

RESEARCH ARTICLE

Editorial Process: Submission:05/14/2025 Acceptance:11/11/2025 Published:11/22/2025

Comparison of Dose-Volume Histograms of Three Whole Breast Radiotherapy Regimes: Conventional, Normal Hypofractionation and FAST-FORWARD Hypofractionation

Amir Hossein Nabizadeh-Javan¹, Pejman Porouhan², Zeinab Jalambadani¹, Seyed Alireza Javadinia³, Reza Chaman³, Gaurav Dhawan⁴, Gunjan Sharma⁵, Vikas Dhawan⁶, Ruhollah Ghahramani-Asl^{3,7*}

Abstract

Objective: This study aims to compare dose-volume histograms of three whole breast radiotherapy regimes there are: conventional radiotherapy (CRT), normal hypofractionation (NHRT) and FAST-FORWARD hypofractionation radiotherapy (FFRT). **Methods:** This retrospective single-center study was conducted in the radiotherapy department of Vasei Hospital in Sabzevar, Iran in 2024. The therapeutic dose for the chest/whole breast and regional lymph nodes was administered using CRT (50Gy/2Gy/25Fx), NHRT (42.56Gy/2.66Gy/16Fx), and FFRT (26Gy/5.2Gy/5Fx) regimens. **Results:** The results of this study showed no statistically significant difference in the average scores of PTV V95%, PTV V107-110%, conformity index, and homogeneity index among the CRT, NHRT and FFRT treatment regimens. However, the average scores of PTV Dmean, lung Vmean, and heart Vmean were significantly higher for CRT and NHRT relative to FFRT group. **Conclusion:** The CRT is not superior to the NHRT and FFRT regimes, and in some cases, especially NHRT, they can be used interchangeably in the unique conditions and crowded government medical centers to provide more treatment services to patients and lower financial burden to the healthcare system.

Keywords: Breast Cancer- Conventional Radiotherapy- Hypofractionation- FAST-FORWARD hypofractionation

Asian Pac J Cancer Prev, 26 (11), 4109-4115

Introduction

Breast cancer is the most common type of cancer in the world and one of the leading causes of cancer-related deaths [1]. When the cancer is limited to the breast and nearby lymph nodes, or if there is minimal spread to other parts of the body, the treatment options include surgery, chemotherapy, radiotherapy, and hormone therapy [2, 3]. It is now considered standard practice to use adjuvant radiotherapy in the treatment of all patients who have undergone breast-conserving surgery, as well as those at high risk of lymph node involvement and chest recurrence, regardless of the initial surgical approach for the primary tumor [4]. This means that patients with four or more affected axillary lymph nodes or tumors classified as T3-4 would also receive adjuvant radiotherapy as part of their breast cancer treatment. In the conventional radiotherapy

(CRT) of breast cancer, patients typically receive a dose of 45-50 Gy over a period of 5-7 weeks, with a daily dose ranging from 1.8-2.0 Gy. This treatment targets the entire breast/chest area and regional lymph nodes, while also boosting the dose for tumor preservation surgery (10 Gy in 5 fractions). However, there has been a shift in recent decades towards using hypofractionation radiotherapy for patients without lymph node involvement. This approach involves a shorter treatment period (3-5 weeks) for the whole breast and is now considered the standard treatment for early-stage breast cancer [5-8]. Most clinical guidelines recommend hypofractionation radiotherapy approach due to low alpha-to-beta ratio in the range of 2.0-4.0 Gy for breast cancer and the low proliferation rate in early breast cancer. Alpha and beta are parameters that describe the linear and quadratic components of cell elimination form linear quadratic model used to describe the effects of

¹Student Research Committee, Sabzevar University of Medical Sciences, Sabzevar, Iran. ²Department of Radiation Oncology, Vasei Hospital, Sabzevar University of Medical Sciences, Sabzevar, Iran. ³Non-Communicable Diseases Research Center, Sabzevar University of Medical Sciences, Sabzevar, Iran. ⁴Sri Guru Ram Das (SGRD), University of Health Sciences, Amritsar, India and Independent Consultant, Hartford, CT, United States. ⁵Medical Physicist, Government Medical College, Amritsar, India. ⁶Urologist, Commanding Officer, Field Hospital, Jammu and Kashmir, India. ⁷Department of Medical Physics and Radiological Sciences, Faculty of Paramedicine, Sabzevar University of Medical Sciences, Sabzevar, Iran. *For Correspondence: ghahramanasl@gmail.com

radiation on cells in radiobiology [2, 9-12].

In recent years, studies have been conducted on the effectiveness of normal hypofractionated radiotherapy (NHRT) for the treatment of breast cancer patients who require chest radiotherapy and regional lymph node treatment. These studies have shown promising results in terms of acceptable side effects and effective local control [13-15]. Furthermore, a recent phase 3 clinical trial by Wang et al. with a large sample size and long-term follow-up demonstrated that compared to the CRT approach, NHRT radiotherapy is an equally effective treatment for adjuvant radiotherapy of the chest and lymph nodes in advanced breast cancer patients [16]. In addition to these findings, there has been a suggestion in recent years to use higher daily therapeutic doses [17-19]. In the extensive trial conducted by Murray Brunt et al. called FAST-FORWARD radiotherapy (FFRT), 4096 breast cancer patients with pT1-3, pN0-1, M0 who underwent breast-conserving surgery (BCS) or modified radical mastectomy (MRM) were treated either with the NHRT regimen of 40 Gy in 15 fractions over three weeks or the FFRT regimen of 26 or 27 Gy in 5 fractions [20]. The results of this study demonstrated that the 26 Gy in 5 fractions over one week regimen is a safe and effective treatment option with proper local control. Since each technique uses a different total dose, comparing dosimetric factors from dose-volume histograms (DVH) would be futile. To address this issue, an equivalent dose will be used.

Given the ongoing and the growing workload of radiotherapy centers all over the world, there is an increasing need for the implementation of the NHRT and FFRT regimens in the treatment of breast malignancies. This study aims to assess the radiation complications associated with radiation treatment, evaluate its clinical efficiency, and establish local control through a clinical trial. Specifically, the study will compare DVHs in adjuvant radiotherapy for breast cancer patients using three regimens of CRT, NHRT and FFRT.

Materials and Methods

This retrospective single-center study was conducted in the radiotherapy department of Vasei Hospital in Sabzevar, Iran in 2024. The study focused on analyzing CT images of breast cancer patients who were referred to the department for radiation therapy for adjuvant treatments. The patients included in the study had either completed their treatment or were in the process of completing it. Typically, the patients were treated consecutively according to their radiotherapy appointments. All the patients in the study were similar in terms of factors such as the size of the treatment field, the thickness of the patient's body, and the side being treated.

The sample size was calculated based on Park et al. study [12]. According to the formula, the sample size was determined to be 50, with a confidence level of 95% and a margin of error (d) of 0.05.

$$n = \frac{\left(Z1 - \frac{\alpha}{2}\right)^2 (P \times q)}{(d)^2}$$

A total of 50 patients diagnosed with breast cancer, based on clinical evidence and tests, were referred to the radiotherapy department for treatment by surgeons or other specialists.

The inclusion criteria for this study were as follows:

1. Patients diagnosed with breast cancer.
2. Definite histological diagnosis.
3. Patients who underwent BCS provided that lymph nodes were involved.
4. Negative surgical margin.
5. Indication of adjuvant radiotherapy, including cases where BCS did not sufficiently remove regional lymph nodes or when regional lymph nodes were involved.

The exclusion criteria for this study were as follows

1. History of previous chest radiotherapy
2. Presence of in-situ carcinoma without invasiveness
3. Presence of metastasis
4. Presence of connective tissue diseases
5. Positive surgical margin

Radiotherapy guidelines such as Radiation Therapy Oncology Group (RTOG), Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC), and the results of published articles were used to ensure the reliability and validity of the information tools.

In order to perform radiotherapy, it is necessary to determine the exact location and volume of the lesion inside the body. Therefore, all patients were subjected to CT simulation with 5 mm slice thickness in the supine position and using the breast board. To design the treatment, breast/chest tissue, axillary and supraclavicular lymph nodes, and healthy tissues such as the heart, left lung, right lung, and spinal cord were contoured based on RTOG criteria. The therapeutic dose for the chest/whole breast and the regional lymph nodes is in the regimens CRT (50Gy/2Gy/25Fx), NHRT (42.56Gy/2.66Gy/16Fx), and FFRT (26Gy/5.2Gy/5Fx) regimens. The administration of a tumor bed boost in patients undergoing breast conserving surgery in the CRT and NHRT group is 10 Gy in 5 fractions. In the design of the treatment, two tangent fields were used to cover the chest/whole breast, and two anterior and posterior fields were used to cover the axillary and supraclavicular lymph nodes. Although MRM cases were also treated at our medical center, only breast conserving surgery (BCS) cases were included in this study. In MRM cases, a bolus was considered in the first 13 sessions of treatment.

After performing the necessary treatment calculations and confirming their accuracy, therapeutic doses and DVH for both the treated and healthy tissues were extracted using the ISOgray treatment planning system (*Version 4.3.1.65 L, DOSIsoft®, France*). These data were then prepared for analysis in the checklist. Cumulative histograms were calculated and drawn based on treatment volumes such as the planning target volume (PTV) and clinical target volume (CTV). Additionally, volumes related to lung tissue, heart, and spinal cord were also considered using the treatment planning system. Furthermore, other indices such as Lung V_{20} , Lung V_{17} , Lung V_{16} , Lung V_{mean} , Heart V_{40} , Heart V_{30} , Heart V_{16} and Heart V_{mean} were extracted and compared with two other treatment regimens.

The data were entered into SPSS 16 software. Data description was conducted using frequency tables and average and standard deviation indices. The normality of the research components was assessed using the Kolmogorov-Smirnov test. ANOVA test was used to compare the means of the normal distribution. Chi-square (or Fisher's exact) test was employed to compare frequencies of non-normal distribution. The significance level (P) was set at less than 0.05.

Results

The patient's characteristics and clinical data are presented in Table 1. As reported in this table, the involve side of 100% of patients was the left breast and mostly upper-outer quadrant (UOQ). All patients underwent breast conserving surgery (BCS). The mean age of the patients was 49.20 ± 10.10 years, their radiotherapy treatment technique was 3D conformal and 82% of them were WHRT plus supraclavicular fields. The tumor stage was T2 in 66% of them, the tumor size was between 2-5cm, 62% of patients were grade II and 92% were without metastasis. 36% of patients had no lymph node involvement. In terms of estrogen receptor (ER), 82% were positive, in terms of progesterone receptor (PR), 74% were positive. In terms of Her2 protein receptor, 74% were negative, in terms of molecular subtype, 60% were in the luminal B subtype and the rest were in other subtypes. In terms of chemotherapy regimen, 78% of patients received the ACT-T regimen and the rest received other chemotherapy and hormone therapy regimens.

Table 2 displays the mean score of PTV $V_{95}\%$, PTV $V_{107-110}\%$, conformity index (CI) and homogeneity index (HI) for three treatment regimens of CRT, NHRT and FFRT. The PTV 95%, CI and HI were approximately the same for all three treatment regimens (95.56 ± 2.71 , 0.95 ± 0.027 and 0.41 ± 0.12 respectively). The one-way analysis of variance test revealed no statistically significant difference in the PTV $V_{95}\%$, PTV $V_{107-110}\%$, conformity index and homogeneity index score among the three treatment regimens ($P=0.89$). However, Table 2 displays the average score of PTV D_{mean} , Lung V_{mean} and Heart V_{mean} for three mentioned regimens. The values of these indices were different for each regimen, for example, for the average dose PTV D_{mean} , they were respectively equal to 32.3 ± 11.34 , 42.12 ± 5.71 and 51.90 ± 1.83 Gy for FFRT, NHRT and CRT respectively. The one-way analysis

Table 1. Characteristic and Clinical Data of Fifty Breast Cancer Patients in Present Study

Parameters	Value or number patient (%)
Average age (SD)	49.20 (± 10.1)
estrogen hormone receptor (ER)	9 (18%)-negative 41(82%)- positive
Laterality	Left side (50) Right side (0)
progesterone hormone receptor (PR)	13 (26%) negatives 37 (74%) positive
Her2 protein receptor	37 (74%) negative 13 (26%) positive
Hormone receptor	10 (20%) negatives 40 (80%) positive
Molecular subgroup	11 (22%) luminal A, 30 (60%) luminal B, 3 (6%) Her2 Enriched, 6 (12%) TNBC (Triple Negative Breast Cancer)
Ki67 marker	8 (16%) $<14\%$ 42 (84%) $>14\%$
Disease grade	7 (14%) grade I, 31 (62%) grade II, 12 (24%) grade III
Chemotherapy	39 (78%) ACT-T, 9 (18%) other methods, 2 (4%) hormone
Tumor Stage (size)	13(26%)T1, 33(66%)T2, 4 (8%) T3
Tumor Stage (Lymph node)	18(36%) N0, 16(32%)N1, 6(12%) N2,4(8%)N3, 6(12%)Unevaluable
Radiotherapy fields	9 (18%) WBRT, 41 (82%) WBRT+ Supra clavicular

of variance test indicated statistically significant difference in the PTV D_{mean} , Lung V_{mean} and Heart V_{mean} score among the three treatment regimens.

A comparison of intergroup data for the lung organ reveals no statistically significant difference between different treatment regimens in the lung organ. Therefore, based on the dose received and treatment complications related to the percentage of lung volume in patients, it can be concluded that the CRT regime followed by NHRT is preferable to FFRT ($F=0.71$, $P=0.49$) (Table 3).

Intergroup comparison of the data obtained for the heart organ reveals that there is no statistically significant difference between the three treatment regimens for the heart organ. Therefore, based on the percentage of patients' heart volume reached by the dose, it can be concluded

Table 2. Comparison of the Average Score of Dose Indices in Three Regimens of CRT, NHRT and FFRT Treatment

Variable	FFRT Mean $\pm$ SD	NHRT Mean $\pm$ SD	CRT Mean $\pm$ SD	ANOVA test	
PTV $V_{95}\%$	95.65 $\pm$ 2.71	95.40 $\pm$ 2.77	95.56 $\pm$ 2.68	F= 0.11	P= 0.89
PTV $V_{107-110}\%$	18.44 $\pm$ 15.02	19.20 $\pm$ 15.88	17.15 $\pm$ 14.01	F= 0.23	P= 0.78
PTV D_{mean}	32.30 $\pm$ 11.34	42.12 $\pm$ 5.71	51.90 $\pm$ 1.83	F=87.53	P< 0.001
Conformity index	0.95 $\pm$ 0.027	0.95 $\pm$ 0.028	0.95 $\pm$ 0.027	F=0.3	P= 0.96
Homogeneity index	0.41 $\pm$ 0.12	0.41 $\pm$ 0.10	0.40 $\pm$ 0.10	F=0.10	P= 0.95
Lung V_{mean}	9.99 $\pm$ 2.96	15.84 $\pm$ 4.78	18.17 $\pm$ 6.19	F=38.02	P< 0.001
Heart V_{mean}	6.59 $\pm$ 1.95	10.80 $\pm$ 3.22	12.65 $\pm$ 4.08	F=46.81	P< 0.001

Table 3. Comparison of Three Regimens of CRT, NHRT and FFRT Treatment in the healthy Lung organ

Lung organ	FFRT-Lung V_{16}		NHRT-Lung V_{17}		CRT-Lung V_{20}	
	NHRT-Lung V_{17}	CRT-Lung V_{20}	FFRT-Lung V_{16}	CRT-Lung V_{20}	FFRT-Lung V_{16}	NHRT-Lung V_{17}
Mean difference	-2.91	-3.45	2.91	-0.53	3.45	0.53

F=0.71; P=0.49

Table 4. Comparison of Three Regimens of CRT, NHRT and FFRT Treatment in the Healthy Heart Organ

Heart organ	FFRT-Heart V_{16}		NHRT-Heart V_{30}		CRT-Heart V_{40}	
	CRT-Heart V_{40}	NHRT-Heart V_{30}	CRT-Heart V_{40}	FFRT-Heart V_{16}	NHRT-Heart V_{30}	FFRT-Heart V_{16}
Mean difference	1.82	0.3	1.52	-0.30	-1.52	-1.82

F=0.58; P=0.56

that the CRT regime and NHRT is preferable to FFRT in terms of the dose received and treatment complications (F=0.58, P=0.56) (Table 4).

Discussion

This study was conducted to assess the radiation toxicity and complications associated with 3D conformal radiation treatment of patients with breast cancer. Also, evaluate its clinical efficiency, and establish local control by comparison of DVHs in radiotherapy of breast cancer patients using three different regimens of CRT, NHRT and FFRT. The whole breast 3D conformal radiation therapy with doses of 45 to 50 Gy delivered over 5 to 6 weeks as a conventional adjuvant therapy is the standard of care for post-lumpectomy patients. In 3D-CRT regime, two tangential radiation fields and two supraclavicular radiation fields from high-energy 6 megavolt X-rays from a linear accelerator was used to destroy or damage cancer cells. The prescribed dose per fraction varies between 2 and 5.2 Gy, depending on the selected treatment regimen [21-23]. In our study, fifty breast cancer patients were treated with therapeutic doses for the chest/whole breast as well as regional lymph nodes using CRT (50Gy/2Gy/25Fx) and NHRT (42.56Gy/2.66Gy/16Fx) regimens, as well as the FFRT regimen (26Gy/5.2Gy/5Fx).

All patients had left side breast cancer involvement with mean age of 49.2 ± 10.1 years. Clinical data related to patients including estrogen receptor (ER) status, progesterone receptor (PR) status, Her2 protein receptor, hormone receptor, molecular subgroup type, Ki67 marker percentage, disease grade, chemotherapy status, and tumor stage in terms of size and lymph node involvement are mentioned in Table 1. 18% of patients had only whole breast radiation fields and 82% had whole breast and supraclavicular radiation fields.

The results of the one-way analysis of variance test showed a statistically significant difference in the Lung V_{mean} and heart V_{mean} score among the CRT, NHRT, and FFRT treatment regimens ($P < 0.001$). Since that the CRT treatment regime delivered a higher average dose to the lungs and heart of patients, so the chance of radiation complications may be higher. Dunnett's test revealed the CRT treatment regime hasn't a higher priority than NHRT and FFRT in terms of radiation protection of healthy

organs. The obtained data indicated a significant reduction in the average dose for the left breast (PTV D_{mean}), heart, and lung in FFRT and NHRT regimes compared to the CRT dose fraction. However, the values of the CI and HI did not provide any meaningful information regarding the benefits of any of the differential treatment regimens.

Furthermore, there was no significant difference in the received dose in the lung and heart volume. The results showed that FFRT and NHRT treatment regimens with a smaller number of treatment fractions and a higher dose per fraction (> 2 Gy) compared to the conventional dose fraction regimen resulted in a reduction in the dose to the heart and lung on the same side. These findings are consistent with the results of previous studies. According to the recommendations of the International Commissions on Radiation Protection such as ICRP, compliance with the dose to healthy tissues should be considered even in diagnostic areas such as radiography, angiography and nuclear medicine procedures [24-27].

The result of the one-way analysis of variance test showed a statistically significant difference in the PTV D_{mean} score among the three treatment regimens of CRT, NHRT and FFRT ($P < 0.001$). Furthermore, Dunnett's test revealed that the CRT treatment regime is more effective than NHRT, and NHRT is more effective than FFRT in terms of PTV D_{mean} score and biological effective dose.

In a study by Bouziane J. et.al in 2025, acute skin reactions were investigated in patients treated with Fast-Forward regimen (26Gy in five daily fractions). About 93% of patients had tumors staged T1 or T2. They found that although acute radiodermatitis occurred a mean period of 1.6 months after of adjuvant radiotherapy in a small percentage of patients (about 16%), further consultation during treatment seems necessary to diagnose and treat these reactions [28].

The dose to normal organs was not considered during this treatment protocol, but in our study, the dose to normal organs such as the heart and lungs during the use of this treatment protocol was examined and compared with the standard and hypofractionation regimes. In addition, Murray Brunt A. et.al in 2020 reported that 26 Gy in five fractions over 1 week is non-inferior to the standard of 40 Gy in 15 fractions over 3 weeks for local tumour control of BCS or mastectomy patients. They also announced that Fast-Forward fraction is as safe in terms of normal tissue

effects up to 5 years for patients prescribed adjuvant local radiotherapy after primary surgery for early-stage breast cancer [20].

In other study conducted by Kazemzadeh et al., similar to our present study, dosimetry indicators were investigated in a NHRT regimen of 40.5 Gy in 15 sessions compared to the CRT. This study found that the average absorbed dose of the left breast in the NHRT regimen was significantly lower at 41.64 Gy compared to 51.4 Gy in the CRT regimen [29]. However, there were no significant differences in the CI and HI indices. The results of the one-way analysis of variance test showed that there is no statistically significant difference between the CI and HI scores with three treatment regimens.

Hosseini et al. in another study compared the canonical treatment regime with the field-in-field method. In the CRT regime, the average dose reached to the breast was 46.6 Gy, and the HI and CI were reported as 0.16 and 0.94, respectively. The volume of 95 and 107 percent of the breast in all treatment regimens did not show any significant difference, and the same average was obtained [30]. In the present study, consistent with Hosseini's study, the results showed that there is no statistically significant difference between PTV $V_{95}\%$ and PTV $V_{107-110}\%$ with three treatment regimens of CRT, NHRT and FFRT.

One of the limitations of the study is the lack of access to other treatment modalities such as tomotherapy of breast cancer patients. Another limitation is the lack of access to post-treatment clinical examination data. The researchers of this study make the following suggestions:

1. Conducting an inter center study with a larger sample size.
2. Following up on clinical examinations and paraclinical data after patients' complete radiotherapy.
3. Conducting long-term follow-up and examining patients for symptoms of complications, such as skin toxicity.
4. Calculating the effects of conventional and hypofractionation treatments on tomotherapy and IMRT devices.
5. Conducting a study on patients who have undergone MRM.

6. Using radiobiological software to predict the side effects of radiotherapy in these treatment techniques.

In conclusion, the results of the present study indicate that in terms of dose indices, such as average scores of PTV $V_{95}\%$, PTV $V_{107-110}\%$, CI, and HI delivered to the treatment target, all three treatment regimens are almost similar, but the PTV D_{mean} and biological effective dose is higher in CRT treatment regime. Also, in terms of dose indices such as lung V_{mean} and heart V_{mean} delivered to healthy organs, the CRT is not superior to the NHRT and FFRT regimens, and in some cases, especially NHRT, they can be used interchangeably in the unique conditions and crowded government medical centers to provide more treatment services to patients. As well as the economic aspects and lower financial burden on patients and the healthcare system, it may be possible to utilize NHRT regime to shorten the radiotherapy duration for the comfort of patients.

Author Contribution Statement

Ghahramani-Asl R and Javadinia SA contributed to the design and implementation of the research. Nabizadeh-Javan AH and Porouhan P, Dhawan G, Sharma G and Dhawan V contributed in collecting data, and drafting the manuscript. Jalambadani Z and Chaman R contributed to the analysis of the results. Furthermore, it was ensured that all authors reviewed and approved the final version of the manuscript before submission.

Acknowledgements

The authors would like to thank all the participants who kindly cooperated in the process of the study. The research protocol conducted under the ethical code IR.MEDSAB.REC.1400.175, with financial support provided by the Research Ethics Committee of Sabzevar University of Medical Sciences. We acknowledge the Clinical Research Development Unit of Vasei Hospital, affiliated with Sabzevar University of Medical Sciences, for their kind and continuous support. Our study not registered in any registration dataset such as clinical trials, guidelines, meta-analysis.

Data Availability

Anonymized patient data are available upon request, subject to approval by the institutional ethics committee and the patients' consent. Readers interested in accessing the data may contact the corresponding author.

Funding statement

This work was funded by the Research Vice-Chancellor of Sabzevar University of Medical Sciences.

Conflict of interest

The authors declare that there are no conflicts of interest.

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