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A Comparative Dosimetric and Radiobiological Analysis of 3DCRT, IMRT, and VMAT for Left-Sided Breast Cancer Radiotherapy

Aliaa Mahmoud[1], Wahib Mohamed Attia[2], Ehab Marouf Attalla[3], Hany Samy Attallah[4*]

[1]Maadi Armed Forces Radiotherapy Department, Cairo, Egypt
[2]Physics Department, Faculty of Science, Suez Canal University, Ismailia, Egypt
[3]National Cancer Institute, Cairo University, Cairo, Egypt
[4]Radiation Oncology Department, Armed Forces College of Medicine (AFCM), Cairo, Egypt
Email: *hanysamy2006@yahoo.com

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Abstract

Background: Breast cancer is the most common malignancy in women, and adjuvant radiotherapy for left-sided disease raises important concerns regarding cardiac and pulmonary toxicity. Advanced techniques such as intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) may improve dose conformity compared with three-dimensional conformal radiotherapy (3DCRT), but can increase low-dose exposure to normal tissues. **Methods:** In this retrospective planning study, three techniques—3DCRT, IMRT, and VMAT—were compared for left-sided whole-breast irradiation using both conventional dosimetric metrics and Equivalent Uniform Dose (EUD)-based radiobiological modeling, where EUD represents the biologically equivalent uniform dose corresponding to a heterogeneous dose distribution. Sixteen women with left-sided breast cancer treated at a single institution underwent CT simulation and had three separate plans generated on the same dataset (3DCRT, IMRT, VMAT) with identical prescription dose and uniform dose-volume constraints. Planning target volume (PTV) indices and organs-at-risk (OAR) doses were extracted from dose-volume histograms. Tumor control probability (TCP) and normal tissue complication probability (NTCP) for the heart, ipsilateral and contralateral lungs, and contralateral breast were calculated using Niemierko-based EUD models. **Results:** PTV coverage, minimum dose, and 107% hot-spot volume did not differ significantly among the three techniques, indicating comparable target coverage. VMAT produced significantly higher low-dose cardiac exposure (Heart V10), whereas mean heart dose and Heart V25 were similar across techniques. Ipsilateral lung mean dose and V20 were broadly comparable,

with only modest, non-significant numerical differences between modalities. VMAT yielded significantly higher maximum doses to the contralateral lung and contralateral breast compared with 3DCRT, while mean doses to these structures remained similar. Radiobiological modeling showed no significant difference in TCP between techniques; however, NTCP estimates for the heart and ipsilateral lung were lower with IMRT and VMAT than with 3DCRT, whereas NTCP for contralateral structures did not differ significantly. **Conclusion:** IMRT and VMAT offer radiobiological advantages for modeled cardiac and pulmonary toxicity compared with 3DCRT, while maintaining comparable target coverage, but VMAT is associated with a broader low-dose bath to contralateral structures. These exploratory findings support individualized technique selection that balances target coverage, organ-at-risk sparing, and long-term survivorship considerations in left-sided breast radiotherapy.

Keywords

Breast Cancer, Intensity-Modulated Radiotherapy, Volumetric Modulated Arc Therapy, Dosimetric Comparison

1. Introduction

Breast cancer continues to represent the most commonly diagnosed malignancy among women and remains a significant contributor to cancer-related mortality worldwide [1]. Postoperative radiotherapy plays a pivotal role in enhancing local disease control and survival, especially in patients treated with breast-conserving surgery or those undergoing mastectomy with nodal involvement [2] [3].

Despite these benefits, delivering effective radiation therapy to the left breast presents inherent challenges, largely due to the anatomical proximity of the heart and lungs [4] [5]. Evidence indicates a dose-dependent increase in the risk of cardiovascular morbidity and mortality, with even modest increases in mean heart dose correlating with heightened long-term cardiac events [6] [7]. Similarly, elevated pulmonary doses—especially V20 and mean lung dose—are linked to adverse pulmonary sequelae such as radiation pneumonitis and fibrosis [8] [9].

The complexity of left-sided breast irradiation is further heightened by factors such as large breast volume, use of a boost field, and inclusion of regional lymphatic areas, all of which may contribute to higher exposure of adjacent normal tissues [10] [11]. Historically, 3DCRT has served as the standard radiotherapeutic technique for breast cancer. However, limitations in achieving dose homogeneity and sparing of nearby critical structures, especially in anatomically challenging cases, have prompted interest in more advanced modalities [12] [13].

Techniques like IMRT and VMAT enable improved modulation of radiation

dose distribution, potentially enhancing conformity and reducing dose to OARs [14] [15]. Comparative dosimetric studies and meta-analyses suggest these modalities may improve target coverage and mitigate hot spots, though concerns regarding a wider low-dose distribution persist [16] [17]. Thus, the decision to adopt one modality over another is often guided by institutional capabilities, treatment planning expertise, and patient-specific factors [15] [18].

Radiobiological modeling tools, particularly the Equivalent Uniform Dose (EUD)-based formulations developed by Niemierko, offer deeper insight into the clinical trade-offs associated with different radiotherapy techniques by complementing physical dosimetric indices with estimates of Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP). In this model, EUD is defined as:

$$EUD = \left(\sum_i v_i D_i^a \right)^{\left\{ \frac{1}{a} \right\}}$$

where *vi* represents the fractional volume receiving dose *Di*, and *a* is a tissue-specific parameter describing volume effect (negative for tumors, positive for normal tissues). TCP was calculated using Niemierko's logistic equation:

$$TCP = \backslash frac\{1\}\left\{1 + \left(\backslash frac\{EUD\}\{TCD_{\{50\}}\} \right)^{\{4\gamma_{\{50\}}\}} \right\}$$

while NTCP was estimated using the analogous normal-tissue formulation:

$$NTCP = \backslash frac\{1\}\left\{1 + \left(\backslash frac\{TD_{\{50\}}\}\{EUD\} \right)^{\{4\gamma_{\{50\}}\}} \right\}$$

Organ-specific biological parameters (TD_{50}, γ_{50}, and where applicable the α/β ratio) were selected from previously validated datasets. For the breast target, TCP modeling used TCD_{50} = 52.3 Gy, γ_{50} = 1.5, and α/β = 4 Gy. NTCP for the ipsilateral lung corresponded to the risk of radiation pneumonitis (TD_{50} = 29.9 Gy, γ_{50} = 1.19, α/β = 3 Gy), while NTCP for the heart represented long-term cardiac morbidity (TD_{50} = 52 Gy, γ_{50} = 1.28, α/β = 3 Gy). Contralateral lung and contralateral breast NTCP estimates reflected the risk of radiation-induced secondary carcinogenesis, with the endpoint defined as the probability of a secondary malignant neoplasm (excess absolute risk), adopting parameter sets consistent with published modeling work in low-dose exposure scenarios [19].

This study aims to compare 3DCRT, IMRT, and VMAT in a single patient cohort, analyzing each technique in terms of PTV coverage, dose to OARs, and radiobiological modeling outputs (TCP and NTCP). The goal is to provide evidence to inform personalized and institutionally feasible decision-making in the modern era of breast radiotherapy. We hypothesized that, compared with 3DCRT, IMRT and VMAT would achieve similar tumor control probability for the breast target but lower normal tissue complication probability for the heart and ipsilateral lung, at the cost of increased low-dose exposure to contralateral structures, particularly with VMAT.

2. Patients and Methods

2.1. Study Design and Patient Selection

This retrospective planning study included 16 female patients diagnosed with left-sided breast cancer who were treated with adjuvant radiotherapy at the Department of Radiation Oncology, International Medical Center (IMC), Cairo, Egypt. Treatment was initially administered using one of three modalities based on the treating physician's discretion: five patients received VMAT, six were treated with 3DCRT, and five underwent IMRT. For the purpose of this dosimetric comparison, each patient subsequently had two additional plans generated using the other two techniques, allowing for a within-subject comparison across all three modalities.

The sample size of sixteen patients reflects the total number of consecutively treated left-sided breast cancer cases that met the strict inclusion criteria during the study period. Because this investigation represents a retrospective planning study without clinical endpoints, no formal power analysis was required. Similar dosimetric comparative studies in breast radiotherapy have used comparable sample sizes, providing adequate within-subject power for repeated-measures comparisons.

2.2. Simulation and Imaging

Patients were immobilized in a supine position with both arms elevated above the head using a breast board to ensure reproducibility and stability. A planning CT scan was acquired for each patient using a 64-slice spiral CT scanner (GE Medical Systems), with axial images reconstructed at 5 mm slice thickness. The scan extended from the mandible to the inferior thoracic border to ensure complete anatomical coverage of the breast and adjacent structures.

2.3. Target Volume and OAR Delineation

The Clinical Target Volume (CTV) was defined as the entire left breast. A uniform isotropic expansion of 5 mm around the CTV was applied to generate the Planning Target Volume (PTV), following institutional standards. Organs at Risk (OARs) included the ipsilateral lung, contralateral lung, heart, contralateral breast, and spinal cord. All contours were delineated by an experienced radiation oncologist according to institutional protocols and reviewed for consistency. Contouring and planning were performed using the Eclipse™ Treatment Planning System version 15.6 (Varian Medical Systems, Palo Alto, CA).

2.4. Treatment Planning Techniques

Each patient had three separate radiotherapy plans generated—3DCRT, IMRT, and VMAT—on the same planning CT dataset to maintain uniformity in anatomical conditions (Table 1). All plans were prescribed to deliver the same total dose, and dose-volume constraints for PTV and OARs were applied uniformly across all plans.

2.4.1. 3DCRT

3DCRT plans employed 6, 10, or 15 MV photon beams arranged tangentially with isocentric alignment. Gantry angles were optimized using beam's-eye view (BEV) to minimize irradiation of the contralateral breast. For patients with larger breast volumes, a field-in-field technique was applied to improve dose homogeneity. Dose calculations were performed using the Anisotropic Analytical Algorithm (AAA).

2.4.2. IMRT

IMRT plans were generated using 6 MV photons with 5 to 8 static fields arranged tangentially around the isocenter. Beam angles were selected to optimize conformity while reducing dose to OARs. All IMRT plans were inverse-planned with dose constraints specified for both target and OARs.

2.4.3. VMAT

VMAT plans used two coplanar full arcs (clockwise and counter-clockwise) of 6 MV photon energy. The arc start and end angles were modified (abducted) between 10˚ and 25˚ relative to tangential baselines to limit low-dose exposure to contralateral structures. A collimator rotation of 5˚ and a fixed couch angle (0˚) were used. The maximum dose rate was set at 600 MU/min.

2.5. Dosimetric Evaluation

All dosimetric parameters were extracted from Dose Volume Histograms (DVHs). The following dosimetric indices were extracted for each technique:

2.5.1. For PTV

- Maximum and minimum dose percentages (PTV Max %, PTV Min %);
- Volume of PTV receiving ≥107% of the prescribed dose;
- PTV100% volume (absolute volume of PTV receiving 100% of the dose);
- D_2, D_{98}, and D_{50} (dose received by 2%, 98%, and 50% of the PTV);
- Conformity Index (CI) = Body volume receiving 100% of the prescribed dose/PTV volume;
- Homogeneity Index (HI) = $(D_2 - D_{98})/D_{50}$.

2.5.2. For OARs

- **Ipsilateral lung**: V10, V20, mean dose (Gy);
- **Contralateral lung**: V5, V10, mean and maximum dose (Gy);
- **Heart**: Mean dose (Gy), V5, V10, V25 (%);
- **Contralateral breast**: Mean and maximum dose (Gy);
- **Body**: Volume receiving 100% of the prescribed dose (cc).

2.6. Radiobiological Modeling

Radiobiological outcomes were calculated using established Equivalent Uniform Dose (EUD)-based models for TCP and NTCP. The Niemierko formalism was employed, with organ-specific parameters referenced from prior validated litera-

ture [20] [21]. The endpoints assessed included:

- TCP (%) for the left breast, representing the modeled probability of tumor control;
- NTCP (%) for the ipsilateral lung and heart, representing the modeled probability of clinically relevant radiation pneumonitis and long-term cardiac morbidity, respectively;
- NTCP (%) for the contralateral lung and contralateral breast, representing the modeled risk of radiation-induced secondary malignant neoplasms (excess absolute risk) in these organs.

Table 1. 3DCRT, IMRT and VMAT beam arrangements.

Technique	Photon Energy	Field Arrangement	Algorithm
3DCRT	6, 10 and 15 MV	Tangential field/Isocentric Gantry angles were selected using the beam's eye view of the Eclipse treatment planning system, avoiding direct exposure of the contralateral breast; . In large breast field-in-field technique was used to reduce hot spots.	AAA
IMRT	6 MV only	5 - 8 fields (Isocentric, Static with tangential field setup)	
VMAT	6 MV only	Two double arcs (clockwise and antic lock wise) to disperse field, abduction of 10˚ - 25˚ by tangent field as starting and ending angle each way, with collimator angle 5˚, treatment couch angle 0˚, maximum dose rate 600 MU/min.	

3. Statistical Analysis

All quantitative variables were analyzed using IBM SPSS Statistics version 20. The choice of statistical test was guided by the distributional characteristics of each variable. Because each patient contributed three radiotherapy plans (3DCRT, IMRT, and VMAT), all analyses were performed using repeated-measures statistical tests. The distribution of each dosimetric and radiobiological variable was assessed using the Shapiro-Wilk test. Variables that met the assumption of normality were analyzed using a repeated-measures analysis of variance (RM-ANOVA). A p-value < 0.05 was considered statistically significant.

For variables that did not satisfy normality assumptions, the non-parametric Friedman test was employed to compare the three techniques. Post-hoc comparisons for RM-ANOVA were performed using Bonferroni-adjusted pairwise tests, while Friedman-based analyses were followed by Wilcoxon Signed-Rank tests with Bonferroni correction (p-value < 0.017 considered statistically significant).

4. Ethical Issue

The study protocol was reviewed and approved by the Faculty of Science Canal University, Ismailia 41522, Egypt. It has been passed by Committee No. 8.

5. Results

A comprehensive assessment of distributional characteristics using the Shapiro-Wilk test revealed that the dosimetric variables exhibited mixed patterns of normality. The Lung Mean Dose and Lung V20 were normally distributed across the three planning techniques and therefore met the assumptions required for parametric testing. Subsequently, we analyzed these variables using RM-ANOVA. In contrast, all remaining structure-specific dosimetric indices, including PTV parameters (maximum dose, minimum dose, and volume receiving 107%), cardiac metrics (Heart V10, Heart V25, and heart mean dose), pulmonary low-dose metrics (Lung V10), and contralateral organ doses (breast and lung mean and maximum doses), demonstrated non-normal distributions. Similarly, all radiobiological variables (TCP, NTCP Left Lung, NTCP Contralateral Lung, NTCP Heart, and NTCP Contralateral Breast) violated normality assumptions. These variables were therefore analyzed using the non-parametric Friedman test, followed when appropriate by Wilcoxon Signed-Rank post-hoc comparisons with Bonferroni correction (adjusted $\alpha = 0.017$).

5.1. Planning Target Volume (PTV) Dosimetric Comparison

The comparison of planning target volume (PTV) dosimetric parameters across the three radiotherapy techniques, demonstrated no statistically significant differences. The maximum PTV dose showed a modest trend toward higher values with 3DCRT (mean rank = 2.31) compared with IMRT (1.88) and VMAT (1.81), although this pattern did not reach statistical significance ($p = 0.276$). Similarly, minimum PTV dose values were nearly indistinguishable among the three techniques ($p = 0.886$), with IMRT displaying a slightly higher mean rank (2.09). The hotspot volume receiving 107% of the prescribed dose, also did not differ significantly across techniques ($p = 0.570$), although 3DCRT showed a numerically higher tendency (mean rank = 2.19) (Table 2).

Table 2. PTV dosimetric.

	3DCRT	IMRT	VMAT	p-value
	Mean Rank			(Friedman test)
PTV Max (%)	2.31	1.88	1.81	0.276
PTV Min (%)	1.94	2.09	1.97	0.886
107% Volume (%)	2.19	1.81	2.00	0.570

5.2. Organs at Risk (OARs) Comparison

The Friedman test demonstrated no statistically significant difference in Heart Mean Dose ($p = 0.523$) or Heart V25 ($p = 0.066$) across 3DCRT, IMRT, and

VMAT. In contrast, Heart V10 showed a statistically significant overall difference ($p = 0.002$). Post-hoc Wilcoxon signed-rank testing, applying the Bonferroni-adjusted significance threshold ($\alpha = 0.017$), revealed that VMAT produced significantly higher Heart V10 values compared with both 3D-CRT ($p = 0.001$) and IMRT ($p = 0.006$). The comparison between 3DCRT and IMRT was not statistically significant ($p = 0.313$). No other pairwise differences reached statistical significance (Table 3).

Table 3. Heart dosimetric.

	3DCRT	IMRT	VMAT	p-value (Friedman test)	
	Mean Rank				
Heart Mean Dose (Gy)	1.78	2.09	2.13	0.523	
Heart V25 (%)	1.81	1.72	2.47	0.066	
Heart V10 (%)	1.50	1.81	2.69	0.002 3D vs IMRT: 0.313 3D vs VMAT: 0.001 IMRT vs VMAT: 0.006	Wilcoxon Signed-Rank

For Lung Mean Dose, the repeated-measures ANOVA indicated a statistically significant overall difference among techniques ($p = 0.043$). However, after Bonferroni-adjusted pairwise comparisons, none of the technique pairs reached statistical significance, with p-values of 0.109 (3DCRT vs IMRT), 0.116 (3DCRT vs VMAT), and 1.000 (IMRT vs VMAT). This apparent discrepancy reflects the fact that the omnibus RM-ANOVA tested for any global difference at the conventional $\alpha = 0.05$ level, whereas the Bonferroni-adjusted post-hoc tests applied a more stringent significance threshold ($p < 0.017$) to control for multiple comparisons, resulting in no individual pairwise contrast meeting this corrected criterion.

For Lung V20, the RM-ANOVA did not reveal a significant overall effect ($p = 0.135$), and all pairwise comparisons were also non-significant. For Lung V10, assessed using the Friedman test due to non-normal distribution, no statistically significant difference was observed among the three techniques ($p = 0.399$), and therefore no post-hoc pairwise testing was required (Table 4).

Table 4. Pulmonary dosimetric.

	3DCRT	IMRT	VMAT	p-value	Statistical Test	Pairwise Comparisons
	Mean ± SD					
Lung Mean Dose (Gy)	17.75 ± 7.91	22.19 ± 5.22	22.38 ± 7.82	0.043	RM-ANOVA	3D vs IMRT: 0.109 3D vs VMAT: 0.116 IMRT vs VMAT: 1.000 (Bonferroni-adjusted)

Continued

Lung V20 (%)	20.75 ± 2.93	17.81 ± 6.25	20.38 ± 6.61	0.135		3D vs IMRT: 0.132 3D vs VMAT: 1.000 IMRT vs VMAT: 0.395 (Bonferroni-adjusted)
Lung V10 (%)	1.78	Mean Rank 2.25	1.97	0.399	Friedman test	NA

For Contralateral Lung Mean Dose, the Friedman test showed no statistically significant difference across the three techniques (p = 0.744). In contrast, Contralateral Lung Max Dose demonstrated a significant overall difference (p = 0.001). Post-hoc Wilcoxon testing indicated that the comparison between 3DCRT and VMAT reached statistical significance (p = 0.002), whereas the 3DCRT vs IMRT (p = 0.041) and IMRT vs VMAT (p = 0.181) comparisons did not meet the Bonferroni-adjusted significance threshold. For Contralateral Breast Mean Dose, no significant difference was detected between techniques (p = 0.721). Contralateral Breast Max Dose showed a statistically significant global difference (p = 0.001), with Bonferroni-corrected Wilcoxon comparisons indicating significant differences only between 3DCRT and VMAT (p = 0.001), while the 3DCRT vs IMRT (p = 0.083) and IMRT vs VMAT (p = 0.556) comparisons were not statistically significant. Finally, Body Volume 100% demonstrated no significant variation among the three planning techniques (p = 0.444) (Table 5).

Table 5. Contralateral structures and body dosimetric.

	3DCRT	IMRT	VMAT	p-value	
	Mean Rank			(Friedman test)	
Contralateral Lung Mean Dose (Gy)	2.13	2.00	1.88	0.744	
Contralateral Lung Max Dose (Gy)	1.34	2.09	2.56	*0.001* 3D vs IMRT: 0.041 3D vs VMAT: *0.002* IMRT vs VMAT: 0.181	Wilcoxon Signed-Rank
Contralateral Breast Mean Dose (Gy)	2.09	2.06	1.84	0.721	
Contralateral Breast Max Dose (Gy)	1.31	2.13	2.56	*0.001* 3D vs IMRT: 0.083 3D vs VMAT: *0.001* IMRT vs VMAT: 0.556	Wilcoxon Signed-Rank
Body Volume 100%	1.94	2.25	1.81	0.444	

5.3. Radiobiological Comparison

Table 6 presents the tumor control probability (TCP) and normal tissue complication probability (NTCP) outcomes across the three radiotherapy techniques. TCP for the breast target did not differ significantly between 3DCRT, IMRT, and VMAT (p = 0.138). For NTCP of the left lung, the Friedman test demonstrated a statistically significant difference across the three techniques (p < 0.001). Post-hoc

Wilcoxon analyses showed that the comparison between 3DCRT and VMAT was statistically significant (p = 0.001), while the comparisons of 3DCRT vs IMRT (p = 0.009) and IMRT vs VMAT (p = 0.285) did not meet the Bonferroni-adjusted significance threshold. NTCP for the contralateral lung showed no statistically significant overall difference (p = 0.071). For NTCP of the heart, a significant difference was detected (p = 0.002). Wilcoxon pairwise testing revealed statistically significant differences between 3D-CRT and IMRT (p = 0.003) and between 3DCRT and VMAT (p = 0.003). The IMRT vs VMAT comparison was not statistically significant (p = 1.000). Finally, NTCP for the contralateral breast did not show significant variation across the three techniques (p = 0.159).

Table 6. TCP/NTCP dosimetric.

	3DCRT	IMRT	VMAT	p-value (Friedman test)	
	Mean Rank				
TCP (%) Breast	1.63	2.16	2.22	0.138	
NTCP Left Lung	2.81	1.72	1.47	*<0.001* 3D vs IMRT: *0.009* 3D vs VMAT: *0.001* IMRT vs VMAT: 0.285	Wilcoxon Signed-Rank
NTCP Contralateral Lung	1.69	2.34	1.97	0.071	
NTCP Heart	2.63	1.66	1.72	*0.002* 3D vs IMRT: *0.003* 3D vs VMAT: *0.003* IMRT vs VMAT: 1.000	Wilcoxon Signed-Rank
NTCP Contralateral Breast	2.31	1.78	1.91	0.159	

6. Discussion

This retrospective planning study compared three contemporary techniques—3DCRT, IMRT, and VMAT—for left-sided whole-breast irradiation using both dosimetric indices and EUD-based TCP/NTCP modeling. Overall, the three techniques achieved comparable PTV coverage, while showing meaningful differences in selected OAR endpoints and corresponding NTCP estimates. In particular, advanced techniques (IMRT and VMAT) improved modeled cardiac and ipsilateral lung risk relative to 3DCRT, at the cost of higher contralateral maximum doses with VMAT and a broader "low-dose bath." These findings are broadly consistent with the evolving literature on breast radiotherapy planning, in which modern techniques tend to trade improved conformity and proximal organ sparing for increased low-dose spread to more distant tissues. The absence of statistically significant differences in PTV maximum dose, minimum dose, or 107% hot-spot volume across 3DCRT, IMRT and VMAT indicates that, in a controlled planning environment, all

three modalities can achieve adequate and broadly comparable target coverage. This aligns with previous multi-technique comparisons in left-sided whole-breast irradiation (WBI). Schubert *et al.* reported that 3DCRT, forward-planned IMRT, inverse-planned IMRT, and tomotherapy all provided clinically acceptable PTV coverage when optimized according to common constraints, with only modest technique-dependent differences in homogeneity indices [14]. Similarly, more recent work comparing hybrid IMRT and VMAT plans following breast-conserving surgery has shown that both techniques can meet target coverage requirements, with differences emerging primarily at the level of OAR sparing rather than TCP surrogates [22]. The lack of statistically significant differences in PTV metrics in the present cohort therefore suggests that, when planning expertise and dose-volume objectives are consistently applied, technique choice is unlikely to be driven by target coverage alone. Instead, the selection between 3DCRT, IMRT, and VMAT should be guided by their differential impact on OAR doses and the institutional priorities regarding cardiac, pulmonary, and contralateral tissue protection.

Cardiac protection remains a central concern in left-sided breast radiotherapy, given robust epidemiologic evidence for a linear increase in major coronary events—approximately 7% per Gy increase in mean heart dose—with no apparent threshold [6]. In this study, mean heart dose and Heart V25 did not differ significantly between techniques, yet Heart V10 was significantly higher with VMAT than with either 3DCRT or IMRT. This pattern is consistent with the general dosimetric behavior of arc therapy, which tends to reduce high-dose volumes near the target while distributing low doses more broadly across surrounding tissues [14].

Despite the higher low-dose cardiac exposure with VMAT (Heart V10), the EUD-based NTCP modeling in this analysis indicated a significantly lower NTCP for cardiac morbidity for both IMRT and VMAT compared with 3DCRT, with no significant difference between the two advanced techniques. This reflects the fact that the NTCP model is more strongly driven by the higher-dose portion of the DVH (in line with QUANTEC data on heart dose-volume effects), where 3DCRT typically delivers larger volumes at intermediate-high dose levels [23]. The present findings therefore support a nuanced interpretation: IMRT and VMAT can reduce modelled long-term cardiac risk relative to 3DCRT, even if VMAT incurs a higher low-dose cardiac bath.

These results are in line with previous dosimetric and clinical modeling studies. Systematic reviews of heart exposure in breast RT have consistently shown that more conformal techniques and breath-hold approaches reduce mean heart dose and reduce predicted cardiac event rates compared with older tangential techniques. Studies such as Merino Lara *et al.* and Drost *et al.* have further quantified the translation of mean heart dose to estimated absolute excess cardiac events, reinforcing the importance of even modest dose reductions in long-term survivors [11] [12]. Within that context, the reduction in modeled cardiac NTCP with IMRT and VMAT in our cohort, though derived from a small sample and subject to parameter uncertainty, suggests potential clinical benefit if these dosimetric

gains are reproducible in larger, prospectively treated populations.

For the ipsilateral lung in our cohort, Lung Mean Dose showed a statistically significant overall difference on RM-ANOVA, but no pairwise comparison remained significant after Bonferroni correction, and Lung V20 and V10 were not significantly different across techniques. Thus, in this small cohort, the three techniques achieved broadly comparable high-dose pulmonary exposure at the physical DVH level. However, the NTCP modeling for the ipsilateral lung (pneumonitis endpoint) demonstrated a significant global difference, with lower NTCP values for IMRT and particularly VMAT compared with 3DCRT, and only the 3DCRT-VMAT contrast remaining significant after multiplicity adjustment. This illustrates how EUD-based models can amplify relatively subtle changes in the mid-to-high dose region into larger differences in predicted complication probability, especially when the model parameters are steep in the clinically relevant dose range [24]. These observations are compatible with prior QUANTEC-based analyses and clinical-dosimetric studies. Marks *et al.* and subsequent work have emphasized the predictive value of V20 and mean lung dose for radiation pneumonitis [9] [23]. While we did not observe large absolute differences in V20, the combination of modest reductions in mid-dose volumes and the more favorable shape of the VMAT DVH may help explain the lower modeled NTCP. Comparable trends—reduced calculated lung complication risks with IMRT/VMAT relative to 3DCRT when constrained to similar target coverage—have also been reported in other breast and thoracic cohorts using Niemierko-type models [24].

A key finding of this study is the significant increase in maximum dose to contralateral lung and contralateral breast with VMAT compared with 3DCRT, while mean doses to these organs remained similar and no significant differences were seen for IMRT. This is consistent with prior reports that VMAT, by virtue of its rotational delivery and large arc span, tends to increase the volume of tissue receiving low to intermediate doses, including contralateral organs and more distant normal tissues [14].

The clinical implications of this "low-dose bath" are complex. Epidemiologic and modeling studies suggest that the risk of radiation-induced secondary malignancies correlates with both integral dose and the volume of tissue exposed to low and moderate doses, especially in younger patients with long life expectancy [25]. In breast cancer, this has raised specific concerns regarding contralateral breast cancer and second primary lung cancers when using highly modulated or arc-based techniques. While absolute risks remain small compared with the survival benefit of adjuvant radiotherapy, these considerations argue for caution in routine use of wide-arc VMAT in young, low-risk patients when equivalent target coverage and OAR protection can be achieved with less distributive techniques. From a planning perspective, the present data reinforce the need to explicitly constrain contralateral organ doses and to consider arc truncation, partial arcs, or hybrid techniques if VMAT is selected. They also underscore the importance of integrating both NTCP for deterministic endpoints (e.g., pneumonitis, cardiac events)

and long-term stochastic risks (secondary cancers) into patient-tailored decision making rather than focusing solely on local DVH reductions around the target.

The use of Niemierko's EUD-based TCP and NTCP formulations allowed this study to move beyond purely geometric dose comparisons and explore the potential clinical impact of the observed dosimetric differences [24]. TCP for the breast target did not differ significantly between 3DCRT, IMRT, and VMAT, reflecting the comparable PTV coverage and moderate dose heterogeneity across techniques. This is in line with previous modeling-based comparisons in breast radiotherapy, where advanced techniques rarely show large gains in TCP if the prescribed dose and coverage constraints are standardized across plans [26].

By contrast, NTCP estimates for ipsilateral lung and heart showed significant reductions with IMRT and VMAT relative to 3DCRT. These findings echo the QUANTEC-derived expectation that even small reductions in mean dose and high-dose volumes for these organs may translate into meaningful changes in long-term toxicity risk. However, several caveats must be emphasized. First, NTCP values are model-dependent and sensitive to the choice of parameter sets (TD_{50}, γ_{50}, α/β), which are derived from heterogeneous historical cohorts with different fractionation, techniques, and comorbidities. Second, NTCP modeling assumes uniform applicability of dose-response relationships across populations, which may not hold in contemporary, cardio-oncology-aware breast cancer cohorts with improved supportive care. Third, the small sample size in the present planning study magnifies statistical uncertainty, so that the absolute magnitude of NTCP differences should be interpreted cautiously and viewed as hypothesis-generating rather than definitive [23].

Taken together, the radiobiological results support the qualitative conclusion that IMRT and VMAT are unlikely to compromise tumor control compared with 3DCRT and may reduce the risk of major cardiac and pulmonary toxicity in appropriately selected patients. At the same time, the potential offsetting increase in low-dose exposure and secondary cancer risk with VMAT highlights the importance of contextualizing model outputs within a broader, lifetime-risk framework [25].

Modern left-sided breast radiotherapy increasingly combines advanced planning techniques with motion-management strategies, particularly deep-inspiration breath-hold (DIBH). Multiple studies have shown that DIBH, by increasing the heart-chest wall distance and expanding lung volume, substantially reduces mean heart dose and cardiac substructure doses across a range of beam arrangements, including 3DCRT, IMRT, and VMAT [25]. Our study was conducted on free-breathing CT datasets and therefore reflects the relative performance of the three techniques under standard conditions. In centers where DIBH is routine, absolute heart and lung doses would be expected to decrease for all modalities; however, the relative ranking between 3DCRT, IMRT, and VMAT might persist, albeit at lower absolute dose and NTCP levels. It is also plausible that the magnitude of the observed cardiac and pulmonary NTCP differences between 3DCRT

and more conformal techniques could be attenuated under DIBH, particularly if tangential 3DCRT benefits disproportionately from the increased heart-chest wall separation, although residual advantages for IMRT or VMAT may remain in anatomically complex cases.

Similarly, prone positioning, partial breast irradiation approaches, and hybrid techniques (e.g., combining tangential 3DCRT or IMRT with limited VMAT arcs) have been explored as means of balancing target coverage, OAR sparing, and secondary cancer risk [14]. The present data support such individualized, technique-agnostic planning strategies: when a simple tangential 3DCRT or forward-planned IMRT plan already achieves excellent PTV coverage and OAR protection, the incremental benefit of full-arc VMAT may be small and must be weighed against low-dose bath concerns. Conversely, in anatomically complex cases or when nodal targets are included, the superior modulation and NTCP profile of IMRT or carefully constrained VMAT may justify their preferential use.

7. Strengths and Limitations

This study has several strengths. The within-patient design, in which three plans were generated for each individual, eliminates inter-patient anatomical variability and allows robust comparison of technique-specific dosimetric and radiobiological differences. Plan generation adhered to contemporary contouring standards and was performed using a single planning system with uniform dose-volume constraints, minimizing planning heterogeneity and reducing technique-driven bias. Furthermore, the incorporation of EUD-based TCP and NTCP modeling provided a biologically informed complement to physical DVH evaluation, enhancing the interpretability of differences observed across radiotherapy modalities.

However, several limitations must be acknowledged. First, the relatively small sample size of sixteen patients—though consistent with similar dosimetric planning studies—limits statistical power and increases the risk of type II error. The exploratory nature of the analysis and absence of a formal power calculation further underscore the need for cautious interpretation, particularly for variables that approached but did not reach statistical significance (e.g., Lung Mean Dose, Heart V25, NTCP for contralateral lung). Second, the study is purely planning-based, without clinical follow-up or toxicity outcomes to validate the modeled TCP and NTCP estimates. As emphasized in QUANTEC and subsequent work, NTCP models involve substantial parameter uncertainty and should guide, but not dictate, clinical decision-making.

Third, the findings are contingent on the specific planning assumptions employed—free-breathing CT simulation, fixed prescription dose, choice of beam energies, and distinct beam geometries (including the use of full dual arcs for VMAT). Modifications such as deep-inspiration breath-hold (DIBH), partial arcs, alternative energy selection, or different institutional OAR constraints may produce different dose-response relationships.

An important consideration when interpreting these results is the broader low-dose exposure characteristic of VMAT. Although VMAT enhances conformity and can reduce high-dose volumes, its rotational delivery inherently distributes low-dose radiation to larger volumes of normal tissue. This "low-dose bath" introduces theoretical concerns regarding secondary malignancy risk, particularly in younger patients and long-term survivors. Existing evidence indicates that second-cancer risk is associated with both integral dose and the extent of low-dose exposure, underscoring the need for careful patient selection and dose-constraint enforcement when employing arc therapy in breast irradiation. In our cohort, this issue is directly relevant to the finding of significantly higher maximum doses to the contralateral lung and contralateral breast with VMAT compared with3DCRT.

Finally, the study did not formally model secondary cancer risk. Consequently, the discussion of carcinogenesis associated with contralateral organ exposure remains qualitative and extrapolates from external epidemiologic and modeling literature rather than from patient-specific predictions within this cohort. This limitation implies that we cannot quantitatively determine whether the apparent reductions in modeled cardiac and ipsilateral lung NTCP with IMRT/VMAT are partially offset by an increased long-term stochastic risk in contralateral tissues, highlighting formal second-cancer risk modeling as an important avenue for future investigation. Finally, the study did not formally model secondary cancer risk. Consequently, the discussion of carcinogenesis associated with contralateral organ exposure remains qualitative and extrapolates from external epidemiologic and modeling literature rather than from patient-specific predictions within this cohort.

8. Future Directions

Future research should prioritize prospective or registry-based observational studies that systematically link advanced planning techniques with detailed substructure-level dosimetry and long-term clinical outcomes, including cardiac morbidity, pneumonitis, and second primary malignancies. Integrating contemporary cardio-oncology risk stratification, assessment of competing mortality risks, and patient-reported outcomes would provide a more holistic understanding of the net clinical benefit of IMRT and VMAT relative to 3DCRT. Methodologically, refinement and re-parameterization of TCP and NTCP models using modern breast radiotherapy cohorts—particularly those incorporating deep-inspiration breath-hold (DIBH), hypofractionated schedules, and detailed cardiac substructure delineation—may enhance the reliability and applicability of radiobiological estimates. From a technical standpoint, exploration of hybrid IMRT/VMAT strategies, constrained-arc or partial-arc VMAT designs, and advanced modalities such as proton therapy or ultrahigh-dose-rate FLASH radiotherapy for selected high-risk cases could help optimize the balance between target coverage and normal-tissue protection. The development of automated or knowledge-based plan-

ning systems that explicitly optimize NTCP and secondary cancer risk metrics represents another promising avenue toward increasingly personalized, risk-adapted breast radiotherapy.

9. Conclusion

This planning study demonstrates that 3DCRT, IMRT, and VMAT can all achieve comparable target coverage for left-sided breast irradiation, yet they differ in their impact on organs at risk. IMRT and VMAT showed lower modeled cardiac and ipsilateral lung toxicity relative to 3DCRT, whereas VMAT was associated with greater low-dose exposure to contralateral structures. These findings indicate that advanced techniques may confer radiobiological advantages in appropriately selected patients, but the broader low-dose bath characteristic of VMAT warrants careful consideration—particularly in younger patients and long-term survivors. Given the small cohort and planning-only design, these results should be interpreted as exploratory and support an individualized selection of radiotherapy technique based on patient anatomy, institutional capabilities, toxicity priorities, and survivorship expectations.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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