RESEARCH ARTICLE

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Optimizing Radiotherapy for Left Breast Cancer: A Dosimetric Evaluation of Hypofractionated vs. Conventional VMAT with DIBH

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Abstract

Purpose: This study aimed to determine whether the hypofractionated regimen offers dosimetric and radiobiological benefits compared to a conventional regimen delivered with deep inspiration breath-hold (DIBH) for left breast cancer patients following breast-conserving surgery using the VMAT technique. The primary objective was to assess whether the hypofractionated regimen provides equivalent target coverage and improved sparing of organs at risk (OARs). **Methods:** Twenty-four patients with histologically confirmed left-sided breast cancer, aged between 42 and 68 years, were included and divided into two fractionation protocols: 12 received a conventional regimen (50 Gy in 25 fractions), and 12 received a hypofractionated regimen (40 Gy in 15 fractions). Dosimetric parameters including clinical target volume (CTV) coverage, homogeneity index (HI), conformity index (CI), number of monitor units (MUs), and dose to critical structures were compared between the two regimens. The biological impact of the different fractionation schemes was assessed by calculating the biological effective dose (BED) and the equivalent dose in 2 Gy fractions (EQD2). For statistical analysis, an independent-sample t-test was used ($P < 0.05$). **Results:** Both treatment approaches provided excellent target coverage, with no significant differences observed in CI. The conventional VMAT plan demonstrated better dose homogeneity (HI = 0.165 ± 0.038) compared to the hypofractionated plan (HI = 0.304 ± 0.090; $p < 0.001$). The hypofractionated approach showed a tendency for increased sparing of organs at risk, notably a 28.7% reduction in mean heart dose (6.24 Gy vs. 8.91 Gy), a lower EQD_2 (4.27 Gy vs. 5.99 Gy), and a significantly reduced dose to the contralateral lung (5.62 Gy vs. 7.32 Gy; $p = 0.029$). For the contralateral breast, no statistically significant difference was observed ($p > 0.05$). **Conclusion:** Research indicates that hypofractionated VMAT with DIBH offers potential dosimetric advantages over the conventional regimen, most notably by reducing radiation exposure to the heart and contralateral lung.

Keywords: Hypofractionated regimen- left breast cancer- DIBH- conventional regimen- biological effective dose (BED)

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Introduction

Breast cancer continues to be the most commonly diagnosed cancer and the top cause of cancer-related death in women around the world. This presents a major global health challenge. According to GLOBOCAN 2022, there were about 2.3 million new cases and 685,000 deaths reported worldwide. This represents around 11.7% of all cancer diagnoses and 15.5% of cancer deaths among women [1].

For left-sided breast cancer, special considerations must be given to limiting radiation exposure to critical organs such as the heart and lungs, which may lead to long-term complications, including cardiac toxicity and radiation pneumonitis [2]. Recent advances in radiotherapy techniques have prioritized minimizing damage during treatment. For this, the volumetric modulated arc therapy (VMAT) method enables the precise delivery of a three-dimensional (3D) dose distribution while reducing radiation exposure to healthy tissues. This precision is achieved when combined with Deep Inspiration Breath-Hold (DIBH), a technique that increases lung volume during inspiration and physically displaces the heart away from the chest wall, reducing cardiac and lung irradiation [3]. When Zhang et al. evaluated the free-breathing and deep inspiration breath-hold techniques in VMAT, they observed that the DIBH approach resulted in significantly lower doses for the heart, left and right lungs, and right breast [4].

A significant advancement in breast radiotherapy is the implementation of moderate hypofractionation, which typically involves treatment schedules of 15-16 fractions

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compared to conventional regimens of 25-28 fractions. Several randomised clinical trials, including START-A, START-B, and the Canadian trials, have yielded similar results in terms of local control and survival rates, with potential improvements in convenience and cost-effectiveness [5]. Several international guidelines have endorsed moderate hypofractionation as a new standard of care.

However, additional study suggests that hypofractionated breast irradiation increases the risk of heart-related deaths, particularly in patients who had cardiac risk factors before treatment [6]. Severe hypofractionation (43 Gy in 10 daily fractions) may raise the risk of cardiac injury, according to a study done by Tjessem et al. [7]. The results show that the Biological Effective Dose (BED) model, which standardizes radiobiological evaluations, provides a framework for measuring the biological effects of different fractionation schedules. The α/β ratio is defined as a measurement of the inherent radiosensitivity of a particular tissue, expressed in Gy. α and β are two constants that represent two mechanisms of radiation-induced cell death, indicating the proportional significance of each process [8]. Literature results suggest that the α/β ratio of breast cancer falls within the range of 3-5 Gy. A low estimated α/β ratio for breast cancer suggests that it is likely as sensitive to fraction size as dose-limiting normal tissue, and hypofractionation for breast cancer may actually be beneficial [9].

Although clinical research indicates the benefits of hypofractionation, limited studies have thoroughly examined the radiobiological equivalence and dosimetric advantages of hypofractionated versus standard radiation schedules in patients with left-sided breast cancer who were treated with VMAT-DIBH. For this, a comparative analysis is necessary to gain a deeper understanding of the radiobiological effects and to guarantee treatment safety.

This study conducts a retrospective analysis comparing various fractionation methods and the radiobiological impacts of hypofractionated versus conventional radiotherapy protocols using the deep inspiration breath hold technique for patients with left-sided breast cancer. The analysis provides insightful observations on the comparative effectiveness of hypofractionated and conventional VMAT techniques for left-sided breast cancer radiotherapy.

Paper outline: Section 2 details materials/methods, including patient selection, contouring, planning objectives, and dosimetric analysis. The results, including clinical target volume (CTV) and organs at risk dosimetric and radiobiological evaluations, are presented in Section 3. The results are discussed in Section 4 along with their limitations and current clinical evidence. Key findings and recommendations for future research and clinical practice were presented at the end of Section 5.

Materials and Methods

Patient enrollment

Twenty-four patients with histologically confirmed invasive left-sided breast cancer aged between 42 and 68 years (mean value: 55 years) were enrolled between 2024 and 2025, divided into two fractionation protocols: 12 received a conventional regimen of 50 Gy in 25 fractions and 12 recieved a hypofractionated regimen of 40 Gy in 15 fractions, all using the VMAT technique, treated at the Department of Radiation Therapy at Ain Wazein Medical Village (AWMV) hospital. Both treatment groups were performed with deep inspiration breath hold (DIBH) CT scans using the Elekta ABC gating breathing system in the supine position with a dedicated breast board.

Inclusion criteria were: breast-conserving surgery, no prior thoracic radiotherapy, and exclusion criteria were Eastern Cooperative Oncology Group (ECOG) Performance Status Scale, metastatic disease, presence of pacemaker or metal implants, and comorbidities.

For planning, a Siemens 64-slice multi-slice CT scanner, with a slice thickness of 3 mm, was used. A further position check was conducted using a daily CBCT to ensure the accuracy of the internal organs at risk position. A treatment planning system, Monaco version 5.11.03, was used, where the radiotherapy plans were generated.

Contouring and planning objectives

According to the ICRU reports 50-62, the clinical target volume (CTV) was defined, and the process of contouring the relevant organs at risk was delineated under the supervision of the radiation oncologist according to the criteria of the radiation oncology treatment group (RTOG) 0319 Breast Cancer Atlas [10, 11] . The dose calculation was carried out with the Monte Carlo (MC) algorithm from the Monaco Treatment Planning System. The VMAT planning technique consists of multiple beam segmentations with 6 MV photon beams in both regimens and with a 3mm grid resolution. Because breast cancer can spread toward the patient's surface, an auto flash margin (ranging from 1.5 cm to 2.4 cm) was induced, causing the multileaf collimator (MLC) leaves to open beyond the body contour. The collimation rotation was 0° for all plans. Figures 1 and 2 illustrate a comparison of the distribution of dose for the target volume and the organs at risk in a DVH for a representative patient with left-sided breast cancer after breast-conserving surgery between these two regimens.

The primary focus of treatment planning was dosage coverage. The CTV breast was required to receive a dose of 95% of the CTV volume in both plans. To ensure a valid comparison of plans in terms of OAR doses, the CTV requirements should be kept as consistent as possible. For the organs at risk, the following constraints were:

a) Heart: $D_{mean} \leq 5$ Gy and $V_{25Gy} \leq 10\%$
b) Ipsilateral lung: $V_{20Gy} \leq 30\%$, V_(5Gy)≤ 40%
c) Contralateral breast: $D_{mean} \leq 3$Gy for both plans.

Where D_{mean} is the mean dose absorbed by the entire volume, and dosimetric parameters V20% and V25% indicate a percentage of the volume of a particular normal organ that is exposed to at least 20 Gy and 25 Gy of radiation, respectively.

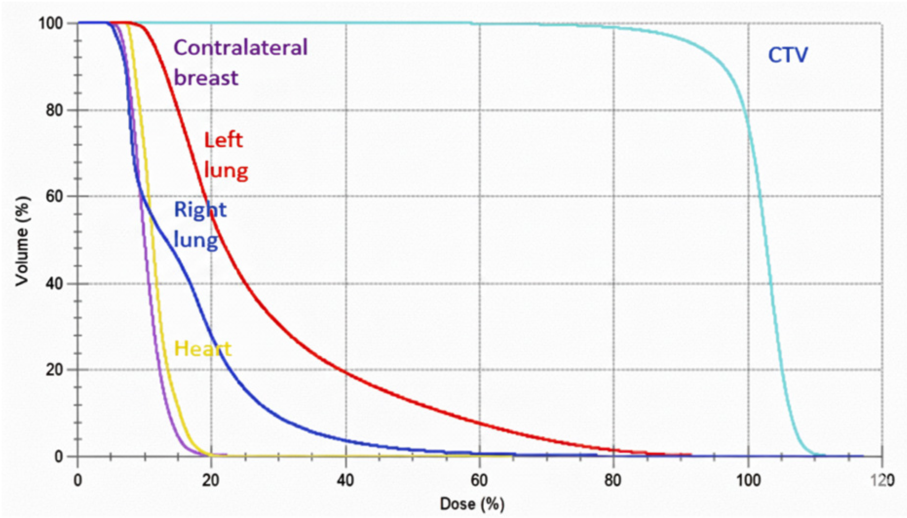

Figure 1. Dose-Volume Histogram (DVH) in a Hypofractionated Regimen with DIBH for a Patient with Left Breast Cancer

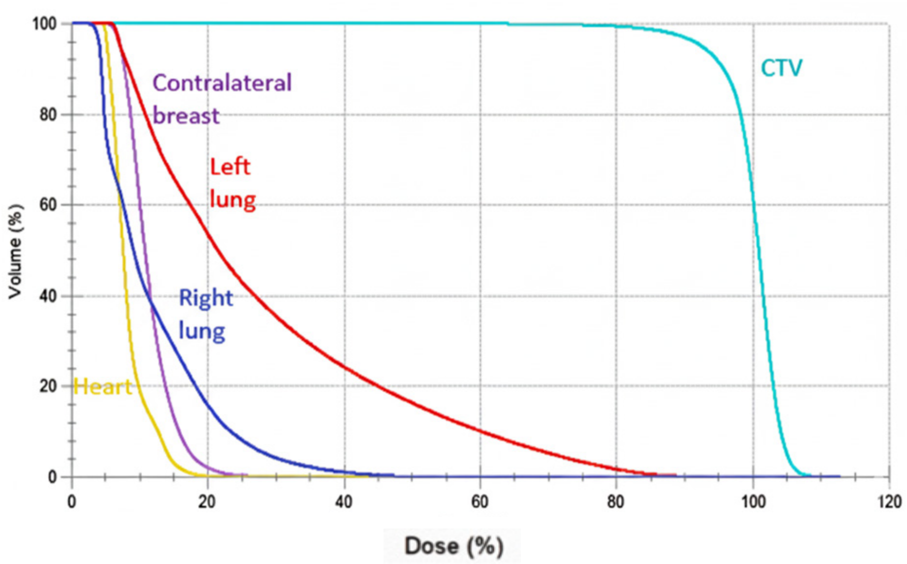

Figure 2. Dose-Volume Histogram (DVH) in a Conventional Regimen with DIBH for a Patient with Left Breast Cancer

Dosimetric analysis

To evaluate the plan, dose-volume histogram (DVH) analysis was used. Quality metrics such as homogeneity index (HI), conformity index (CI), and the number of monitor units (MU) were compared for both treatment plans. For the CTV breast, HI, CI, D2%,D95%,D98% and MU(s) were evaluated.

Monitor units indicate the number of units delivered by the linear accelerator to achieve the required dose. For each plan, MU was immediately recorded from the Monaco TPS. D95% is the dose that covers 95% of the CTV volume. The near-minimum dose is D98, which covers 98% of the volume, and a higher dose is preferable for adequate coverage. Conversely, the near-maximum dose is D2, which affects only 2% of the volume, and a lower dose is preferred to minimize hotspots. The better the conformal coverage, the closer the CI values to 1. For homogeneity, an HI value around 0 indicates more homogeneity of the dose distribution [12].

a) The homogeneity index (HI) is computed using the formula [13] :

$$HI=(D2\%-D98\%)/ Dp \quad (1)$$

D2 and D98 are received by 2% and 98% of the CTV volume, respectively.

Dp is the prescribed dose.

b) The Conformity Index (CI), as determined by the Radiation Therapy Oncology Group (RTOG 0236), is the degree of conformity of the prescription isodose to the CTV, where V_RI is the volume covered by the reference isodose line (95%), and TV is the target volume [14]:

$$CI=V_{RI}/TV \quad (2)$$

The biological impact of varying fractionation schemes was assessed by calculating the biological effective dose (BED) and equivalent dose in 2 Gy fractions (EQD2) represented as [15]:

$$BED = n \times d\ (1 + \frac{d}{\alpha/\beta}) \quad (3)$$

$$EQD2 = \frac{BED}{1 + \frac{2}{\alpha/\beta}} \quad (4)$$

Where n is the number of fractions and d is the dose per fraction.

Statistical analysis

The results were expressed as mean ± standard deviation (SD) of the dosimetric parameters, and an Independent Sample t-test was employed to assess the differences in quality metrics between the two regimens with DIBH. The analysis for this study was conducted using OriginLab Software. The criterion for statistical significance was determined to be 5% (P <0.05).

Results

Comparisons were conducted between the dosimetric and radiobiological effects of the conventional and hypofractionated treatment regimens. The target volume dosimetric parameters, which include the homogeneity index (HI), conformity index (CI), D2%, D95%, D98%, and monitor units (MUs), are summarized in Table 1. Relevant dose parameters for organs at risk, such as the heart, ipsilateral lung, contralateral lung, and contralateral breast, are also presented in Table 2.

a) CTV dosimetry evaluation

In terms of target coverage dosimetry evaluation, statistically significant differences were observed in certain parameters. D98% was significantly lower in the hypofractionated group (35.73 ± 1.35 Gy vs. 44.47 ± 1.59 Gy; p < 0.001).

In contrast, the homogeneity index (HI) was substantially higher for the hypofractionated regimen (0.304 ± 0.090) than for the conventional regimen (0.165 ± 0.038; p < 0.001). The conventional plan showed a more uniform radiation dose delivery, with a more homogeneous dose distribution within the CTV, as shown in Figure 3.

No statistically significant differences were found in CI, D95%, or D2% between the two regimens (p > 0.05). The number of monitor units MU(s) was increased in the hypofractionated plan, with statistical significance (p<0.001, t = -8.058) compared to the conventional plan.

b) Evaluation of organs at risk dosimetric parameters

Heart dosimetry

In the conventional group, the mean heart dose (Dmean) was 8.91 ± 4.95 compared to 6.24 ± 3.38 in the hypofractionation group. A reduction of 30% occurred, but the difference was not statistically significant (p=0.137). For both dose levels, V5% and V25%, dosimetric parameters for the heart were lower in the hypofractionated plan, but these variations were not found to be statistically significant (p>0.05).

Ipsilateral and contralateral lungs dosimetry

Dosimetric analysis of the ipsilateral lung found no statistically significant distinctions between the two treatment plans for average dose (Dmean), volume receiving 5 Gy, or volume receiving 20 Gy, as all parameters had p-values greater than 0.05. For the contralateral lung, the hypofractionated regimen resulted

Table 1. Dosimetric Comparison for Target Volume Metrics between Conventional and Hypofractionated VMAT Regimens with DIBH

Parameters	Conventional regimen (Mean±SD)	Hypofractionated regimen (Mean±SD)	P- value	t-test
D98%	44.47±1.59	35.73±1.35	<0.001	14.47
D2%	52.29±2.77	50.23±2.66	0.077	-1.851
D95%	94.60±1.56	95.12±1.29	0.387	0.881
HI	0.165±0.038	0.304±0.090	<0.001	-4.93
CI	0.756±0.082	0.709±0.097	0.211	1.289
MU (s)	1364.12±229.224	1969.85±260.9	<0.001	-6.042

Table 2. Dosimetric Parameters Comparison between Conventional and Hypofractionation Regimens with DIBH for Organs at Risk

Organs at risk	Parameters	Conventional regimen (Mean±SD)	Hypofractionated regimen (Mean±SD)	P-value	t-test
Heart	D_{mean} (Gy)	8.912±4.952	6.24±3.382	0.136	1.54
		74.14±28.69	49.21±32.56	0.059	1.99
		2.38±3.80	1.11±3.20	0.38	0.88
Ipsilateral lung	$V_{5\%}$	78.67±11.41	78.35±7.57	0.93	0.083
	$V_{20\%}$	19.84±3.58	19.28±2.32	0.65	0.45
	D_{mean} (Gy)	12.95±1.28	12.31±0.63	0.13	1.548
Contralateral lung	D_{mean} (Gy)	7.32±2.08	5.62±1.43	0.03	2.32
Contralateral breast	D_{mean} (Gy)	4.08±0.86	3.72±0.95	0.33	0.97

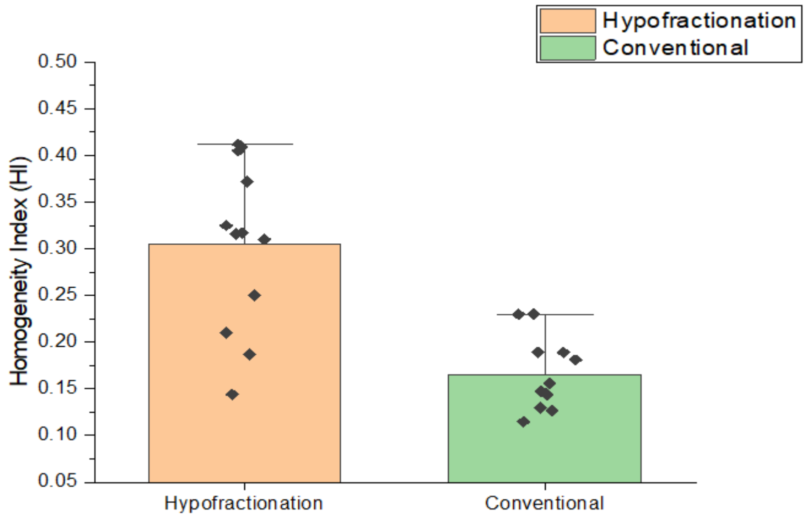

Figure 3. Comparison of the Homogeneity Index between Conventional and Hypofractionated VMAT regimens with DIBH

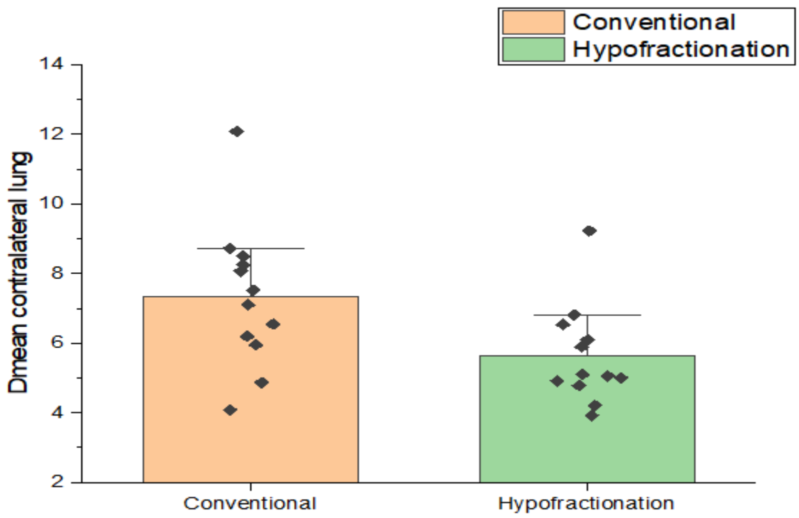

Figure 4. Comparison of the Mean Dose for the Contralateral Lung between Conventional and Hypofractionated VMAT Regimens with DIBH

in a lower mean dose of 5.62 Gy compared to 7.32 Gy in the conventional regimen. The findings in the mean values of the contralateral lung are summarized in Figure 4.

Contralateral breast dosimetry

In the hypofractionated group, the mean dose was lower at 3.72 Gy compared to the conventional group, which received 4.08 Gy, but this difference was not statistically significant (p>0.05).

c) Radiobiological Evaluation

To evaluate possible variations in biological response between different fractionation schedules, the biological effective dose (BED) and equivalent dose in 2 Gy fractions (EQD2) were calculated using an α/β ratio of 3 Gy for the heart and lung [16]. A reported estimate of 3 Gy exists for the α/β ratio concerning the fractionation sensitivity of breast cancer. Results are presented in Table 3.

Table 3. Radiobiological Dose Calculation for Organs at Risk (α/β = 3 Gy)

Organs at risk	Fractionation schedules	BED (Gy)	EQD2 (Gy)
Heart	Conventional regimen (50 Gy / 25 fractions)	9.98	5.99
D_{mean} (Gy)	Hypofractionation regimen (40 / 15 fractions)	7.11	4.27
Ipsilateral lung	Conventional regimen (50 Gy / 25 fractions)	15.19	9.11
D_{mean} (Gy)	Hypofractionation regimen (40 / 15 fractions)	15.67	9.41

Discussion

Randomized trials that evaluated routine and moderately hypofractionated radiotherapy with a total of 7,000 patients did not show clear differences in treatment effectiveness or the occurrence of late post-radiotherapy complications during a follow-up period of 5 to 10 years [17].

This study compared the dosimetric results of hypofractionated and conventional treatment plans developed with VMAT and DIBH for patients with left breast cancer. Both plans offered excellent coverage of the target area, with no statistically significant difference in CTV coverage: hypofractionation (95.12 ± 1.29) compared to conventional (94.60 ± 1.56), and the p-value was greater than 0.05. This aligns with existing studies that show VMAT's capacity to deliver precise doses to the breast, regardless of the fractionation schedule [18].

In terms of CTV conformity and homogeneity, both regimens demonstrated similar conformity indices, indicating effective dose distribution around the target volume ($p > 0.05$, $t = 1.342$). These results are consistent with a study by Youssef et al. [19], where CI values were similar for both conventional and hypofractionated regimens .

The conventional VMAT approach showed a notable improvement in dose homogeneity compared to the hypofractionated treatment protocol (HI = 0.165 ± 0.038 vs. 0.304 ± 0.090; $p < 0.001$, $t = -5.1$) as shown in Figure 3. A more uniform dose distribution reduces the chances of hotspots or underdosing within the target area, which is significant for maintaining tumor control while minimizing toxicity [20]. These results may suggest a potential advantage of the VMAT technique in enhancing treatment uniformity, particularly when DIBH is used to stabilize target positioning.

Regarding treatment delivery efficiency, the hypofractionated regimen required a significantly higher number of monitor units (MUs), specifically 1969.85 ± 260.9, compared to 1364.12 ± 229.2 for the conventional regimen. The higher dose per fraction and more complex modulation techniques may be necessary to meet dose constraints. The dose received by the heart is an important consideration in left-sided breast radiation therapy due to long-term risks of ischemic heart disease [21]. This study showed that the average heart dose was lower for the hypofractionated group (6.24 Gy) than it was for the conventional group (8.912 Gy). The biological effective dose (BED) refers to the potential dose needed to produce a specific biologic effect in very small fractions [22]. Lowering BED and EQD2 values for OAR suggests a decreased likelihood of late complications, including pneumonitis or ischemic heart disease.

The BED of the Dmean of the heart was decreased by about 28.7% in the hypofractionated group using an α/β ratio of 3 Gy for the heart. This indicates reduced biological damage with hypofractionation, resulting in a BED of 9.98 Gy and an EQD2 of 5.99 Gy for the conventional plan, compared to a BED of 7.11 Gy and an EQD2 of 4.27 Gy in the hypofractionated plan. This finding supports using hypofractionation to reduce cardiac exposure during left breast cancer radiotherapy and is consistent with the study by Jain et al. [23]. Furthermore, for V5% and V25%, the hypofractionated regimen showed better cardiac sparing than the conventional regimen, though with a p-value greater than 0.05.

Radiation exposure to the lungs is an unavoidable side effect of breast radiotherapy, which may increase the risk of pneumonitis and secondary cancers [24]. The study found that the hypofractionated regimen resulted in a slightly lower V20 for the ipsilateral lung, but the difference was not statistically significant ($p = 0.58$). This aligns with a recent study by Mazonaski et al., which indicated that lung doses in conventional plans were higher than in hypofractionated plans [25]. The average lung dose was 12.31 Gy (EQD2: 9.41 Gy) with hypofractionation, while the conventional plan had a marginally lower EQD2 of 9.11 Gy (using $\alpha/\beta = 3$ Gy) as indicated in Table 3. This suggests that the conventional method may provide a slightly greater lung-sparing effect. Additionally, both treatment regimens produced comparable results for V5% in the ipsilateral lung: the conventional regimen had a mean value of 78.67 Gy, while the hypofractionated regimen had a mean of 78.35 Gy.

In contrast, the hypofractionated plan for the contralateral lung resulted in a significantly lower dose exposure ($p = 0.029$, $t = 2.49$), highlighting the clinical value of combining hypofractionation with DIBH in lowering the lung exposure. No statistically significant difference was found for the contralateral breast with a p-value of 0.33.

In conclusion, this research examined both hypofractionated and conventional VMAT treatment strategies for patients with left-sided breast cancer using DIBH techniques. Both approaches provided excellent tumor coverage and similar conformity indices, showing precise and effective dose delivery. The conventional VMAT method offered better dose homogeneity, leading to a more consistent dose distribution within the target.

On the other hand, the hypofractionated VMAT plan noted a tendency for organs at risk (OAR) to be increasingly spared, especially regarding a lower average heart dose and decreased exposure to the contralateral lung, all while maintaining target coverage. These results indicate that hypofractionated VMAT can provide effective protection for the heart and lungs, reinforcing its viability as an effective and patient-friendly treatment option for left-sided breast cancer.

The study has limitations that need consideration. Larger patient cohorts are necessary to achieve higher clinical value, interpret the findings correctly, and understand the significance of the observed effects. Careful attention to bias is essential for interpreting results and guiding clinical practice. To provide a more thorough assessment of the effectiveness of these two regimens, the study includes tumor control probability (TCP) and normal tissue complication probability (NTCP) modeling. These radiobiological metrics offer a better understanding of the balance between tumor control effectiveness and the risk of toxicity to surrounding organs.

Author Contribution Statement

Nourhane Moussawi: Conceptualization, Data curation, Formal analysis, Writing-original draft, Methodology; Wassila El Kanawati: Validation, Project administration, Investigation, Supervision, Writing-review &editing; Hanna El Balaa: Visualization, review

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Scientific Body Approval / Thesis Information

This work was conducted as part of a thesis project approved by the Department of Physics, Faculty of Science, Beirut Arab University.

Data Statement

The data underlying this study's findings cannot be publicly shared due to ethical considerations, including the need to protect privacy and maintain confidentiality.

All figures and images have not been taken or modified from previously published works or external sources.

Study Registration

This study did not involve patient interventions and therefore was not registered in a clinical trial or guideline registration database.

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