

RESEARCH ARTICLE

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Comparison of Mammographic Findings after Conventional Radiotherapy and forward Intensity-Modulated Radiation Therapy in Breast Conservative Therapy

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Abstract

Objective: This study aimed to determine and compare mammographic findings after conventional radiotherapy and forward intensity-modulated radiation therapy for breast conservation. **Methods:** Eighty-six patients with BCT (373 mammograms) were included between 2010-2015 and had post-treatment mammograms available for review. All mammograms were taken with an 18 × 24 cm detector and 0.070 mm pixel size (Selenia Dimensions, Hologic, Marlborough, Massachusetts, US). We documented the radiation technique, dose, and mammographic findings (e.g., edema, thickening, scarring, and calcification). We tracked the stability duration for each patient and grouped mammographic findings into 1-, 2, and 3 years post-treatment. SPSS version 26 and Stata version 18 were used for analysis. **Results:** The FIMRT group received a lower total radiation dose ($p=0.030$), a higher dose per fraction ($p=0.030$), and a lower maximum skin dose ($p<0.001$). The time to stable was shorter in the FIMRT group (975 days for CRT vs. 478 days for FIMRT; $p=0.001$). Among the 86 patients, the FIMRT group showed less breast parenchymal edema and noticeable scarring at 1, 2, and 3 years post-treatment than the CRT group, although the difference was not statistically significant. **Conclusion:** In the FIMRT group, post-BCT mammographic findings, including breast parenchymal edema and marked scar appearance, were fewer than those in the CRT group, and the duration to stable was significantly reduced.

Keywords: Breast conservative therapy- mammographic findings- conventional radiotherapy

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Introduction

Breast cancer is a health issue in women, with an incidence of approximately 25% of all female cancers [1]. More than half of all breast cancer mortalities occur in low- and middle-income countries such as Thailand (1). In the early stages of breast cancer, breast conservation therapy (BCT) is a standard treatment procedure that refers to breast-conserving surgery followed by postoperative radiation therapy. Onitilo et al. 2014 [2] demonstrated that equivalent survival rate after breast conservation therapy similar to mastectomy.

Local recurrence for breast conservative therapy is 1-2% per year [3-5] and Recht et al. 1988 [6] reported a recurrence peak between 2-6 years after treatment. Previous meta-analyses have found that postoperative radiotherapy reduces the risk of both recurrence and mortality in all women with node-positive breast cancer, including axillary, supraclavicular, and internal mammary lymph nodes [7, 8].

Currently, postoperative radiation in BCT involves several techniques. Conventional radiotherapy (CRT) is conventionally delivered using external beam radiation, and the dose delivered to adjacent organs at risk, such as the lungs and heart, may be higher than predicted [9]. Forward intensity-modulated radiotherapy (FIMRT) is superior to conventional radiotherapy in planning the target volume dose distribution and improves normal tissue sparing in organs at risk owing to the homogeneity of the planning target volume [10].

Mammographic findings changed after BCT, including skin thickening, skin edema, breast parenchymal edema, post-surgery fluid collection, seroma, fat necrosis, scarring, and dystrophic calcifications, which increased up to six months after BCT. In cases of recurrence, patients may present at clinical examination or only suspicious mammogram findings, such as suspicious microcalcifications or masses [11]. Other findings, such as an increase in breast density, scar enlargement, axillary nodal recurrence, or Paget's disease, were suspicious

for recurrent breast cancer [12]. Therefore, interpreting the findings in post-breast conservative treatment mammograms can be challenging for radiologists because surgery and radiotherapy alter normal breast architecture [3, 12].

In this study, we compared mammographic findings and duration to stable after conventional radiotherapy and forward intensity-modulated radiation therapy in breast conservative therapy. However, mammographic findings after conventional radiotherapy and forward intensity-modulated radiation therapy in breast conservative therapy remain unknown at our institute. To the best of our knowledge, this is the first report from our center.

Materials and Methods

In this retrospective observational descriptive study, all 86 patients who had a history of breast conservative therapy for pathologically proven malignant breast disease at Srinagarind Hospital, Khon Kaen University, between January 2010 and December 2015, and had to have at least one mammographic after treatment completion were available for review (Figure 1). Post-treatment mammograms were obtained outside our institute, patients underwent radiotherapy outside our facilities, or unavailable adequate information including radiation technique, medication records, specific histories of type, and duration of radiation therapy. were excluded from the study. Finally, the post-treatment mammograms of women who received CRT (N=40) were compared with those of women who received FIMRT (N=46). All mammograms were assessed by two radiologists blinded to the patients' radiation planning, and differences in opinion were resolved by consensus.

We recorded the following information for each patient: the study identification number, age, tumor site, tumor size and location, radiation planning (CRT or

FIMRT), radiation duration, radiation dose (total dose and dose per fraction), and maximum dose to the skin. In addition, the number of follow-up mammograms, median follow-up time, and median duration to stable were recorded for each patient. Stability was defined as no interval change in the two mammographic studies (Figure 2).

For each mammogram after conservative breast treatment, the following findings were recorded: asymmetrical breast size, breast edema, focal skin thickening, calcification, surgical scar appearance, mass density lesion, and fluid collection or seroma. The results are presented in Figures 3-8. Findings of mammograms performed at 1, 2, and 3 years after treatment completion were studied individually. In the cases of over half a year, follow-up duration was rounded up to 1 year, and the over 3-year follow-up duration was counted in the 3-years group.

Increased breast density and generalized skin thickening have been documented to represent parenchymal edema. Benign calcification was defined as vascular calcification, skin calcification, coarse or popcorn-like calcification, large rod-like calcification, round calcification, eggshell or rim calcification, dystrophic calcification, milk of calcium, and suture calcification. Suspicious calcification is defined as a group of amorphous, coarse heterogeneous, fine pleomorphic, and fine linear branching. The extent of the scar appearance was noted by the radiologist as mild, moderate, or marked. The definitions of mild, moderate, and marked scar appearances were none, minor, and obvious architectural distortions, respectively. Any new dense lesion on mammography should be evaluated using ultrasound to determine whether it is a seroma, fluid collection, or a solid lesion. Five cases were found to have recurrence breast cancer occurred during follow-up, which presented as a mass, suspicious calcification, axillary lymphadenopathy, and metachronous ipsilateral breast tumor recurrence. Recurrents were found 1 case in CRT

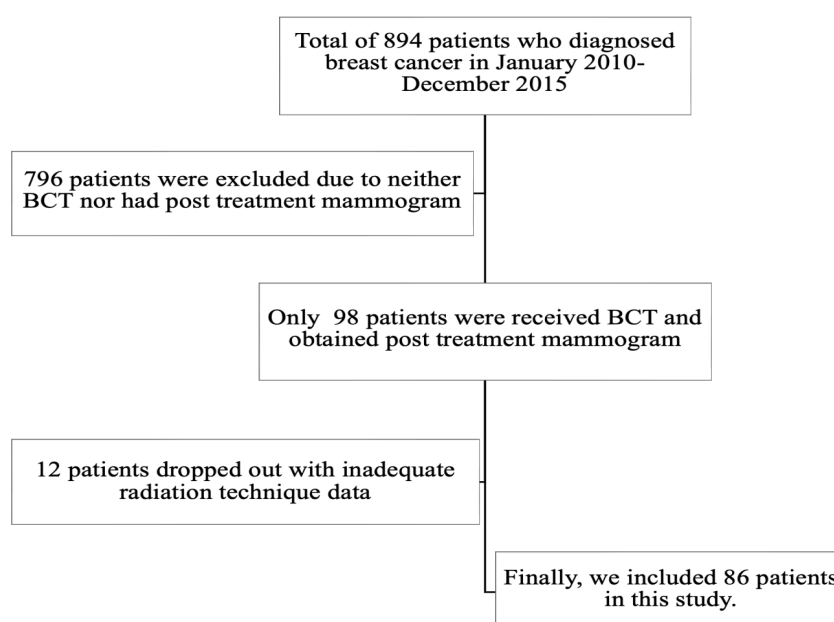


Figure 1. Flowchart Showing the Selected Population based on the Inclusion and Exclusion Criteria

Table 1. Characteristics of Participants.

Characteristics	CRT	FIMRT	p-value
N = 86 patients	N = 40 patients n (%)	N = 46 patients n (%)	
Age (year), mean \pm SD	48.37 \pm 9.437	49.39 \pm 12.212	0.671
Site of tumor			0.311
Right breast	20	28	
Left breast	20	18	
Tumor size			0.72
Unknown	1	2	
<20 mm	23	21	
20–50 mm	15	22	
>50 mm	1	1	
Tumor location			0.689
Upper outer quadrant	20	16	
Upper mid quadrant	4	5	
Upper inner quadrant	6	12	
Lower outer quadrant	3	1	
Lower mid quadrant	2	3	
Lower inner quadrant	2	2	
Mid outer quadrant	3	4	
Mid inner quadrant	0	1	
Subareolar location	0	1	
Radiation duration (days), mean \pm SD	45.33 \pm 7.37	45.11 \pm 9.293	0.906
Radiation dose			
Dose per fraction (cGy), mean \pm SD	200 \pm 0	207.33 \pm 20.97	0.03
Total radiation dose (cGy), mean \pm SD	5000 \pm 0	4917.33 \pm 236.45	0.03
Maximum dose at skin (%), mean \pm SD	114.44 \pm 5.27	108.92 \pm 3.40	<0.001

BRT, conventional radiotherapy; FIMRT, forward intensity-modulated radiation therapy.

group and 4 cases in FIMRT group, as an example of recurrent tumor shown in Figures 9 and 10.

All lesions included in this report were analyzed on a standardized basis using the mediolateral oblique (MLO) and craniocaudal (CC) views. All mammograms were obtained at our institute using amorphous selenium

TFT-based direct capture technology with an 18 \times 24 cm detector and 0.070 mm pixel size (Selenia Dimensions, Hologic, Marlborough, Massachusetts, US).

The data were entered into a database and statistical analyses were conducted using SPSS Statistics version 26 and Stata version 18. A t-test was used to compare the

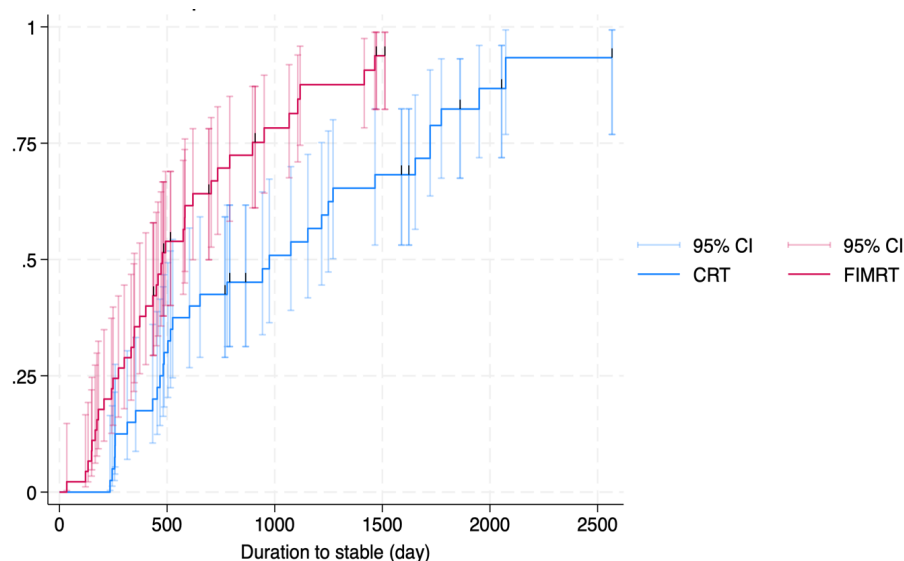


Figure 2. The Comparison of duration to Stable in CRT and FIMRT Groups.

Table 2. Mammographic Findings Following CRT and FIMRT

Characteristics N = 86 patients	CRT N = 40 patients n (%)	FIMRT N = 46 patients n (%)	p-value
Average number of follow up mammograms (n)	4.75	3.98	0.042
Follow up mo., median \pm SD	67.44 \pm 20.55	42.85 \pm 14.11	<0.001
Median duration to stable	975	478	0.001

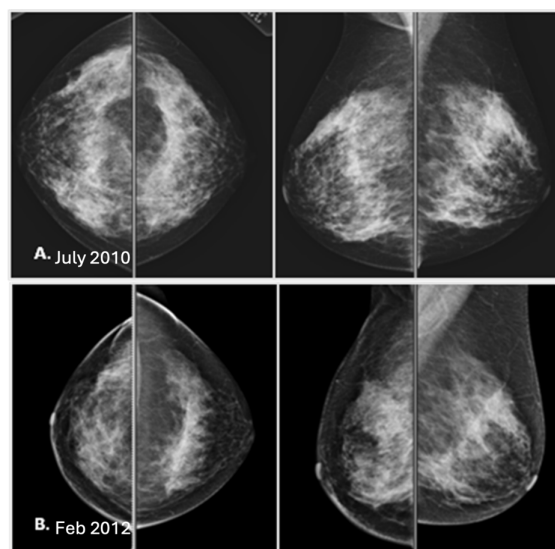


Figure 3. The Patient Underwent Right BCT in the CRT Group. (A) Pre-treatment imaging on CC and MLO views, while (B) asymmetrical size in the first post-therapy mammogram, 12 months after treatment completion.

means of the data. Duration to stable was estimated using the Kaplan-Meier curve, and a statistically significant difference was calculated using the log-rank test, considered at $p \leq 0.05$.

Results

Participants' characteristic details

This retrospective study group consisted of 86 patients

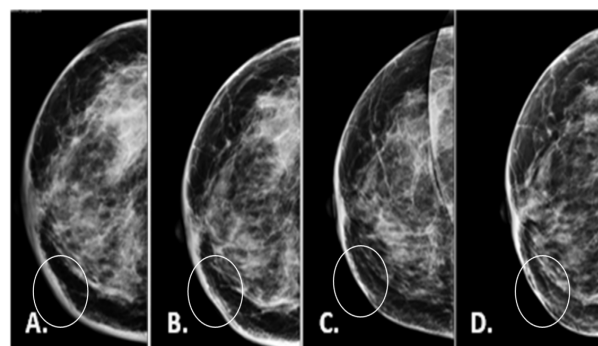


Figure 4. The Patient Underwent Lumpectomy, Followed by CRT. A-C: (A) Diffuse increases in skin thickness and diffuse increase in breast density are seen in the first post-therapy mammograms, which decreased on subsequent mammograms at 23 months (B), 56 months (C), and 69 months (D) post-treatment, respectively.

who underwent breast conservative therapy, including postoperative radiotherapy. Forty patients received CRT and another Forty-six of patients received FIMRT.

As shown in Table 1, there were no significant differences in the patient or tumor characteristics. The mean age of all CRT patients was 48 years and the mean age of all FIMRT patients was 49 years. Tumor site, tumor size, tumor location, and radiation duration were not significantly different between the two groups. The mean total radiation dose and the dose per fraction were significantly different between the CRT and FIMRT groups. The FIMRT group had a higher dose per fraction and a lower total radiation dose than the CRT group ($p=0.030$). The mean maximum skin dose was significantly lower in the FIMRT group in comparison to the CRT

Table 3. Mammographic Findings Following CRT and FIMRT at Year 1

Characteristics	CRT N = 29 patients n (%)	FIMRT N = 39 patients n (%)	p-value
Increase breast density	18 (62.10%)	18 (46.20%)	0.193
Generalized skin thickening	13 (44.80%)	13 (33.30%)	0.335
Asymmetrical breast size	15 (51.70%)	29 (74.40%)	0.053
Calcification			0.46
Benign calcification	8 (27.6%)	7 (17.9%)	
Suspicious calcification	0 (0.0%)	1 (2.6%)	
Scar appearance			0.403
Mild (No distortion)	16 (55.2%)	22 (56.4%)	
Moderate (Minor distortion)	10 (34.5%)	16 (41.0%)	
Mark (Obvious distortion)	2 (6.9%)	0 (0.0%)	
Focal skin thickening	11 (37.90%)	21 (53.80%)	0.193
Mass density lesion	1 (3.40%)	1 (2.60%)	0.831
Fluid collection or seroma	3 (10.30%)	4 (10.30%)	0.991

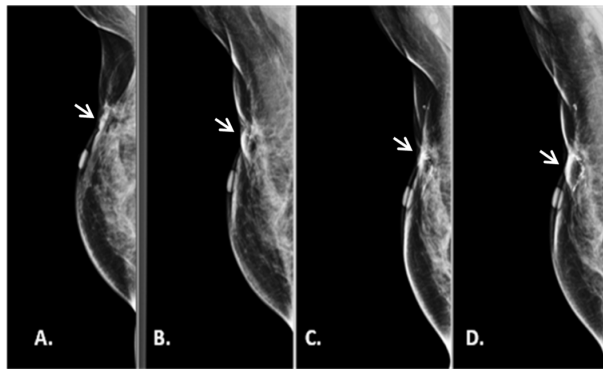


Figure 5. In a Patient who Received Breast-Conserving Therapy in the CRT Group, a Scar in the Right Breast that is Contiguous with the Skin Contour Deformity is Seen in (A) 29-month follow up, (B) 41-month follow up, (C) 60-month follow up, and (D) 66-month follow up. Increased benign calcification was also observed on subsequent mammograms.

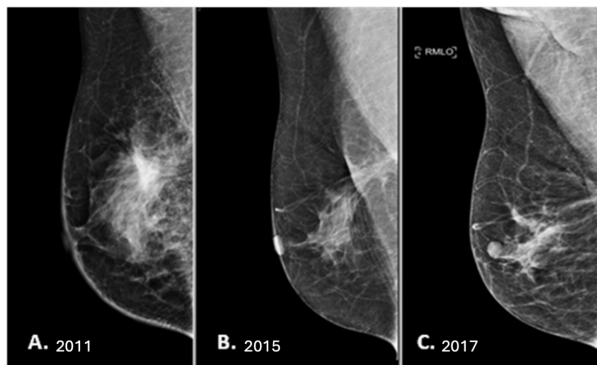


Figure 6. After FIMRT, Scar Density and Size Decreased on Serial Imaging. (A), (B), and (C) demonstrate a postsurgical scar in the right breast on the MLO view, which is contiguous with the skin contour deformity.

group ($p < 0.001$).

Mammographic findings

In total, 373 mammograms (190 in the CRT group and 183 in the FIMRT group) were reviewed and

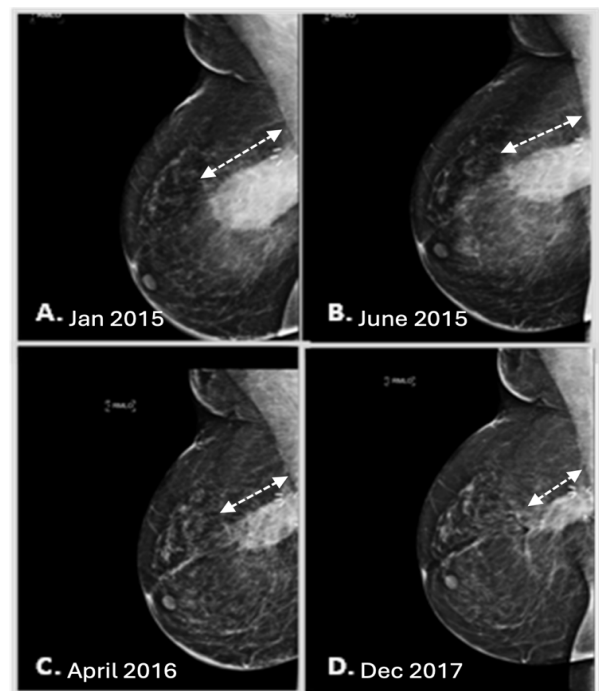


Figure 7. (A), (B), (C), and (D) show serial continuous reduction in the size of the postoperative collection (seroma) in post-breast-conserving therapy of the right breast in the CRT group.

evaluated. Table 2 demonstrates the average number of follow up mammograms in the CRT group found more than the FIMRT group but no statistically significant. (CRT and FIMRT; 4.7 and 3.9 follow up mammograms, respectively). Similarly, the length of follow-up was significantly different between the two groups in the CRT group (CRT versus FIMRT: 67 vs. 42 months, $p \leq 0.001$). While the median duration to stable was significantly different, the duration to stable was shorter in the FIMRT group (CRT versus FIMRT; 975 days versus 478 days, $p = 0.001$).

Our results in Table 3 show the mammogram findings for the 68 patients at 1-year after treatment completion, which showed no statistically significant difference

Table 4. Mammographic Findings Following CRT and FIMRT at Year 2

Characteristics N = 53 patients	CRT N = 22 patients n (%)	FIMRT N = 31 patients n (%)	p-value
Increase breast density	11 (50.0%)	13 (41.9%)	0.561
Generalized skin thickening	8 (36.4%)	8 (25.8%)	0.409
Asymmetrical breast size	17 (77.3%)	23 (74.2%)	0.797
Calcification			0.486
Benign calcification	7 (31.8%)	10 (32.3%)	
Suspicious calcification	1 (4.5%)	0 (0.0%)	
Scar appearance			0.203
Mild (No distortion)	10 (45.5%)	17 (54.8%)	
Moderate (Minor distortion)	10 (45.5%)	12 (38.7%)	
Mark (Obvious distortion)	2 (9.1%)	0 (0.0%)	
Focal skin thickening	10 (45.5%)	18 (58.1%)	0.365
Mass density lesion	1 (4.5%)	1 (3.2%)	0.804
Fluid collection or seroma	3 (13.6%)	2 (6.5%)	0.378

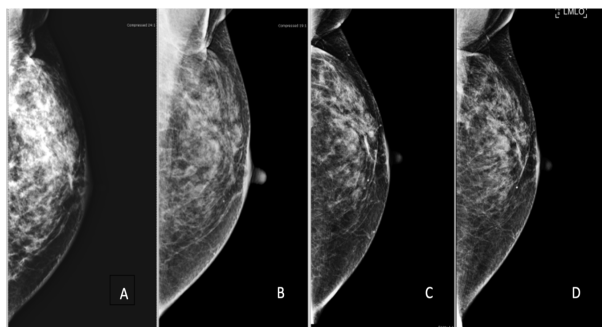


Figure 8. Increased Breast Density due to Edema after CRT. (A) Left breast MLO view shows diffusely increased density secondary to radiation-induced edema. 41-month (B), 53-month (C), and 65-month (D), decreased density was observed, consistent with resolving edema.

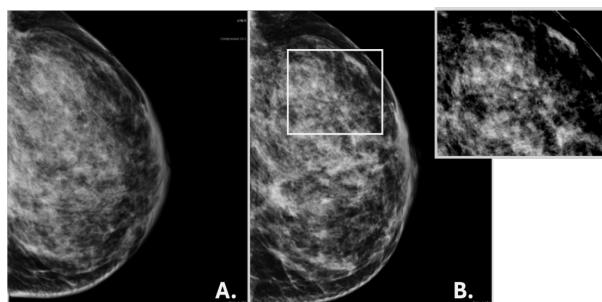


Figure 9. In a Patient Post-Breast-Conserving Therapy, Tamoxifen, and CRT with Nipple Discharge, new amorphous calcification in segmental distribution in the upper middle quadrant of the left breast was detected 2 years after the first post-treatment mammogram (approximately two years after complete treatment). Pathologically proven recurrent invasive ductal carcinoma, Grade 2.

even though increased breast density, generalized skin thickening, and marked scar appearance were found in the FIMRT group compared to the CRT group. Other findings (CRT vs. FIMRT) were as follows: increased breast density ($n=18$, 62% vs. $n=18$, 46%; $p=0.193$),

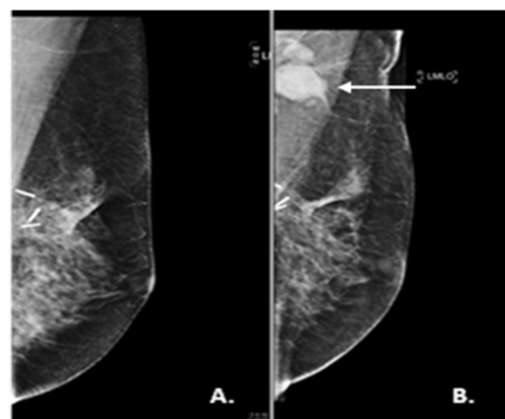


Figure 10. In a Patient Post BCT (FIMRT group) in 2014 then Loss Follows up Presented with Left Axillary Mass (about four years after complete treatment), a round shape lymph node at left axillary region (size 2.1 cm, as an arrow) confirmed as recurrent invasive ductal carcinoma on core needle biopsy. (A) One year after treatment completion. (B) Four years after treatment completion.

generalized skin thickening ($n=13$, 44% vs. $n=13$, 33%; $p=0.335$), asymmetrical breast size ($n=15$, 51.7% vs. $n=29$, 74%; $p=0.053$), calcification ($p=0.460$), scar appearance ($p=0.403$), focal skin thickening ($p=0.193$), mass density lesion ($p=0.831$), and fluid collection or seroma ($p=0.991$).

Table 4 demonstrates the mammographic findings at 2-year after treatment, with no significant difference in the mammographic findings between the two groups. Further analysis of the data at 3-year after treatment completion, as shown in Table 5, revealed that generalized and focal skin thickening were significantly different between the CRT and FIMRT groups. There was less generalized skin thickening in the FIMRT group than in the CRT group (31.8% vs. 5.6%, $p=0.039$). Moreover, focal skin thickening was lower in the CRT group than that in the FIMRT group (CRT vs. FIMRT: 45.5% vs. 77.8%, $p=0.038$). The other mammographic findings were not significantly different between the two groups.

Table 5. Mammographic Findings Following CRT and FIMRT at Year 3

Characteristics	CRT	FIMRT	p-value
N = 40 patients	N = 22 patients n (%)	N = 18 patients n (%)	
Increase breast density	10 (45.5%)	5 (27.8%)	0.251
Generalized skin thickening	7 (31.8%)	1 (5.6%)	0.039
Asymmetrical breast size	12 (54.5%)	13 (72.2%)	0.251
Calcification			0.318
Benign calcification	10 (45.5%)	5 (27.8%)	
Suspicious calcification	0 (0.0%)	1 (5.6%)	
Scar appearance			0.111
Mild (No distortion)	11 (50.0%)	14 (77.8%)	
Moderate (Minor distortion)	9 (40.9%)	3 (16.7%)	
Mark (Obvious distortion)	2 (9.1%)	0 (0.0%)	
Focal skin thickening	10 (45.5%)	14 (77.8%)	0.038
Mass density lesion	0 (0.0%)	1 (5.6%)	0.263
Fluid collection or seroma	1 (4.5%)	1 (5.6%)	0.884

Discussion

Breast conservative treatment includes adjuvant radiotherapy. Radiotherapy for breast cancer has changed over the past few years, leading to the development of individualized risk-adapted treatment strategies. Historically, the choice of RT was limited to conventional fractional therapy, but nowadays, the technique is a new standard of care for breast cancer, with the aim of reducing high doses to healthy tissues and organs at risk or even improving cosmetic outcomes [13]. The FIMRT group showed a higher radiation dose per fraction and lower total radiation dose than the CRT group.

In our institute, hypo-fractionation and modern techniques, such as FIMRT, have been considered the standard regimen of care since 2014. Therefore, the CRT population was treated before the FIMRT population. The mean number of follow-up mammograms and the length of follow-up were higher in the CRT group than in the FIMRT group. However, we considered that the median follow-up time in both groups (67 and 42 months) had no impact on the interpretation and analysis.

Several studies have shown a dosimetric benefit of FIMRT compared to CRT in that the FIMRT technique enables a more homogeneous planning target volume [10, 14] and more effectively reduces the higher dose delivered to organs at risk and the skin. Likewise, Jo et al. 2017 [15] showed that IMRT has a more prominent skin-sparing effect than CRT without compromising target volume coverage. Therefore, the mean maximum skin dose and scar appearance were significantly lower in the FIMRT group than those in the CRT group.

Moreover, the duration to stable was shorter than that in the FIMRT group, which confirmed the benefit of FIMRT. Similar to the findings of breast parenchymal edema, including diffuse skin thickening and diffuse increase in breast density, which was also less in the FIMRT group following less duration to stable. The shorter median time to stability in the FIMRT group may be beneficial for better interpretation of the post-BCT mammograms. Owing to the lower skin dose and shorter duration to stable in the FIMRT group, more mammograms of no diffuse skin thickening were observed in the FIMRT group, which may have affected the increased amount of focal skin thickening due to more obvious focal thickening of the skin.

The reasons for asymmetrical breast size may be related to the surgical technique, tumor characteristics (size and location), and the patients' breast volume; thus, there was no significant difference. This study has several limitations. First, only a small number of patients were included in this study. At the time of this retrospective study, only 86 patients met the inclusion criteria and had available posttreatment mammograms for review. Our mammographic findings showed that FIMRT has better outcomes, including less breast parenchymal edema, less marked scar appearance, and less duration to stable; not all of these were not statistically significant, but we considered that it might be statistically significant with a larger population. Another limitation of the study was that not all patients were followed by the subgroups of 1-year,

2-year, and 3-year post-treatment completion because the retrospective study setting cannot perform effective standard routine follow-up. However, CRT has recently been shown to no longer play a role in radiotherapy for breast conservative treatment in our institute. Therefore, it is difficult to study both CRT and FIMRT prospectively. The continued trend toward larger clinical trials and effective standard routine follow-up will be necessary to evaluate the outcomes.

In conclusion, in the FIMRT group, post-BCT mammographic findings including breast parenchymal edema and marked scar appearance were less as compared with CRT and significantly reduced in duration to stable, which supports former studies about the benefit of FIMRT in reducing the higher dose delivered to the skin and superior cosmetic outcomes. Perhaps this decreased duration to stable will at least improve the sensitivity of mammography to detect breast cancer recurrence.

Author Contribution Statement

All authors contributed to protocol/project development and approved the final version of the manuscript. SJ and KS: data collection; SJ, PP, and KT: analysis; SJ, KS, and KT: manuscript writing/editing.

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Ethical consideration

The study protocol and informed consent documents were approved by the Khon Kaen University Ethics Committee for Human Research (Ref. No. HE621544).

Availability of data

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare no conflicts of interest in this study.

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