±1.793	
	Dmean	42.883 ±0.301	
	Dmedian	42.7165 ±0.264	
	V90		99.9 (99.85–99.9)
	V95	98.9865 ±0.371	
	V100	93.469 ±1.94	

CTV 48	V95		100 (99.945–100)
	V100	98.46 ±0.89	
CTV 40.5	V95		99.9 (99.75–100)
	V100	97.072 ±1.278	

Table 6. Dosimetry results – PTV coverage, conformity, and homogeneity

ORGAN	PARAMETER	MEAN ± SD	MEDIAN (IQR)
IPSILATERAL LUNG	Dmean	10.845 ±0.733	
	V20	12.2455 ±1.215	
	V18	15.6825 ±1.485	
	D2cc	38.3585 ±1.396	
	Volume	937.5755 ±82.107	
	Dmax	43.9465 ±1.302	
HEART–GENERAL	Dmean	7.421 ±1.112	
	V18	6.3165 ±4.346	
	V40	0	
	D2cc	23.32 ±3.438	
	Dmax	29.852 ±3.597	
	V30		0 (0–0.7)
	V25	1.144 ±0.629	
	D0.1cc	27.2015 ±3.779	
HEART–LEFT SIDED MALIGNANCY	Dmean	9.735 ±0.424	
	V18	12.12 ±7.124	
	V30	0.603 ±0.262	
	V25	2.288 ±0.742	
	V40	0	
HEART–RIGHT SIDED MALIGNANCY	Dmean	5.107 ±0.685	
	V18	0.513 ±0.487	
	V30	0	
	V25	0	
	V40	0	
CONTRALATERAL LUNG	Dmean	4.449 ±0.367	
SPINAL CORD	Dmax	15 ± 4.17	
ESOPHAGUS	Dmax	26.1375 ±7.028	
	Dmean	10.7375 ±2.688	
CONTRALATERAL BREAST	Dmean	3.935 ±0.422	
SKIN 5mm	V37Gy	14.7775 ±1.513	
	V42Gy	1.558 ±0.562	
	V47Gy	0.143 ±0.0898	
	Dmean	19.535 ±2.45	
	Dmax	48.358 ±1.303	
	Volume	465.8495 ±56.86	
SKIN 3mm	V37Gy		3.42 (2.615–4.68)
	V42Gy		0 (0–0.55)
	V47Gy		0 (0–0)
	Dmean	18.276 ±1.768	
	Dmax	45.785 ±1.145	
	Volume	294.6995 ±46.306	

Table 7. Dosimetry results – OAR doses

PARAMETER	GRADE 1 n (%)	GRADE 2 n (%)	GRADE 3 n (%)	GRADE 4 n (%)	GRADE 5 n (%)
PNEUMONITIS	18 (90)	0	0	0	0

Table 8. Acute Radiation–induced pneumonitis grading using CTCAE Version 5.0–maximum attained

GRADE OF PNEUMONITIS ON HRCT	BASELINE n (%)	6 MONTHS POST–RT n (%)
0	20 (100%)	7 (35%)
1	0	7 (35%)
2	0	6 (30%)
3	0	0

Table 9. Grading of pneumonitis on High–Resolution Computed Tomography (HRCT), based on Nishioka et al scoring system at baseline and 6 months post completion of radiotherapy

DOSIMETRIC CORRELATION FOR GRADE 2 OR ABOVE ACUTE RADIOLOGICAL CHANGES IN LUNGS

	GRADE OF PNEUMONITIS	MEAN (%)	SD (%)	95% CI	P VALUE (STUDENT T–TEST)
D MEAN	<GRADE 2	10.61	1.81	9.66–11.55	0.365
	≥ GRADE 2	11.37	1.27	1.35–12.38	
V20 Gy	<GRADE 2	11.49	2.63	10.11–12.86	0.061
	≥ GRADE 2	14	2.43	12.05–15.94	
V18 Gy	<GRADE 2	14.77	3.23	13.07–16.46	0.061
	≥ GRADE 2	17.79	2.94	15.43–20.14	
D2cc	<GRADE 2	37.46	3.16	35.80–39.11	0.056
	≥ GRADE 2	40.4	2.27	38.58–42.21	
VOLUME	<GRADE 2	972.32	183.97	875.952–1068	0.213
	≥ GRADE 2	856.48	184.64	708.74–1004.22	

Table 10. Dosimetric correlation between grade 2 and above acute radiological changes in lungs and volume of lungs receiving specific doses

PARAMETERS	GRADE < 2	≥ GRADE 2	P VALUE FISCHER'S EXACT TEST
AGE DISTRIBUTION			
<45 YEARS	8	3	1
>/= 45 YEARS	7	3	
NEOADJUVANT CHEMOTHERAPY			
YES	7	3	1
NO	7	3	
TAMOXIFEN			
YES	2	3	0.13
NO	12	3	
AXILLARY LN RT			
NIL	7	0	0.03
LEVEL 3, SCF	5	2	
LEVEL 3, SCF, LEVEL 1,2	2	4	
TUMOR BED BOOST VOLUME			
<200 cc	10	4	1
>/=200 cc	4	2	

Table 11. Influence of patient factors, tumor characters, radiotherapy volumes, chemotherapy, hormonal therapy, dosimetric parameters on acute radiological changes in lungs

VARIABLE	BASELINE (T0)		AT 6 MONTHS POST RT (T1)		COMPARISON OF T0 AND T1
	MEDIAN	RANGE	MEDIAN	RANGE	(p)
FEV1/FVC (%)	80.4	(74.5–90.915)	84.2	(75.6–90.1)	0.406
FVC (% PREDICTED VALUE)	65.1	(46.95–78.4)	53.65	(42.5–69.55)	0.00906
FEV1 (% PREDICTED VALUE)	64.35	(56.3–74.8)	51.4	(42.15–70.7)	0.00804

Table 12. Comparison of changes in parameters of Pulmonary function tests at baseline and post 6 months of RT using Wilcoxon Test

GROUP	n	CHANGE IN FEV1 (p)	CHANGE IN FVC (p)
TAMOXIFEN			
Yes	13	0.60	0.38
No	7		
I/L LUNG V20			
<12 Gy	11	0.59	0.76
>12 Gy	9		
NEOADJUVANT CHEMOTHERAPY			
Yes	10	0.02	0.96
No	10		
AXILLARY IRRADIATION (LEVELS 1,2,3 AND SCF)			
Yes	6	0.9	0.65
No	10		
AXILLARY IRRADIATION (LEVEL 3 AND SCF)			
Yes	7	0.79	0.65
No	7		

Table 13. Comparison of mean of percent decrease in FEV 1 and FVC from before RT to 3 months after RT by using Mann Whitney U Test in subgroups

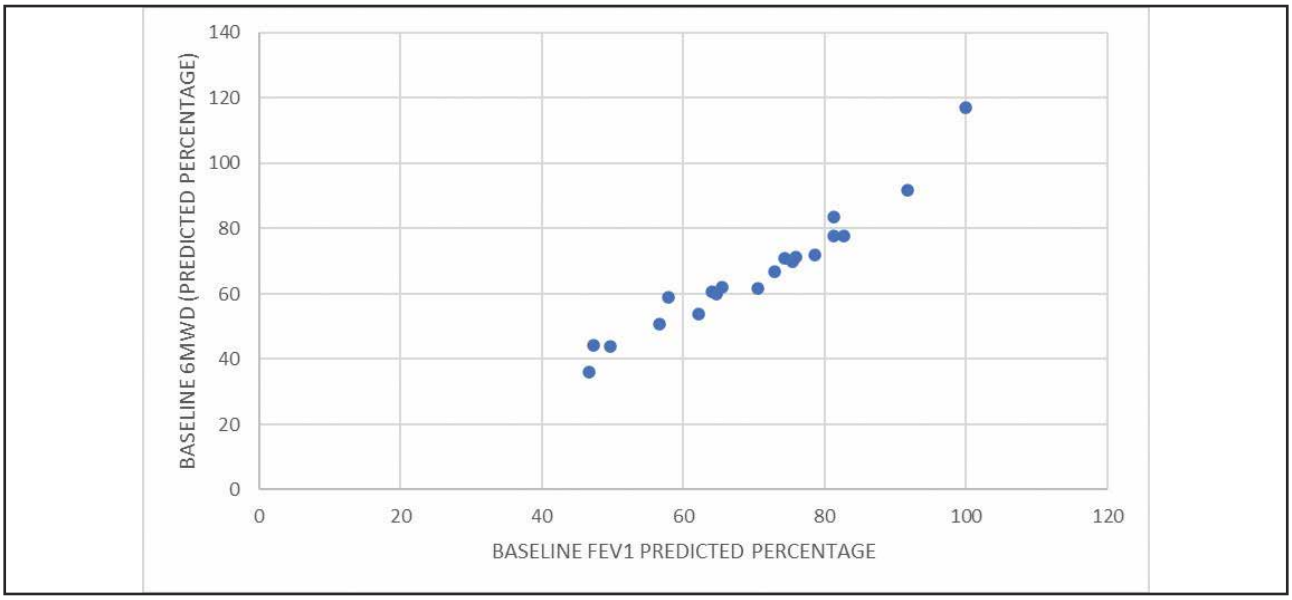


FIGURE 1. Scatter diagram showing co–relations between baseline 6MWD (predicted percentage) and baseline FEV1 predicted percentage

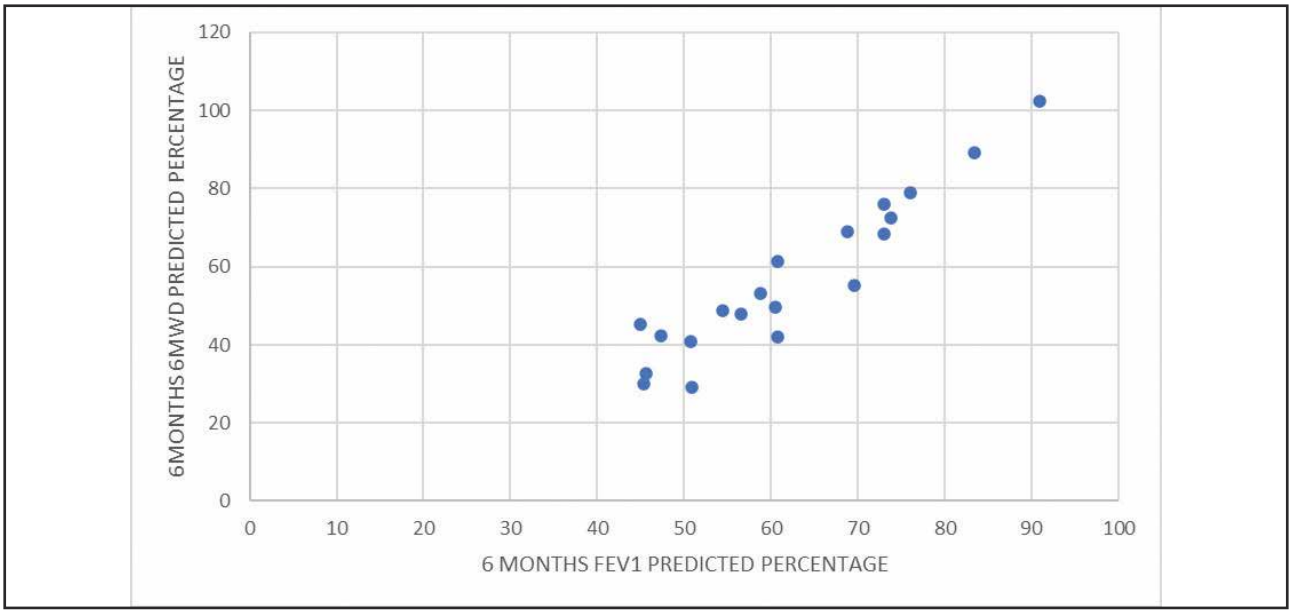


FIGURE 2. Scatter diagram showing co–relations between 6 months post–RT– 6MWD (predicted percentage) and 6 months post–RT– FEV1 predicted percentage

CHARACTERISTICS	MEAN +/– SD	RANGE
6MWD (METERS)–BASELINE	401.25 ±39.603	250–550
6MWD (% PREDICTED)–BASELINE	69.986 ±6.276	46.6–100
6MWD (METERS)–POST 6 MONTHS OF RT	361.25 ±38.081	250–550
6MWD (% PREDICTED)–POST 6 MONTHS OF RT	62.2715 ±5.847	29.1–102.3

TABLE 14. Statistical analysis of patients 6MWD (meters) and predicted percentage of 6 MWD (%)

PARAMETERS	6–MINUTE WALK DISTANCE (POST 6 MONTHS OF RT)		% PREDICTED 6–MINUTE WALK DISTANCE (POST 6 MONTHS OF RT)	
	'r'	'p'	'r'	'p'
AGE (YEARS)	–0.37	0.1	0.15	0.5
HEIGHT (cm)	–0.04	0.84	–0.15	0.5
WEIGHT (Kg)	–0.46	0.04	–0.10	0.6
BMI	–0.32	0.16	0.04	0.8
FEV1 (% PREDICTED)	0.87	<0.01	0.94	<0.01
FVC (% PREDICTED)	0.80	<0.01	0.94	<0.01
FEV1/FVC	0.18	0.44	0.22	0.3

Table 15. Correlation of 6MWD and % predicted 6MWD with parameters of patients using Pearson correlation coefficient

ATS SOCIETY GRADING	FEV1 PREDICTED PERCENTAGE (%)	NUMBER OF PATIENTS (n=18)	6–MINUTE WALK DISTANCE (MEAN +/– SD)
MILD	>70	3	487.5 ±46.91
MODERATE	60–69	3	356.6667 ±45.73
MODERATELY SEVERE	50–59	2	320 ±39.2
SEVERE	35–49	7	312.8571 ±36.65
VERY SEVERE	<35	3	291.6667 ±16.33
F–STATISTIC VALUE: 9.40, p VALUE–<0.01			

Table 16. Significant difference in 6MWD among patients in different severity stages was assessed using the ANOVA test.

CHARACTERISTICS	MEAN +/– SD	RANGE
BORG SCALE–BASELINE	3.8 ±0.691	2–7
BORG SCALE–POST 3 MONTHS OF RT	4 ±0.636	2–7
BORG SCALE–POST 6 MONTHS OF RT	4.7 ±0.854	2–7

Tabel 17. Borg scale mean and standard deviation for baseline,3rd, and 6th–month follow–up

PARAMETERS	BORG SCALE (BASELINE)	
	'r'	'p'
FEV1 PREDICTED PERCENTAGE (BASELINE)	–0.68	<0.01

Table 18. Correlation of baseline Borg scale and baseline FEV1 % of patients using Pearson correlation coefficient

PARAMETERS	BORG SCALE (6 MONTHS POST RT)	
	'r'	'p'
FEV1 PREDICTED PERCENTAGE (6 MONTHS POST RT)	–0.74	<0.01

Table 19. Correlation of 6 months post RT Borg scale and 6 months post RT FEV1 % of patients using Pearson correlation coefficient

PARAMETER	GRADE 1 n (%)	GRADE 2 n (%)	GRADE 3 n (%)	GRADE 4 n (%)	GRADE 5 n (%)
PERICARDITIS	2 (10)	0	0	0	0

Table 20. Acute Radiation–induced pericarditis toxicities using CTCAE Version 5.0 – maximum attained

TEST	PERICARDIAL CHANGES n (%)
ECG	2 (10)
ECHO	0
CTCAE v5.0	2 (10)

Table 21. Incidence of acute radiation–induced pericarditis using various tests

PARAMETERS	DIFFUSE ST SEGMENT ELEVATION n (%)	PR SEGMENT ELEVATION IN aVR n (%)	PR SEGEMENT DEPRESSION IN V5V6 n (%)	DIFFUSE T WAVE INVERSIONS n (%)	POOR R WAVE PROGRESSION n (%)	ATYPICAL CHANGES n (%)
ECG (BASELINE)	0	0	0	0	0	0
ECG (POST 3 MONTHS OF RT)	0	0	0	0	0	0
ECG (POST 6 MONTHS OF RT)	0	0	0	1 (5%)	1 (5%)	0

Table 22. Characteristic pericardial changes observed in the ECG

PARAMETERS	YES	NO	P VALUE FISCHER'S EXACT TEST
ECG CHANGES			
BASELINE	1	19	0.6
3 MONTHS POST–RT	1	19	
6 MONTHS POST–RT	3	17	

Table 23. Influence of radiation therapy on ECG features suggestive of pericarditis changes

PARAMETERS	ECHO (BASELINE) n (%)	ECHO–POST 3 MONTHS OF RT n (%)	ECHO–POST 6 MONTHS OF RT n (%)
CARDIAC TAMPONADE	No Changes	No Changes	No Changes
DILATATION OF IVC > 20mm			
PERICARDIAL THICKENING			
CALCIFICATION			
INCREASED ECHOGENICITY			
BULGE OF INTERVENTRICULAR SEPTUM DURING DIASTOLE			
RESTRICTIVE DIASTOLIC FILLING			
DIASTOLIC FLATTENING OF LEFT VENTRICULAR POSTERIOR WALL			
EXPIRATORY FLOW REVERSAL IN THE HEPATIC VEINS			
REGIONAL WALL MOTION ABNORMALITY			
ABNORMAL VALVES			
ABNORMAL CHAMBERS			
LEFT VENTRICULAR SYSTOLIC DYSFUNCTION			
EJECTION FRACTION <60%			
VEGETATION/CLOT/PULMONARY EMBOLISM			

Table 24. Characteristic acute pericarditis changes observed in the ECHO

PARAMETERS	YES	NO	P VALUE FISCHER'S EXACT TEST
ECHO CHANGES SUGGESTIVE OF PERICARDITIS			
BASELINE	0	20	1
3 MONTHS POST–RT	0	20	
6 MONTHS POST–RT	0	20	

Table 25. Influence of radiation therapy on ECHO features suggestive of pericarditis changes

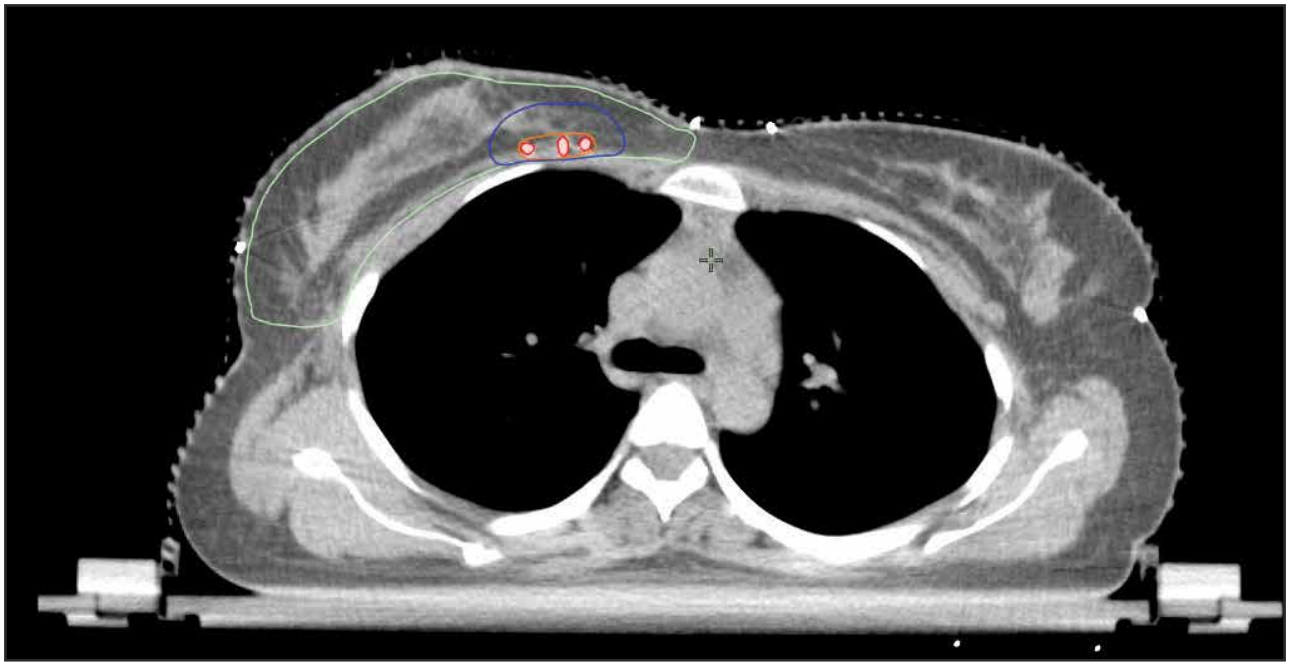


Figure 3. Clips are contoured and clip volume – tumor bed boost volume contoured

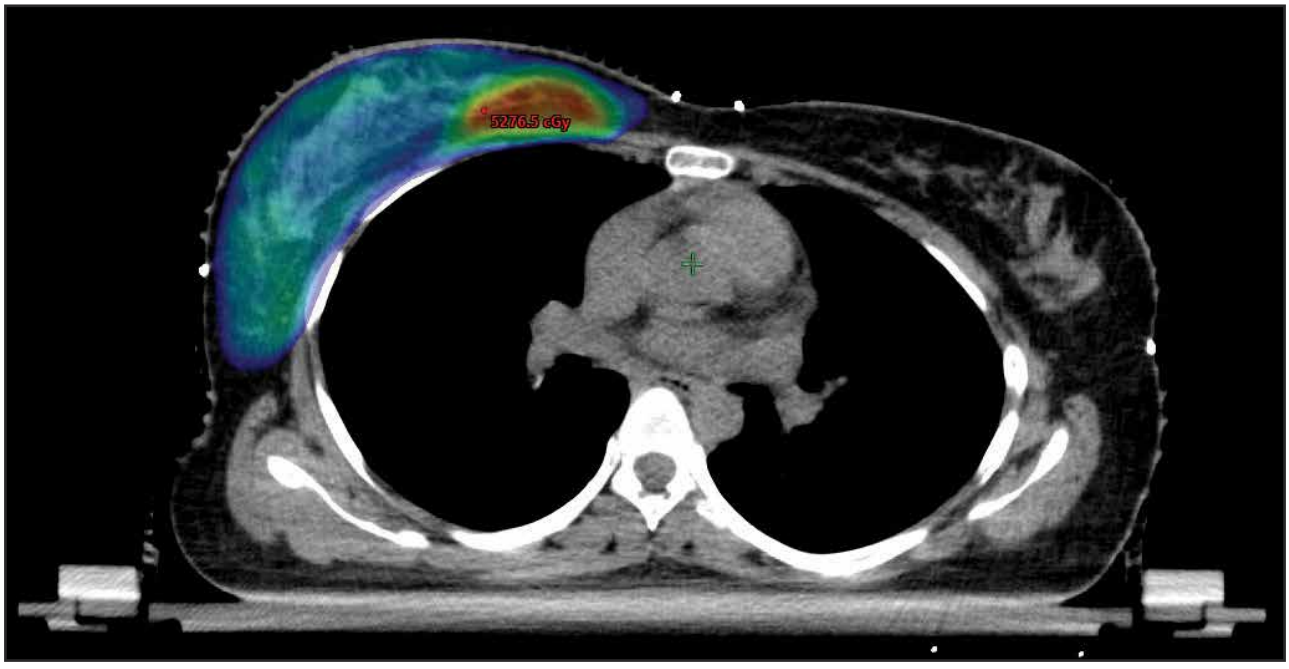


Figure 4: Dose color wash of the whole breast volume for 95% prescription for the PTV

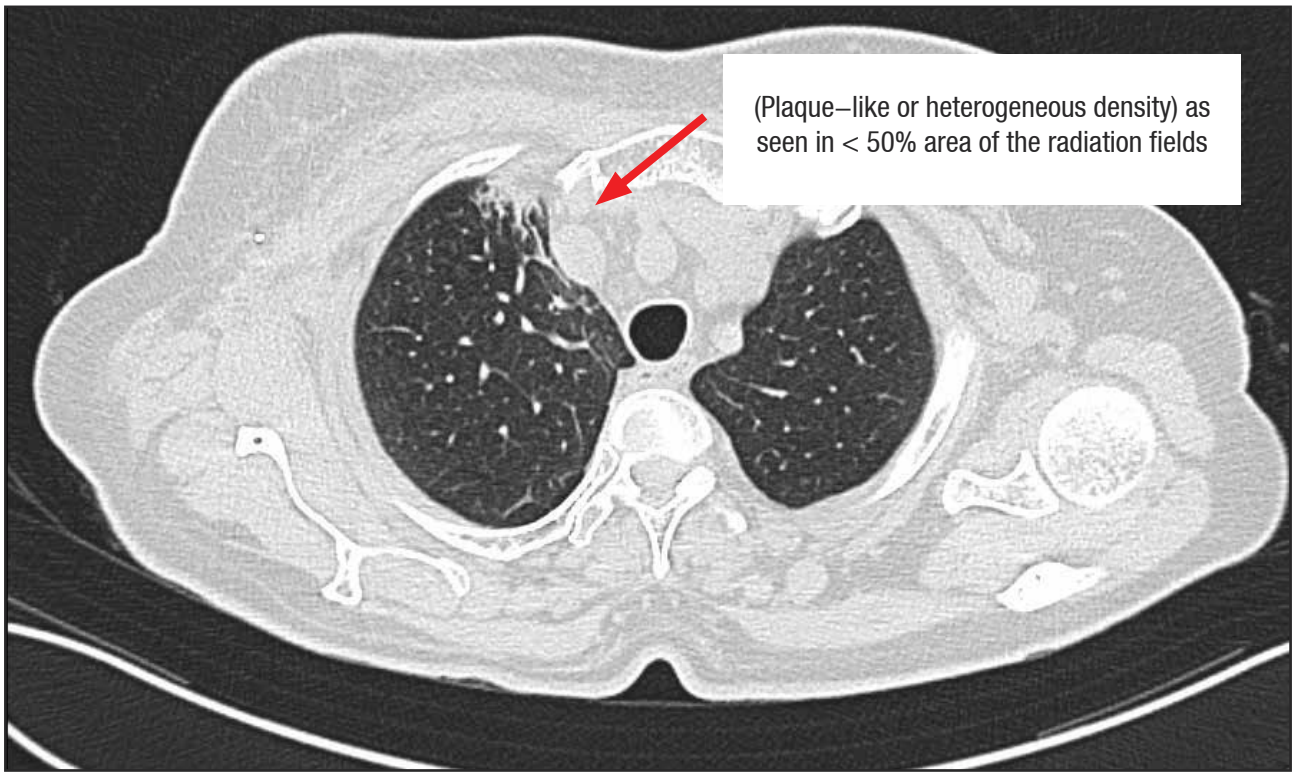


Figure 5. HRCT Thorax demonstrating Grade 2 chronic pulmonary changes: Pulmonary changes (plaque–like or heterogeneous density) as seen in less than 50% area of the radiation fields

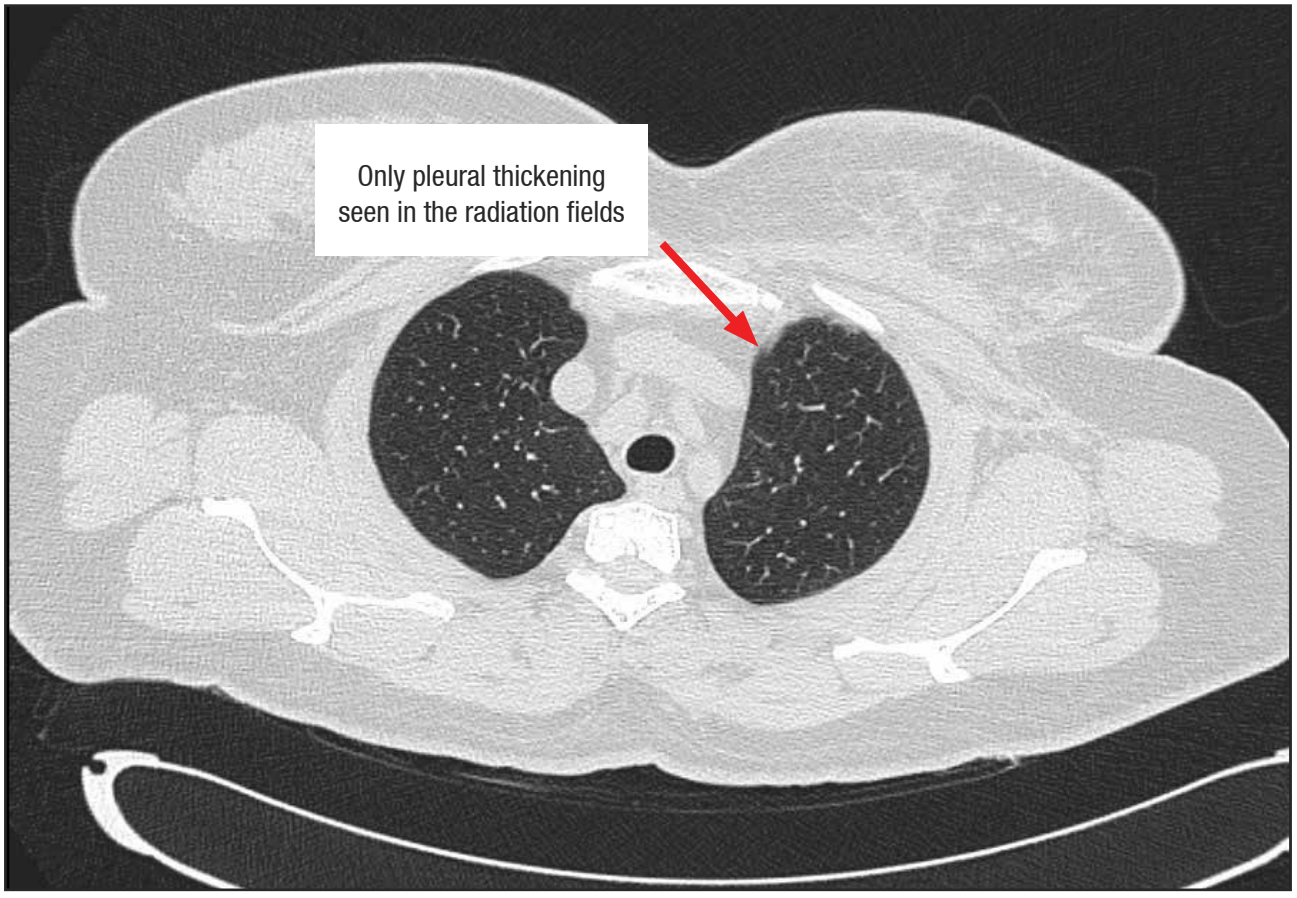


Figure 6. HRCT Thorax demonstrating Grade 1 pulmonary changes: Only pleural thickening seen in the radiation fields

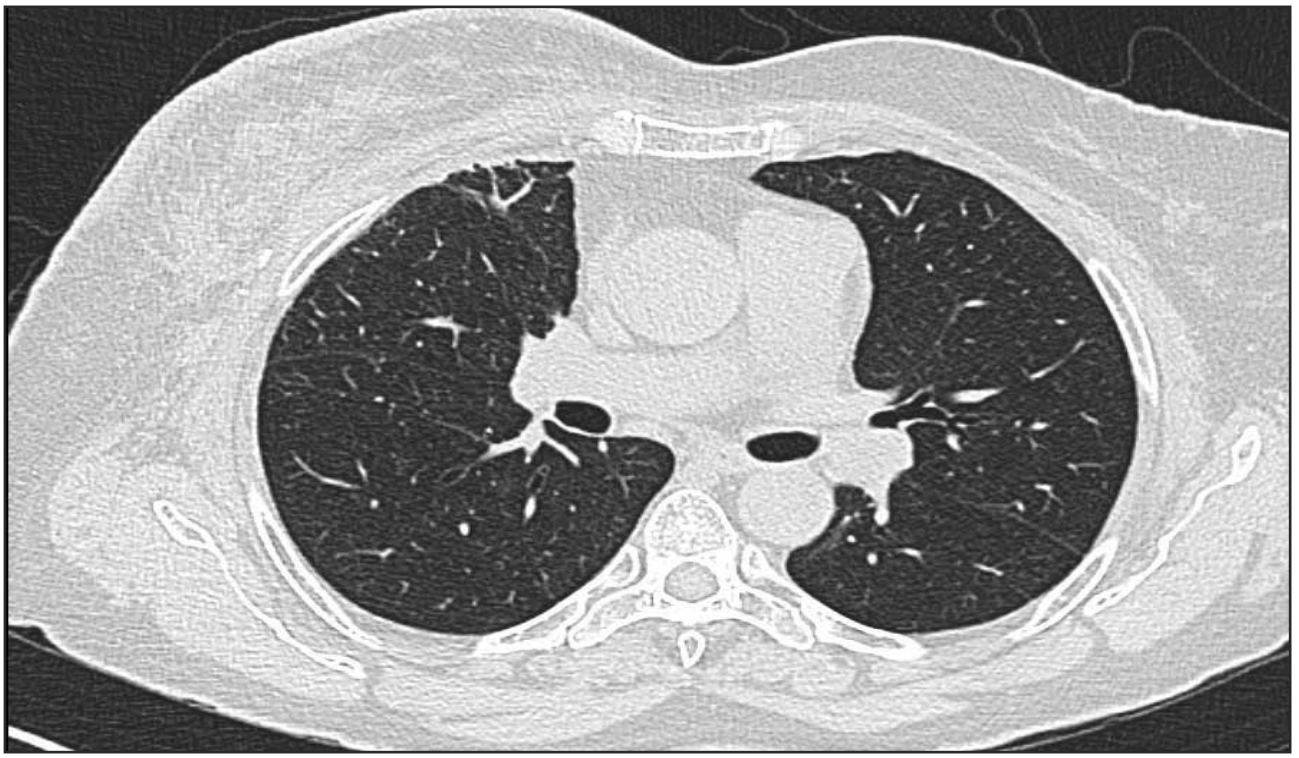


Figure 7. HRCT thorax with Grade 0 chronic pulmonary changes: No significant changes in the radiation fields

Discussion

The primary objectives of our study involved meticulous screening of patients for the development of acute radiation pneumonitis or fibrosis. To do so, patients underwent clinical assessments using CTCAE v5.0, pulmonary function tests, and a six–minute walk test. Baseline and 6–month post–completion of RT, HRCT thorax were taken and assessed by an experienced radiologist to provide radiological proof of acute radiation pneumonitis.

Our study observed that the incidence of radiation–induced pneumonitis varied according to the scale used. Using CTCAE v5.0, 90% of patients had grade I radiation–induced pneumonitis, while none had grade 2 or above. According to HRCT thorax, 7 (35%) patients had no pneumonitis changes, 7 (35%) had Grade 1, and 6 (30%) had Garde 2 pneumonitis changes. Based on the American Thoracic Society grade based on pulmonary function tests, 3 patients had mild grades, 3 patients had moderate grades, 2 patients had moderately severe grades, 7 patients had severe, and 3 patients had very severe grades.

A study by Pinnaro et al. assessing the toxicity of accelerated hypofractionated radiotherapy in 39 patients post–BCS setting reported no incidence of symptomatic radiation pneumonitis after a median follow–up of 43 months. This study utilized the same Nishioka et al. HRCT grading criteria used in our study but reported no significant HRCT findings suggestive of radiation fibrosis in any patient, 1–year post–irradiation[10].

Another study by Fragkandrea et al. noted that the incidence of grade 3 radiation pneumonitis by HRCT thorax, at the end of 1–year post–adjuvant hypofractionated whole breast irradiation, was 0%, similar to the results observed in our study[11].

Upon investigating the dosimetry of the ipsilateral lung and its relationship with the development of grade 2 or above late radiation pneumonitis (diagnosed by HRCT thorax), we found no statistically significant relationship between the volume of lung receiving a particular dose and the incidence of grade 2 and above lung changes radiologically. Unlike earlier studies, we did not find a significant association between mean lung dose and Radiation pneumonitis grades, which may be due to a small number of patients.

We also analyzed the influence of various patient factors, such as age, neoadjuvant chemotherapy, concurrent tamoxifen, RT to the axillary region, and tumor bed boost volume, on the development of radiological changes in the lungs. We found significant radiological changes in ipsilateral lung fields when regional nodal irradiation was given.

In our study, there were statistically significant changes in FVC and FEV1 predicted percentages when compared with baseline and 6–month post–RT spirometry. Patients

who had received neoadjuvant chemotherapy had a higher chance of radiation–induced pneumonitis, as some chemotherapeutic agents act as a radiosensitizer.

We also found a significant strong positive correlation between 6–minute walk distance and predicted FEV1 percentage both in baseline and 6–month follow–up. The 6–minute walk test acts as an alternative method to spirometry in predicting pulmonary reserve.

During radiation therapy (RT) for radiation–induced pericarditis, 20 patients were clinically assessed using CTCAE v5.0. Baseline ECG and ECHO were taken and compared with 3rd & 6th months post–RT for any signs of radiation–induced pericarditis. Out of 20 patients, only 3 patients had ECG findings suggestive of pericarditis, with one patient having baseline T–wave inversion that persisted during the 6–month follow–up. One patient developed T–wave inversion during the 6–month post–RT, and one patient developed poor R–wave progression during the 6–month follow–up. However, none of the patients developed signs of pericarditis in ECHO during the follow–up period. There was no statistically significant correlation between pericardial changes in ECG and ECHO due to hypofractionated radiation during the 6–month follow–up.

According to the expert consensus from the European heart journal, acute radiation–induced pericarditis is a rare phenomenon, and delayed acute pericarditis occurs within weeks after radiotherapy and presents as asymptomatic pericardial effusion or symptomatic pericarditis. Cardiac tamponade is rare and can take up to 2 years to resolve [12]. The risk of radiation–induced heart disease increased linearly with the mean absorbed dose to the heart by about 7% per Gray, according to Darby et al[13].

The typical changes in ECG due to acute pericarditis are similar to acute coronary syndromes, including widespread ST elevation, along with reciprocal ST segment depression in aVR & V1, elevation of the PR segment in aVR, depression of the PR segment in other leads of limbs. These changes typically occur in the first hours to days followed by diffuse T wave inversions in the sub–acute phase, and their duration is highly variable, ending in normalization of ECG waves. Atypical changes are seen in up to 40% of cases[14]

ECHO features suggestive of acute pericarditis after RT are very rare[15]. Characteristic findings of acute pericarditis on ECHO are cardiac tamponade, IVC plethora, pericardial thickening, calcification, increased echogenicity, restrictive diastolic filling, expiratory flow reversal in the hepatic veins, the bulge of the interventricular system during diastole[16].

Radiotherapy for breast cancer is associated with long–term cardiac toxicities, with an increased incidence of coronary heart disease[17], especially for hypofractionated regimens. However, in our study population, none of the patients developed grade 2 or above late cardiac toxicities, possibly due to our shorter follow–up duration, as late cardiac toxicities become evident after the first to second decade of radiation therapy. Patients with left–sided disease received a higher mean heart dose, but whether this higher mean dose has clinically translated to increased cardiac morbidity needs further investigation in a larger population with a longer follow–up.

The RTOG 1005 guidelines were used for contouring whole breasts and boosting volumes. Dosimetric parameters achieved were encouraging, with reasonably achieved dose conformity and homogeneity. Ipsilateral lung and heart doses were well achieved with VMAT. The incidence of acute radiation–induced pneumonitis and pericarditis was comparable with existing data.

In our study, we found that toxicities were well within the acceptable limits, and none of the patients required any hospital administration or intervention due to toxicities. Based on our present findings, we propose that hypofractionated SIB using VMAT techniques in an adjuvant setting for early breast cancer patients who had undergone breast–conserving surgery is feasible and is an apt alternative to conventional fractionation, with acceptable acute lung and pericardial toxicities. However, a longer period of follow–up will be required to assess the real impact concerning for late toxicities.

Conclusion

Breast cancer is the most common cancer globally, making it important to improve the standard of care for breast cancer management. Hypofractionation in adjuvant breast irradiation is common in Western countries, but not universally accepted in India due to concerns about higher normal tissue toxicities, particularly for the heart and lungs. A study was conducted to evaluate acute radiation–induced pneumonitis and pericarditis with hypofractionated whole breast irradiation radiotherapy using the SIB–VMAT technique at a prescription of 40.5 Gy to the whole breast and 48 Gy to the tumor bed boost delivered in 15 fractions. The study was a prospective observational study with a sample size of 20 patients who had undergone breast–conserving surgery. The study found that hypofractionated adjuvant radiotherapy with SIB for patients with early breast cancer is feasible and safe regarding acute toxicity of the lung and heart. There were good cosmetic outcomes, and none of the patients required active intervention due to acute toxicities. 6MWD and Borg scale would be a suitable and easy alternative for clinically diagnosing and grading

restrictive patterns of lung disease in this COVID–19 era since performing PFT put the performing physician at risk of getting COVID–19 infection due to aerosol generation However, larger sample sizes and longer follow–up are required to assess chronic toxicity.

Funding and Conflict of Interest

Nil

Abbreviations

VMAT–SIB: Volumetric modulated arc technique–simultaneous integrated boost

CTCAE v5.0: Common Terminology Criteria for Adverse Events version 5.0

ECOG: Eastern Cooperative Oncology Group

HRCT: High resolution computed tomography

PTV: Planning Target Volume

CTV: Clinical Target Volume

WB: Whole breast

SCF: Supraclavicular Fossa

FEV1: Forced expiratory volume in the 1st second

FVC: Forced Vital Capacity

RT: Radiation therapy

6MWD: 6–minute walk distance

RTOG: Radiation Therapy Oncology Group

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