

Bilateral Lumpectomy for Bilateral Breast Cancer, Comparative Study Between Adjuvant 3DCRT and VMAT Radiotherapy

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Abstract

Objective: This study aimed to assess the treatment methods and results linked to adjuvant three-dimensional conformal radiation therapy (3DCRT) compared to volumetric modulated arc therapy (VMAT) radiotherapy following bilateral lumpectomy for breast cancer.

Methods: This prospective comparative study involved 22 female patients diagnosed with bilateral breast cancer, all of whom underwent bilateral lumpectomy. Treatment planning was performed using the MONACO version 5.1 treatment planning system (TPS), employing X-ray photon beams with energies of either 6 MV or 10 MV. Radiotherapy was delivered using the ELEKTA Agility linear accelerator. A total prescribed dose of 4005 cGy was administered over 15 fractions.

Results: The study compares the performance of volumetric modulated arc therapy (VMAT) and three-dimensional conformal radiation therapy (3DCRT) in various parameters. VMAT shows better dose coverage for planning target volumes (PTVs) and regions of elevated radiation (V105% and V110%). However, 3DCRT shows slightly higher efficacy for the left planning target volume, particularly in the V90% metric. VMAT also shows superior performance in terms of homogeneity and conformity for the target volume. However, there is a significant difference in the left PTV, but no significant difference is found in the right PTV. The results suggest that 3D treatment planning is more effective in reducing the average dose to the heart and left and right lungs compared to VMAT. The discrepancy in average lung dosage between the left and right sides is less prominent in 3DCRT compared to VMAT.

Conclusion: The study reveals that volumetric modulated arc therapy (VMAT) offers better dose coverage for planned target volumes in bilateral lumpectomy for breast cancer. At the same time, 3DCRT minimises radiation exposure to the left PTV. VMAT has better homogeneity and conformity indexes for acceptable goal volumes.

Keywords: Breast neoplasms, radiotherapy, intensity-modulated, radiotherapy, conformal, radiotherapy planning, computer-assisted, mastectomy, segmental

Introduction

Bilateral breast cancer denotes the concurrent occurrence of cancerous growths in both breasts. Breast cancer is typically diagnosed unilaterally, predominantly impacting a single breast. Nevertheless, individuals can acquire cancer in both breasts concurrently or sequentially.¹⁻⁴ Two primary classifications of bilateral breast cancer exist: Synchronous Bilateral Breast Cancer (SBBC) and Metachronous Bilateral Breast Cancer (MBBC). Synchronous bilateral breast cancer refers to the simultaneous or near-simultaneous detection of cancers in both breasts, often occurring within a timeframe of six months. Each breast cancer is regarded as an individual original tumour. Metachronous bilateral breast cancer refers to the occurrence of cancer in the contralateral breast following a substantial period after the initial diagnosis and treatment of breast cancer in the ipsilateral breast.⁵

Furthermore, it is important to note that these basic tumours are distinct entities, and the subsequent manifestation should not be interpreted as a metastatic spread originating from the first breast cancer. Risk factors associated with the development of bilateral breast cancer encompass a familial predisposition to breast cancer, certain genetic abnormalities (such as BRCA1 and BRCA2 mutations), and a personal history of breast cancer in a single breast.⁶

The prevalence of bilateral breast cancer, characterised by the occurrence of cancer in both breasts, is comparatively lower than that of unilateral breast cancer, which refers to

cancer affecting just one breast. The predominant occurrence of breast cancer is typically identified unilaterally. As shown in epidemiological surveys, bilateral breast cancer is significantly determined by a combination of interdependent factors such as hereditary predispositions, family history, and predisposing risk factors. The exact proportion of both variables is currently under research. Still, the development of the contralateral tumor conclusively emphasizes the necessity of very accurate follow-up and customized approaches in all patients with unilateral disease.^{7,8}

The prevalence may exhibit variability among many populations and temporal periods. Based on the statistical data of 2021, it is predicted that around 2–5% of all breast cancer diagnoses are characterised as bilateral instances.⁹ Several risk factors are associated with the development of bilateral breast cancer, such as genetic factors, genealogical background, age, individual background, and hormone replacement therapy (HRT).¹⁰ The care of bilateral breast cancer encompasses a range of therapeutic modalities, including surgical interventions such as lumpectomy or mastectomy, radiation therapy, chemotherapy, hormone therapy, and targeted therapy. Treatment decisions are frequently customised according to several circumstances, such as the disease stage, the specific form of breast cancer, and the patient's overall health status.¹¹⁻¹⁴

There is a significant breakthrough in radiation therapy referred to as 3DCRT because it is better than the previous two-dimensional plans. It allows three-dimensional localisation of tumours, reduces irradiation of healthy surrounding

tissue, allowing greater doses to the target volume and improving cure rates, and at the same time minimising toxicity.^{15–18} The principles ingrained into 3DCRT are still being applied in modern radiation therapy practice. However, the more comprehensive and multidimensional application has taken the form of intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT) in most clinical settings, replacing 3DCRT.^{19–22}

Volumetric Modulated Arc Therapy (VMAT) is a modern radiation therapy method in which the treatment apparatus utilizes a full back-to-back rotational motion around the patient, which facilitates sustained transmission of radiation. The dynamic Multi-Leaf Collimator (MLC) procedure is used to help ensure accurate conformation of the radiation beam about the individual profile of the tumour to reduce the irradiation of normal tissue as much as possible. Treatment planning software also optimises delivery parameters and takes into account the attributes of the tumour and surrounding tissues concurrently. The present technological success by VMAT is an area and extension of the greater technological adaptation of radiation therapy technology, centered on improving treatment precision and addressing the negative consequences of the process. The modality was conceived as a diagnosis of the fundamental weaknesses of the earlier techniques, including all-fields intensity-modulated radiation treatment (IMRT).²³

In a study examining synchronous bilateral breast cancer, Jiang Hua Huang et al. (2019)²⁴ compared fixed-jaw intensity-modulated radiation [F-IMRT] and tangential partial volumetric modulated arc therapy [tP-VMAT] as two radiotherapy modalities. They compared postoperative whole-breast radiation of 42.56 Gy in 16 fractions in 12 patients with those who underwent breast-conserving surgery. F-IMRT was selected as the main method because it is challenging to regulate local hot spots and minimize organ-at-risk doses in the case of standard IMRT. TP-VMAT was chosen as the second technique to enhance cold-spot coverage and to moderate normal tissue exposure.

The study aimed to determine specific parameters and results of the 3-dimensional conformal radiation therapy (3DCRT) and compare them with the outcomes achieved using volumetric modulated arc therapy (VMAT) post-unilateral lumpectomy in patients following bilateral breast cancer.

Methodology

This study was a comparative prospective study, and 22 women with bilateral breast cancer were recruited. It was carried out between December 2021 and June 2023 at the Baghdad Center of Radiation Therapy and Nuclear Medicine in Baghdad, Iraq, using ten participants, who were linked with clinical and histopathological bilateral breast cancer in Ultrasound, magnetic Resonance Imaging, and biopsy. After completion of adjuvant chemotherapy, all patients underwent bilateral lumpectomy. Sampling was done serially. Each patient signed a written informed consent. The treatment planning for patients was conducted using the MONACO 5.1 treatment planning system (TPS), utilising an X-ray photon beam with either 6 MV or 10 MV energy levels. The treatment was accomplished through the Agility model of linear accelerator manufactured by Elekta, Sweden. The prescribed dose is established at 40 Gy per 15 fractions.

Planning Techniques

The techniques of planning form the essence of project management. They give a standard framework to facilitate project component organisation and coordination. During 3-dimensional conformal radiation therapy (3DCRT), the left and right breasts are treated using two isocenters with four additional fields added to the patient targets; one field is used to cover each side. These are centered and tangential fields. The isocenter is positioned, much like IMRT, directly underneath the sternum in comparison to VMAT. The beam used has two half arcs, and limitations are given to both the PTV and the OARS in VMAT.

Planning Evaluation

The systematic analysis of the radiation-oncology planning process is initiated by the study of the absorbed dose distributions of the target volume and the prescribed organs at risk (OARs). This kind of analysis will implement statistical metrics on patient-specific data to infer whether any adjustments should be made to the dose prescription. These parameters are included in this review: confidence interval (CI), hazard index (HI), and numerous dose statistics are recorded and analyzed. To evaluate the global quality of the proposed plan, we use two related but conceptually different criteria of dose homogeneity and dose conformance. Dose homogeneity deals with how the dose is distributed evenly at the target, but dose conformance examines how well the prescribed dose is delivered.

Homogeneity Index (HI)

The characterisation of an absorbed-dose distribution in a target volume is often referred to as dose homogeneity.^{25–27} Various homogeneity parameters have been suggested, but each has been calibrated according to the radiation modality in question. In 2010, the International Commission on Radiation Units and Measurement (ICRU) proceeded with a corrected definition of the HI, solving the intrinsic drawbacks of the previous indices, with tendencies to focus on minimum-maximum ratios of doses, or measures of dose at reference points. The subsequent proposal posits a definition for the homogeneity index:²⁷

$$HI = \frac{D2\% - D98\%}{D50\%} \quad (1)$$

HI is a quantitative parameter of dose homogeneity in a specified area of treatment. Three dose quantities characterize it: D2% is the absorbed dose along the 2% dose isodose line, D98% is the absorbed dose along the 98% dose isodose line, and D50% is the absorbed dose along the 50% dose isodose line. At HI = 0, the absorbed-dose distribution becomes uniform over the system.

Conformity Index (CI)

Conformity index (CI) is a quantitative indicator of the consistency between the high-dose field of an irradiation treatment and the target region, which will be called the planning target volume (PTV). Ideal conformance is said to have been achieved when CI = 1. In radiotherapy practice, conformity is typically assessed by analyzing how much of the actual

treatment dose at the prescriptive isodose volume encapsulates the PTV materially:^{27,28}

$$CI = \frac{V_{PTV} \times V_{TV}}{TV_{PV}^2} \quad (2)$$

- V_{TV} : Volume of the actual prescribed dose.
- V_{PTV} : Volume of the PTV
- TV_{PV}^2 : Volume of the PTV within the V_{TV}

Statistical Analysis

The data analysis was conducted utilizing Statistical Packages for Social Sciences-version 24 (SPSS-28), a widely used statistical software product. The data were presented using statistical measures such as the mean and standard deviation. The student-paired t-test was used to compare two dependent variables. This test was specifically conducted to evaluate the difference between the three meanings. Statistical significance was determined by assessing the *P*-value, which was considered significant if it was less than or equal to 0.05.

Results

The demographic characteristics of female patients included in this study are shown in Table 1.

Table 2 summarises the mean and standard deviation of the patients' results. Based on the obtained data, it is evident that the VMAT technique exhibits notably superior dose coverage for both planning target volumes (PTVs) across several parameters, including V90%, V95%, and the volumes of hot areas (V105% and V110%). However, it is worth noting that the 3DCRT technique performs somewhat better than VMAT for the left PTV, specifically in terms of V90%.

Table 3 presents the outcomes of the cohort of patients who underwent bilateral lumpectomy for both breasts. Based on the computed outcomes, the statistical analysis indicates

Table 1. Demographic characteristics of patients

Demography	
Number of patients	22
Age (Years)	43.85 ± 12.07 (32–67)
Body mass index (BMI) kg/m ²	35.14 ± 11.61 (25.75–38.02)
Previous chemotherapy	

Table 2. Dose coverage for the PTV for bilateral lumpectomy treated with VMAT versus 3DCRT

		3DCRT	VMAT	P-value
LT PTV	V90 (%)	92.51 ± 0.42	99.15 ± 0.57	0.0394*
	V95 (%)	79.14 ± 0.51	98.95 ± 1.74	0.0064*
	V105 (%)	4.19 ± 1.77	42.5 ± 5.24	0.0009*
	V110 (%)	0.03 ± 0.002	0.76 ± 0.24	0.00158*
	V90 (%)	97.14 ± 1.22	99.59 ± 0.59	0.02705*
RT PTV	V95 (%)	72.09 ± 3.88	96.98 ± 1.95	0.00836*
	V105 (%)	8.67 ± 0.90	28.57 ± 8.1	0.00043*
	V110 (%)	0.59 ± 0.002	2.85 ± 0.71	0.0001*

* Statistically significant (*P* < 0.05)

Table 3. Homogeneity and conformity indexes for bilateral lumpectomy treated with VMAT versus 3DCRT

		3DCRT	VMAT	P-value
LT PTV	HI	0.47 ± 0.11	0.18 ± 0.02	0.0053*
	CI	0.33 ± 0.04	0.79 ± 0.15	0.0072*
RT PTV	HI	0.29 ± 0.09	0.12 ± 0.01	0.0645
	CI	0.41 ± 0.07	0.82 ± 0.05	0.00593*

* Statistically significant (*P* < 0.05)

Table 4. Dose comparison for Organs at Risk (OAR) for bilateral lumpectomy treated with VMAT versus 3DCRT

		3DCRT	VMAT	P-value
Heart	Mean	491.66 ± 116.23	541.93 ± 96.68	0.0693
	Lt Mean	532.52 ± 105.96	603.47 ± 128.45	0.0501*
Lung	Lt V ₂₀₀₀ cGy	14.97 ± 6.08	21.98 ± 3.39	0.0438*
	Rt Mean	708.1 ± 55.23	986.32 ± 76.09	0.02042*
	Rt V ₂₀₀₀ cGy	20.71 ± 2.54	38.43 ± 7.43	0.05009

* Statistically significant (*P* < 0.05)

that the homogeneity index (HI) demonstrates superior performance when utilising volumetric modulated arc therapy (VMAT) compared to three-dimensional (3D) treatment. In comparison to 3DCRT, VMAT shows superior outcomes for the appropriate target volume (PTV). A significant difference was found for the left PTV, while no significant difference was found for the right PTV. Regarding the conformity index (CI), both sides demonstrate a significantly high level of conformity in terms of dose distribution while employing volumetric modulated arc therapy (VMAT) followed by three-dimensional conformal radiation therapy (3DCRT).

The numbers about the sparing of the OARs are expressed in this section as Dn%, representing the absolute dose (specifically, the lowest dose required to encompass n% of the structure, known as D95%). Additionally, dose volume metrics are denoted as Vm, indicating the percentage of the structure that receives a dose greater than mGy. The terms examined in this study encompass the average dose administered to the heart and the average dose received by each lung volume exposed to a sparing dose of 2000 cGy. The findings are displayed in Table 4.

The study found that three-dimensional (3D) treatment planning demonstrated greater efficacy compared to volumetric modulated arc therapy (VMAT) in terms of reducing the mean heart dosage and the dose received by the left and right lungs (mean and v 2000 cGy). The observed disparity in mean lung dosage between the left and right sides was less pronounced in the 3DCRT technique than in the VMAT technique.

Discussion

The three-dimensional conformal radiotherapy (3D-CRT) has an evident benefit of reducing the dose delivered to organs at risk (OARs) during the treatment of synchronous bilateral breast cancer (SBBC). However, this mode of treatment also has several drawbacks, the main of which are poor coverage of

the targeted volume (PTV) and poor homogeneity, as well as poor conformity. Such gaps have the effect of an under-dosed area, often referred to as a cold spot. The true reason is a substantial overlap of adjacent planning target volumes (PTVs) and organs at risk (OARs).²⁹ To reduce data disclosure with OARs, physicists use multileaf collimators (MLCs) by limiting or constricting the area that is irradiated. As much as this strategy successfully keeps OARs safe, it also causes a leakage of the dose given to the PTV. Clinical experience shows that 3D-CRT considerably decreases the radiation dose to the heart and thus decreases the likelihood of cardiac mortality due to radiation in patients with breast cancer.^{25,30,31}

The Volumetric Modulated Arc Therapy (VMAT) tool results in measurable advantages in terms of coverage of planned target volumes (PTVs) in multiple dosimetric parameters such as V90%, V95% and the muscles of high-dose areas (V105%, and V110%). The only notable exception is, however, in the case of left PTV: in this left-sided case, Three-Dimensional Conformal Radiation Therapy (3DCRT) outperforms VMAT in terms of V90%.

A range of reasons, such as the geometry and location of the tumour, sensitivity of the optimisation algorithm, treatment planning parameters, dosimetric objectives and constraints, among other patient-specific variables, could explain the apparent difference between VMAT and 3DCRT on the left PTV. These differences are in line with the past observations that interventions in performance differences amongst radiation modalities are dependent on the structural deformation, positioning, and other patient-related determinants.³²

Tumour geometry and the anatomical site of the left PTV can predetermine the level of conformity that specific radiation therapies can achieve. The difference in efficiency of VMAT and 3DCRT comes out due to varying PTV geometries and placements. Optimisation techniques used in VMAT and 3DCRT also react differently to similar anatomical and dosimetric constraints imposed on the left PTV, thus influencing dose coverage.³³ All radiation therapy techniques have unique parameters of planning which can alter the performance of the method in terms of beam angle assumptions, dose prescriptions, and optimisation priorities. All these variables determine the dose distribution in planning.³⁴ Other dose distributions that are determined through the influence of treatment planning include the use of dose coverage requirements and organisation-at-risk limitations. Towards the planning target volume (PTV), variations in targeted-volume goals are also a factor that can produce measurable performance levels.³⁵ Furthermore, both efficacy and radiation absorption characteristics can be refined due to the heterogeneity of patients in their anatomical growth and physiological structure, where certain tissues comprise different compositions and densities.³⁶

The Homogeneity Index (HI) is the measurement of dose homogeneity in the target volume. In normal operations, VMAT readily records higher values of HI than in 3DCRT, which can be explained by the fact that VMAT can recalculate beam intensity as it arcs through the patient hence making it possible to make more precise and homogenous deposition of dose in the target. Therefore, volumetric modulated arc therapy (VMAT) has been proven to produce a better result regarding the relevant target area, PTV, as opposed to 3DCRT. This gap can be attributed to the increased sensitivity level of VMAT to dose distribution, which is beyond the capability of traditional treatment strategies. This sensitivity

contributes to the optimisation of target doses within the PTV, which in turn is achievable in bringing down the dose granted to healthy tissue nearby. Unreliable results in the left versus right PTVs could be explained by differences in the anatomical factors and tumour-specific properties, or may be due to different treatment-planning settings for the left and right sides of the patient. The CI is a number expressing the level of adherence of the given dose to the geometric shape of the target volume, and at the same time, taking into account how much the neighboring normal tissues have been spared in terms of radiation exposure. There is a significant level of conformity of the left and right PTVs in terms of dose distribution when using VMAT and 3DCRT. This means that the two methods have acceptable performance when assessed based on compliance with the planned volume, in that VMAT has a slight advantage.³⁷

The planning of treatment algorithms used in three-dimensional (3D) and VMAT interventions possibly behaves differently in the face of anatomical and dosimetric constraints of crucial structures.³⁸ These effects of the optimisation approach on the dose outcome may be mediated by its ability to reduce doses to organs at risk, including the heart and lungs.³⁹

The mobility of the organs and shape variations during treatment might occur due to dynamic administration and constant rotation of VMAT. The natural variability of this moving nature could explain the difference in the delivery of dose to the heart and the lungs compared to the relatively fixed beam shape used in 3D treatment planning.^{33,40}

The thoracic anatomical and geometric variability may have a significant impact on the therapeutic outcomes, especially when considering the heart size and location, as well as the lung size and location. The ability of volumetric-modulated arc therapy (VMAT) to avoid critical structures is also affected by the anatomical variability of patients. Disparities in patient positioning and set-up, as well as intrinsic limitations of reproducibility, add additional losses to dose precision in VMAT delivery. Since VMAT is relatively sensitive to the displacement of patients, the short-term effects can include impaired dose homogeneity at delivery.^{23,41}

The variation in the cardiac and pulmonary doses experienced among three-dimensional conformal radiotherapy (3DCRT) and VMAT treatment planning can be explained on both the technical side of the planning systems and also on the anatomical nature of the patient. In the current study, 3DCRT was always better in protecting the OARs compared to all clinically acceptable PTVs.⁴²

These findings have been confirmed by Pasler et al. (2015)⁴³ and S.J. Kim et al. (2017).²⁹ Pasler et al. investigated left-sided breast cancers involving regional lymph-node involvement. They used two partial arcs in VMAT planning, noted improved target coverage, improved Hamming distances, and indices of conformity and acceptable OAR sparing. At the same time, S.J. Kim et al. compared 3DCRT, IMRT, and VMAT in patients with synchronous bilateral breast cancer (SBBC) who were treated with the MONACO planning system, with results showing that 3DCRT demonstrated poor PTV coverage and HI/CI and radiation exposure of OARs. In contrast, however, both IMRT and VMAT achieved better homogeneity in the PTV. These techniques also demonstrated improved dose conformity and homogeneity. However, in terms of hot spot distribution, VMAT and

IMRT exhibited higher values than 3DCRT, which aligns with the observations in our study.

Additionally, Karthick et al. (2017)⁴⁴ investigated the use of 3DCRT in six female patients with SBBC and reported favorable homogeneity and conformity indices, alongside adequate sparing of OARs.

Their results differed from ours because we used two iso-centers in 3D-CRT planning and employed different calculation methods in Eclipse TPS from Varian. However, our study agreed with their results in OAR production due to MLC control in 3D techniques.

The administration of radiation treatment fractions can potentially induce harm to the cardiovascular and respiratory systems, thereby elevating the susceptibility to cardiac ailments such as stenosis in the left descending artery (LAD) among individuals with breast conditions, particularly those who have undergone left-sided mastectomy. Implementing planning approaches has been shown to mitigate the average dosage administered to the heart effectively. However, certain anatomical regions close to the central area of the left breast may still experience higher doses.^{45,46} In a study conducted by Cho et al.,⁴⁷ it was observed that there is a positive correlation between elevated mean dose administered to the heart and the incidence of ischemic heart disease. There is now no established maximum threshold for cardiac dosage; hence, it is advisable to reduce it. The lungs are susceptible to significant levels of radiation, resulting in the development of ailments such as pneumonitis. The recommended range for the mean lung dose (MLD) is between 6 and 16 Gy^{29,48–50}

It is imperative to acknowledge that the distinct attributes of the patient, tumour, and treatment regimen can impact the efficacy of radiation therapy procedures. The selection of VMAT (Volumetric Modulated Arc Therapy) and 3DCRT (Three-Dimensional Conformal Radiation Therapy) is contingent upon a multitude of circumstances, encompassing the clinical objectives, tumour attributes, and deliberations of the attending oncology personnel. The disparities identified in performance underscore the significance of tailoring treatment plans to individual patients and the imperative

of thoroughly evaluating and enhancing radiation therapy methods for each individual.

The utilisation of 3D-CRT is prevalent among radiation centres in Iraq due to its efficacy in achieving optimal coverage and safeguarding the organs at risk (OARs) during treatment. This research study is pioneering in its focus on treatment planning strategies, specifically the utilisation of VMAT, owing to the emergence of advanced methodologies in the field. This study can be regarded as a foundational resource for international or regional investigations on the treatment of patients with synchronous bilateral breast cancer who have undergone lumpectomy procedures. This is due to the absence of established or published recommendations specifically addressing such instances.

One of the limitations of this study is the limited sample size. The scarcity of published research studies about these situations, characterised by small sample sizes, limits their generalizability due to the intricate nature of the treatment involved. Additional investigation is required to generalise the findings of the study.

Conclusion

The study reveals that volumetric modulated arc therapy (VMAT) is more effective in providing dose coverage for planned target volumes (PTVs) in regions with high radiation intensity. In contrast, 3DCRT (Three-dimensional conformal radiotherapy) minimises radiation exposure to the left PTV. VMAT has superior outcomes in terms of homogeneity index and conformity index for acceptable goal volumes. However, 3D treatment planning is more effective in minimising the average dose received by the heart and limiting lung exposure to 2000 cGy. This highlights the importance of personalised treatment strategies for bilateral lumpectomy patients.

Conflicts of Interest

Authors declare no conflict of interest. ■

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