ORIGINAL ARTICLE

Left ventricle and left Anterior Descending Coronary Artery Radiation Dose in Patient Receiving Adjuvant Radiotherapy for Left Breast Cancer in Prone Position, A Prospective Study

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Abstract

Background: ***Adjuvant breast irradiation in the supine posture for left-sided breast cancer has a late cardiac damage. Treatment in the prone position is used to minimize radiation exposure to cardiac structures.***

Aim: ***This study aims to evaluate the radiation dosage to the left ventricle(LV)and left anterior descending (LAD)coronary artery in prone position irradiation versus supine position, additionally evaluating associated acute toxicities.***

Patients and Methodology: ***Females with early-stage left breast cancer who underwent breast-conserving surgery(BCS)and needed postoperative radiation without nodal irradiation were included in this research. Both supine and prone plans were used for all patients for dosimetric comparison between positions. However, treatment was received in the prone position, with a total dose of 40Gy in 15 fractions over 3weeks.***

Results: ***The study included 55 women, all managed with BCS, with a median age of 49 years, (34.5%)of whom 34.5% had large breast size(≥1600cm³). The dosimetric comparison between the prone and supine positions revealed a significantly better conformity index in the prone position(mean 0.91 ± 0.13SD)versus the supine position (mean 0.77 ± 0.11SD), with p-value<0.0001. comparing prone and supine positions, critical organ dosage were noticeably lower in prone arm: left lungV16(0.45% ± 1.29SD)versus(19.29% ± 6.30SD), heart Dmean(1.57Gy ± 0.63SD)versus(5.05Gy ± 2.30SD), LAD Dmax(15.19Gy ± 2.71SD)versus(38.71Gy ± 2.35SD), and LV-V5(4.07% ± 4.59SD)versus(26.67% ± 15.77SD)respectively(p-values<0.0001 for all parameters). Moreover, no Grade 3-4 acute toxicities.The incidence of Grade 1–2 acute skin toxicity, fatigue, edema, and pain were100%,65%,86%, and 46%, respectively.***

Conclusion: ***In all study group, patients treated in the prone position and experienced less radiation exposure to key structures, with no grade III-IV toxicities,compared to the supine position. Nonetheless, larger clinical trials are needed.***

Keywords: Breast Cancer; Prone Position; Adjuvant Radiotherapy

1. Introduction

Among female cancer patients, breast cancer is among the most common and deadly, influenced by various factors such as population structure, lifestyle, genetics, and environmental elements. Despite its global prevalence, the incidence and mortality rates vary greatly. Because of these factors, breast cancer survival rates vary greatly. Breast cancer is becoming more common as risk factors change.[1,2]

Breast irradiation reduces recurrence and death rates post-surgery, with supine positioning being the most common approach due to its simplicity, comfort, and accurate positioning. However, during supine therapy, the breast's softness and deformability may lead it to protrude beyond the chest wall, particularly in patients with large, pendulous breasts. This stretching increases the skin fold region and radiation dose received by the ipsilateral lung and heart, leading to short- and long-term adverse events, including skin, lung, and heart toxicity.[3,4]

Accepted 19 January 2025.
Available online 31 March 2025

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https://doi.org/10.21608/aimj.2025.446491

The high radiation doses delivered to the coronaries and LV after left breast irradiation in the supine posture are also associated with an increased risk of cardiovascular death. This underscores the necessity of considering the doses received by these critical organs during left-sided breast irradiation.[5]

Patients diagnosed with breast cancer following BCS started to be treated in the prone position in 1994. Irradiation in the prone position reduced radiation exposure to the lung and improved initial skin reactions, according to the authors of the study. This was particularly true for patients with big and pendulous breasts.[6]

Numerous recent dosimetric studies have shown that prone breast irradiation considerably reduces the mean dose (Dmean) and the volumes of the lung receiving doses equivalent to or greater than 20 Gy, in contrast to conventional supine breast irradiation.[7,8]

We conducted this phase II trial to estimate the efficiency of the prone breast positioning technique to reduce radiation exposure to the coronary arteries and LV during left breast irradiation, compared to the conventional supine position. Additionally, we assessed the acute treatment-related toxicity associated with prone breast irradiation especially in obese or large breast patients with skin folds.

2. Patients and methods

Female patients eligible for adjuvant prone radiation therapy for left-sided breast cancer were enrolled in this prospective phase 2 research. Conducted between January 2020 and January 2023, the study enrolled patients with stage T1-2N0M0 breast cancer according to the 8th TNM staging system. All patients underwent BCS with negative surgical margins and were required to have adequate cardiac function before starting treatment.

Exclusion criteria included patients surgically treated with modified radical mastectomy (MRM), required adjuvant radiotherapy during pregnancy, had a history of prior chest irradiation, or presented with active skin collagen vascular diseases. Additional exclusions applied to patients with kyphosis or scoliosis and those unable to tolerate the prone position.

All enrolled patients were simulated in both prone (using a dedicated breast board) and supine positions (using a supine breast board) for dosimetric comparison. However, treatment was delivered exclusively in the prone position to evaluate acute treatment-related toxicity.

Every patient had delineation done by the same radiation oncologist using the same guidelines and the Eclipse treatment planning system (version 11.6) for radiation therapy planning. Organs at risk (OARs) (heart, left anterior descending (LAD) coronary artery, left ventricle, both lungs, contralateral breast, esophagus, spinal cord, liver, and larynx) were contoured throughout the entire range of obtained CT Cuts. The dose limitations for organs at risk were determined as specified in (Table 1).

One 3D conformal treatment plan was created for the prone position and another plan for the supine position using six MV tangential photon beams and the field-in-field technique. While the patient was in the prone position, 40 Gy was delivered to the whole breast in 15 fractions over the course of 3 weeks. Patients younger than 50 years old, those with tumors of high grades, or those with positive margins were given a 10 Gy boost in five fractions over the course of one week while still in the same treatment posture.

Target volume coverage required >95% of the planning target volume (PTV) to receive ≥95% of the prescribed dose, with a maximum dose not exceeding 105% and a minimum dose not falling below 90%.

Table 1. Recommended Dose Constraints to Organs at Risk

PARAMETERS	CONSTRAINTS
• LEFT LUNG (V16GY)	<20%
• MEAN DOSE TO CONTRALATERAL BREAST	<3 Gy
• MEAN HEART DOSE (MHD)	<5 Gy
• MAXIMUM DOSE FOR LAD	<20 Gy
• LEFT VENTRICLE (V5GY)	<10%
• SPINAL CORD DMAX	<45 Gy
• LIVER(DMEAN)	<30-32 Gy
• LARYNX(DMEAN)	<45 Gy
• ESOPHAGUS(DMEAN)	<34 Gy

The setup of the patient was verified daily within the first three sessions of treatment and weekly thereafter by an electronic portal imaging device. Any shifts exceeding 0.5 cm during the first three sessions were registered and corrected immediately. For shifts greater than 1 cm, patients were repositioned.

Breast size was calculated and classified into three categories based on breast volume: small size breasts (≤500 cm^3 to 975 cm^3), medium size breasts (975 cm^3 to 1600 cm^3), and large size breasts (≥1600 cm^3).

Acute radiotherapy-related toxicities occurring within 90 days of completing radiotherapy were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version five. Patients were monitored weekly during treatment for symptoms and signs of acute toxicity, then monthly for the first three months and every three months for the following two years.

Study Objectives: estimating the radiation dosage received by the LV and LAD coronary arteries were the principal endpoints of this investigation. Acute treatment-related toxicity for patients have adjuvant radiotherapy while lying face down was the secondary goal.

Data were examined using descriptive and inferential statistics as part of the statistical methodology. Means with standard deviations or medians with ranges were used to report continuous variables. The percentages and frequencies of the categorical variables were used for presentation. The paired t-test was used for regularly distributed data, and the Wilcoxon signed-rank test for non-normally distributed variables when comparing the dosimetric positions of the prone and supine postures. Results were deemed statistically significant if the p-value was less than or equal to 0.05.

Ethics approval: Approval of the ethical committee. Written informed consent from every patient is obtained.

3. Results

The study included 55 patients treated with postoperative radiotherapy in the prone position. The median age of the patients was 49 years (range 29–71 years). The median BMI was 35.43 kg/m^2 (range 24.22–49.77). Among the cohort, 9 patients (17%) had average weight (BMI 18–25 kg/m^2), 8 patients (14%) were overweight (BMI 25–30 kg/m^2), 19 patients (34.5%) were obese (BMI 30–40 kg/m^2), and 19 patients (34.5%) were morbidly obese (BMI >40 kg/m^2).

The median breast volume was 1137.0 cm^3 (range 372.10–2884.5 cm^3). Breast size distribution showed 19 patients (34.5%) with large breasts (≥1600 cm^3), 17 patients (31%) with medium-sized breasts (975–1600 cm^3), and 19 patients (34.5%) with small breasts (≤500–975 cm^3) (Table 2).

Most patients had T2 disease (70.9%), while 29.1% were diagnosed with T1. Molecular subtyping revealed that 43.6% of patients had luminal A subtype, 41.8% had luminal B, 3.6% had HER2-enriched disease, and 11% were triple-negative (Table 3).

The prone position had substantial benefits in critical parameters as compared to the supine position in the dosimetric analysis. The conformity index was high (significantly) in the prone position (mean 0.91 ± 0.13 SD) compared to the supine position (mean 0.77 ± 0.11 SD) with $p < 0.0001$. The homogeneity index was 0.13 ± 0.02 for the prone position and 0.12 ± 0.02 for the supine position, with a significant difference statistically ($p = 0.0118$). Additionally, the prone position showed lower values for critical organ doses, including left lung V16 (mean 0.45% ± 1.29 SD), mean heart dose (1.57 Gy ± 0.63 SD), Dmax for the LAD coronary artery (15.19 Gy ± 2.71 SD), and LV V5 (4.07% ± 4.59 SD). In comparison, the supine position yielded significantly higher values: left lung V16 (19.29% ± 6.30 SD), mean heart dose (5.05 Gy ± 2.30 SD), LAD Dmax (38.707 Gy ± 2.35 SD), and LV V5 (26.67% ± 15.77 SD), with p-values < 0.0001 for all comparisons (Table 4).

On the other hand, the contralateral breast received a significantly higher mean dose in the prone position versus the supine position, with doses of 0.72 ± 0.80 and 0.348 ± 0.97, respectively ($p = 0.0218$).

Among the 55 patients analyzed, acute skin toxicity was observed in all cases (100%), with 85.5% experiencing Grade 1 and 14% experiencing Grade 2 toxicity, while no Grade 3 or 4 events were reported. Fatigue occurred in 65% of patients, all of whom had Grade 1 toxicity. Breast edema was reported in 86% of patients, with 75% experiencing Grade 1 and 11% experiencing Grade 2 toxicity, without any higher-grade events. Breast pain was noted in 46% of patients, predominantly Grade 1 (42%), while 4% had Grade 2 toxicity, and no Grade 3 or 4 events were observed (Table 5).

After a median follow-up period of 13 months (range: 3–44 months), none of the 55 treated patients experienced disease relapse, either locally or systemically, throughout the follow-up duration.

Table 2. Patient Criteria (N = 55)

PATIENTS CRITERIA	MEDIAN	RANGE (MIN. – MAX.)
AGE (YEARS)	49.0	29.0 – 71.0
WEIGHT (KG)	90.0	65.0 – 121.0
HEIGHT (CM)	160.0	150.0 – 175.0
BMI (KG/M^2)	35.43	24.22 – 49.77
BREAST VOLUME (CM^3)	1137.0	372.10 – 2884.5

Table 3. Disease Criteria (N = 55)

DISEASE CRITERIA	PATIENTS NUMBER	PERCENTAGE
SIDE OF DISEASE		
• LEFT SIDED	55	100.0
• RIGHT SIDED	0	0
BREAST SIZE		
• SMALL BREAST SIZE (≤500 CM^3-975 CM^3)	19	34.5
• MEDIUM BREAST SIZE (975 CM^3-1600 CM^3)	17	30.9
• LARGE BREAST SIZE (≥1600 CM^3)	19	34.5
HISTOPATHOLOGY		
• IDC	55	100.0
TYPE OF SURGERY		
• BCS	55	100.0
• MRM	0	0
T N M STAGE		
• T1 N0 M0	16	29.01
• T2 N0 M0	39	70.9
LUMINAL TYPE:		
• LUMINAL A	24	43.6
• LUMINAL B	23	41.8
• HER2 POSITIVE	2	3.6
• TRIPLE NEGATIVE	6	11

Table 4. Dosimetric Comparison between Prone and Supine Positions (n =55)

PARAMETERS	REFERENCE	SUPINE (N=55)	PRONE(N=55)	P VALUE
PTV DOSE 95% (COVERAGE) [MEAN ± SD.]	95%	95.415 ± 0.94	95.51 ± 0.60	tp=0.512
HOMOGENEITY INDEX [MEAN ± SD.]	±0	0.12±0.02	0.13±0.02	Zp<0.0118
CONFIRMATORY INDEX [MEAN ± SD.]	±1	0.77±0.11	0.91±0.13	Zp<0.0001
LEFT LUNG DOSE V16 [MEAN ± SD.]	<20%	19.298 ± 6.30	0.45±1.29	Zp<0.0001*
MEAN HEART DOSE [MEAN ± SD.]	<5GY	5.053 ± 2.30	1.57 ± 0.63	Zp<0.0001*
DMAX FOR LAD [MEAN ± SD.]	<20GY	38.707 ± 2.35	15.19 ± 2.71	tp<0.0001*
LV V5 DOSE [MEAN ± SD.]	<10%	26.673 ± 15.77	4.07 ± 4.59	Zp<0.0001*
MEAN DOSE FOR CONTRALATERAL BREAST [MEAN ± SD.]	<5GY	0.348 ± 0.97	0.72 ± 0.80	Zp=0.0218

Z: Wilcoxon signed ranks test, SD: standard deviation, t: paired t-test, and p: p value for comparing prone and supine *: p < 0.05 indicates statistical significance.

Table 5. Treatment Related Acute Skin Toxicity (N = 55)

ACUTE TOXICITY	ANY GRADE	G 1	G 2	G 3	G 4
SKIN	55 (100%)	47 (85.5%)	8 (14%)	0	0
FATIGUE	36 (65%)	36 (65%)	0	0	0
BREAST EDEMA	47 (86%)	41(75%)	6 (11%)	0	0
BREAST PAIN	25 (46%)	23 (42%)	2 (4%)	0	0

4. Discussion

Treating patients with left-sided breast cancer receiving adjuvant radiotherapy is challenging due to the proximity of the LAD and LV to the target volume. Multiple recent studies have established a direct correlation between radiation doses to cardiac substructures, particularly the LAD coronary artery, and increased cardiac-related mortality. For instance, A reanalysis of the RTOG 0617 trial suggests that maintaining the heart's V15 below 10% is associated with fewer cardiac events and improved overall survival. This finding highlights the importance of minimizing radiation exposure to key cardiac structures, such as the LAD, which has been linked to a significantly higher risk of all-cause mortality.[9]

Several trials have revealed that prone positioning during breast radiotherapy can reduce radiation exposure to the heart, including the LAD coronary artery and LV.[8,10,11] For instance, a USA prospective study included 47 patients that demonstrates that prone positioning during left breast radiotherapy significantly reduces radiation dose to the heart and LAD coronary artery, despite the heart's anterior displacement. Prone positioning resulted in a reduction of mean LAD dose by 4.89 Gy, mean heart dose by 0.84 Gy, and left lung dose by 3.75 Gy compared to the supine position.[12]

In our study, PTV coverage was satisfactory across all patients, with PTV95 achieving an average of 95.51%. The radiation doses delivered to the ipsilateral lung, LAD coronary artery, LV, and contralateral breast were notably low. Specifically, the mean V16 of the left lung was 0.45% ± 1.29 SD, while the mean heart dose, Dmax of the LAD, V5 of the LV, and contralateral breast dose were 1.57 Gy, 15.19 Gy, 4.07%, and 0.72 Gy, respectively.

Also, our study's dosimetric comparison showed that the risk organs received noticeably lower doses when they were in the prone posture compared to when they were supine. These results are in agreement with those of the earlier research mentioned.

In another study comparing prone free-breathing with supine deep inspiration breath-hold for left-sided whole-breast irradiation, 62.1% of patients, especially those with high breast pendulousness and moderately large breast sizes, benefited from prone positioning due to the dosimetric advantage. Important factors that could indicate this advantage were a breast volume larger than 282 mL, a breast depth differential greater than 31 mm, a prone breast depth greater than 77 mm, and a prone/supine breast depth ratio greater than 1.6. [13]

Large breast size has been associated with increased skin toxicity during breast irradiation. Factors such as dose heterogeneity and the "bolus effect" in the inframammary fold lead to higher skin doses and a greater risk of acute dermatitis, including moist desquamation. Studies have shown that women with larger breast volumes experience higher rates of acute skin toxicity during radiation therapy. [14,15]

During adjuvant radiation treatment, a randomized clinical experiment by Vesprini et al. compared supine and prone positions for women with large breasts. The results showed that the prone posture minimized cutaneous side effects. Patients treated while supine had a greater risk of wet desquamation than those treated while prone (39.6% vs. 26.9%; OR, 1.78; 95% CI, 1.24-2.56; P =.002), as shown in the study. Using multivariable analysis, the increased risk was confirmed (OR, 1.99; 95% CI, 1.48-2.66; P <.001). Additionally, more extensive fractionation (OR, 2.85; 95% CI, 1.41-5.79; P =.004), larger bra sizes (OR, 2.56; 95% CI, 1.50-4.37; P <.001), and the utilization of a radiation boost (OR, 2.71; 95% CI, 1.95-3.77; P <.001) were each linked to heightened skin toxicity. [16]

In our study, approximately one-third of patients (34.5%) had large breast sizes (breast volume ≥1,600 cm^3). Grade 1 acute skin reactions were observed in 85.5% of all cases, and Grade 2 reactions in 14.5%; notably, no Grade 3 toxicities were reported. These findings indicate a lower incidence of severe skin toxicity versus the study by Vesprini et al., 16, which recorded higher rates of desquamation in patients with large breast sizes. This discrepancy may be attributed to differences in the proportion of patients with large breast sizes, as well as variations in radiotherapy doses and techniques employed between the studies.

Stegman and colleagues demonstrated that delivering whole-breast irradiation in the prone position can achieve long-term disease control similar to that of the traditional supine approach, while also yielding a more favorable toxicity profile. In their study, the 5-year rates for disease-free, disease-specific, and overall survival were reported as 89.4%, 97.3%, and 93%, respectively. Moreover, only 2% of patients experienced acute Grade 3 dermatitis or edema, and chronic Grade 2–3 skin and subcutaneous tissue toxicities were observed in 4.4% and 13.7% of patients, respectively. [17]

None of the patients in our study developed disease relapses, either locally or systemically, during the relatively short follow-up period (13 months). This favorable outcome may be explained by the selection of patients with early-stage disease who did not have positive lymph nodes.

4. Conclusion

Based on the current evidence, delivering adjuvant radiation therapy for left-sided breast cancer in the prone position can significantly reduce exposure to vital organs, namely the ipsilateral lung, LV, and LAD coronary artery. Notably, even patients with larger or pendulous breasts experienced only mild acute skin reactions without any occurrence of Grade III toxicity. When the deep inspiration breath-hold (DIBH) technique is not feasible, particularly for patients with pendulous breasts, these results support the use of prone positioning as a practical alternative to the traditional supine setup. Nonetheless, the selection of the optimal treatment strategy should be tailored to each patient's unique clinical situation, and larger prospective studies with longer follow-up periods are needed to validate these findings.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

Funding

No Funds : Yes

Conflicts of interest

There are no conflicts of interest.

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