

MONOISOCENTRIC VERSUS DIISOCENTRIC HYPOFRACTIONATED ADJUVANT RADIOTHERAPY FOR BILATERAL BREAST CANCER: COMPARATIVE EVALUATION OF HEART AND LUNG DOSES

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ABSTRACT

Background: Among cancers that affect women, breast cancer is one of the most common types, comprising around 2% of all breast cancer patients as bilateral breast cancer (BBC). In the treatment of bilateral breast cancer, there is a high challenge in terms of the larger treatment volume and reducing the radiation to the healthy tissues adjacent to it. This makes radiation treatment in BBC challenging compared to treatment in unilateral breast cancer. Although VMAT technique provides precise dose delivery, it needs to be examined in various methods when applied in BBC treatment.

Methods: In this research, there were ten bilateral breast cancer patients (BBC) who had modified radical mastectomy surgery (MRM). CT scans of all the patients were performed using GE Optima machine with a 5 mm slice thickness in a supine position and raised arms using active breathing coordinate (ABC). The planning target volume (PTV) and organs at risk (OARs) were delineated by clinicians according to the RTOG guidelines. Treatment plans were created by the Elekta Versa HD machine using the Monaco Treatment Planning System, version 6.00.01. In this research, 40 Gy in 15 fractions with 6 MV energy was used as a prescribed dose. The aim was to deliver the prescribed dose in such a way that at least 95% of the PTV would receive 95% of the prescribed dose with keeping the maximum dose to less than 107%. Dose constraints for the OARs according to the QUANTEC guidelines were taken into account for lung doses (D_{mean} , V5Gy, V20Gy) and heart doses (D_{mean} , V25Gy, V30Gy). The dosimetric plans were assessed using DVH, conformability index (CI), and homogeneity index (HI).

Results: The coverage of targets (V95) for ISO2 and ISO1 was observed to be the same; however, ISO2 resulted in a significant decrease in hot spots (V105) with $p = 0.0001$. A reduced dose was given with ISO2 to the lungs and heart with $p < 0.001$, accompanied by improved conformity index (CI) and homogeneity index (HI). Monitor Units were increased only slightly using ISO2, which was statistically insignificant.

KEYWORDS: Bilateral Breast Cancer, Volumetric Modulated Arc Therapy, Dosimetry Comparision, Mono-Isocentric, Dual-Isocentric.

INTRODUCTION

Adjuvant radiation therapy (RT) is key in breast cancer therapy and is associated with decreasing the locoregional recurrence by almost 50% and mortality from breast cancer by about one-sixth. This method is advised to be used for node positive patients undergoing mastectomy. Although RT has many benefits, there are several potential dangers of it, such as toxicity to heart and lungs, as well as a high incidence of secondary malignancies[1].

Synchronous bilateral breast cancer (BBC) is an unusual condition, making up for only 2% of all cases of breast cancer. Research shows that synchronous bilateral breast cancer more frequently happens in younger women, who have smaller-sized early breast cancers when compared to unilateral breast cancer[2]. Besides, HER2/neu positivity is a predictor of bilateral breast cancer[3]. Although survival in patients with BBC and unilateral breast cancer is not different, patients with synchronous BBC have worse results than patients with metachronous BBC, meaning that second tumor is found later than 12 months after the primary tumor detection[4].

Radiotherapy planning in case of synchronous BBC is challenging, especially when the axillary and internal mammary lymph nodes are included into the treatment[5]. The conventional half-field tangential technique can cause high-dose hot spots in proximity to the sternum by causing overlap of fields and can inadequately cover the internal mammary nodes. This technique may also contribute to higher doses to the heart and lungs[6].

Modern techniques like VMAT have been proven to overcome some of the disadvantages of conventional techniques[7]. It has been proved that VMAT provides better dose conformity, volume coverage, and decreased treatment time when compared with fixed-field IMRT. While VMAT does not reduce the mean heart dose in some cases, it reduces the lung doses[8].

Deep inspiration breath-hold (DIBH) has become a widely used technique in the treatment of left-sided breast cancer[9]. DIBH allows expansion of lung volume during treatment, which leads to decrease of cardiac and pulmonary doses, along with the possibility of internal mammary nodes coverage[10]. However, DIBH may not be possible in patients that are

not able to hold breath and follow breathing instructions. DIBH is also helpful in bilateral cases in reducing the doses to lungs and heart[11].

Split-arc VMAT strategies have also been investigated, especially in the case of regional lymph nodes involvement[12]. It has been reported that using this strategy reduces lung and heart doses, in comparison to conventional VMAT and half-field technique, while contralateral breast dose increases slightly. Split-arc VMAT, when used in combination with DIBH technique, enables delivery of an arc during 20 seconds breath-holding period[13].

The present study investigates the use of split-arc VMAT strategy in treating patients with synchronous bilateral breast cancer in the presence of regional lymph nodes. The main goal of the investigation is to compare the dosimetric results for monoisocentric and dual-isocentric VMAT treatment plans and analyze the robustness of dual-isocentric treatment plans for ± 2 mm and ± 5 mm setup errors in lateral, longitudinal and vertical directions.

MATERIALS AND METHODS

The patients involved in the study were 10 BBC patients who underwent MRM with involvement of the SCF from March 2023 through August 2025. The average age of the patients was 43 ± 11.6 years. The patients underwent CT simulation using the Optima GE Healthcare 16 slice machine with 3 mm slice thickness in an active-breathing control technique to reduce heart and lung radiation. The breathing control for the imaging was achieved using a training for home inhalation with 2 L/min oxygen supplementation prior to scanning.

The patient was immobilized supine on a breast board in thermoplastic mold, and a neutral neck position was utilized for enhancing setup reproducibility. Bilateral breasts and SCF CTVs were contoured, and then a margin of 5 mm was added to obtain PTV. PTV was cropped at 3 mm to minimize skin toxicity. 5 mm bolus was selected depending upon the involvement of skin. CT images and contour were transferred to the Monaco treatment planning system (v 6.00.01). VMAT planning was carried out with 6 MV photons, and dose calculation was carried out by Monte Carlo algorithm. Single Isocenter (SIC) and Dual Isocenter (DIC) techniques were utilized for plan generation. The single Isocenter (SIC) plans were made by keeping the isocenter at the sternum while DIC planning technique required setting up separate isocenters at the center of each PTV. In SIC technique, an arc of 150° - 300° was used while 210° - 220° for right chest wall and 150° - 220° for left chest wall arc angle was utilized for DIC technique. Maximum number of control points was limited to 180, segment width of 0.5 cm and fluence smoothing medium was chosen for plan optimization. Grid spacing was set to 0.3 cm with a statistical uncertainty of 3% per calculation. The optimization was done with Agility motorized MLC with 5 mm leaf width. A hypo fractionated dose of 40 Gy in 15 fractions was prescribed for all the patients.

The aim of this study was to ensure that 95% of the prescribed dose was delivered to 95% of the PTV volume, with the maximum dose to 2 cm³ being less than 107%. Heart and both lungs were also recontoured and considered organs at risk (OARs). In PTV, V95, V105, Homogeneity Index (HI), and Conformity Index (CI) were calculated. In lungs, mean dose (Dmean), V5, and V20 were calculated, while in heart, Dmean, V10, and V30 were determined. Planners were required to keep OARs' dose as low as possible.

Moreover, The Homogeneity index (HI) and Conformity Index (CI) (eq.1 and eq.2) were utilized to evaluate the target area.

$$CI = \frac{V_{PTV_{ref}}}{V_{PTV}} * \frac{V_{PTV_{ref}}}{V_{ref}} * 100\%$$

$$HI = \frac{V_{PTV_{95\%}}}{V_{PTV}} * \left(1 - \frac{V_{PTV_{110\%}}}{V_{PTV}} \right) * 100\%$$

where VPTV indicates the Volume of the PTV received the prescribed dose and is denoted as Vref, which means total volume receiving the dose. The symbols VPTV95% and VPTV110% show the volumes of the PTV receiving 95% and 110% of the prescribed dose(PD), respectively. Conformity Index (CI) and Homogeneity Index (HI) have been defined [14]. The closer the value of CI to 100%, the better the conformal dose distribution to the target region, and the closer the value of HI to 100%, the more dose homogeneity within the target region[15].

The treatment plans followed the conditions recommended in the RTOG trial. A value of p less than 0.05 was considered to be statistically significant. Initially, the data was processed in Microsoft Excel and mean and standard deviation was calculated. Statistical analysis and p-value calculation was done in Jamovi (third generation software).

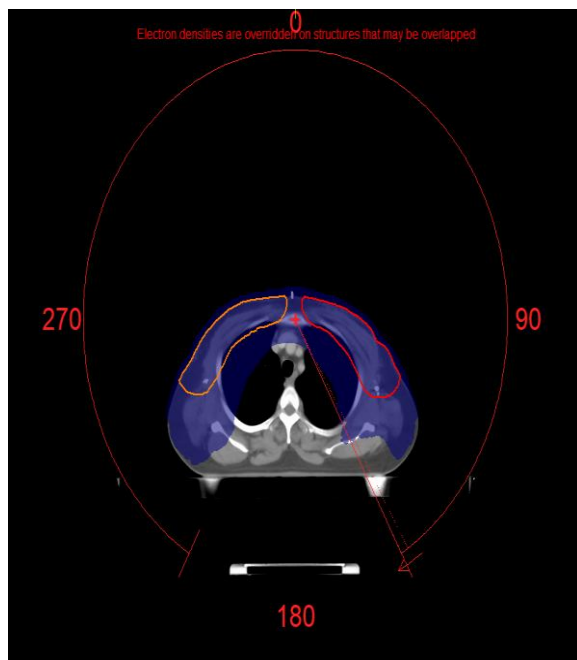


Figure1. Monoisocenter placed at the sternum with the 50% isodose line shown in the transverse view; arc delivered from 150° to 300° in a counterclockwise direction

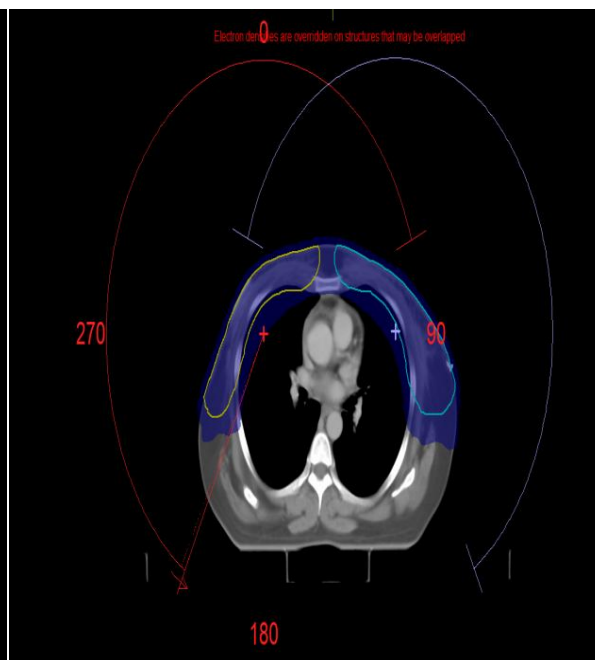


Figure 2. Dual isocenters placed at the centers of the PTVs for the right and left breasts, with the 50% isodose line shown in the transverse view. Arc angles: 210°–220° clockwise for the right breast and 150°–220° counterclockwise for the left breast.



Figure3. Coronal view showing the 50% isodose line for the monoisocenter plan

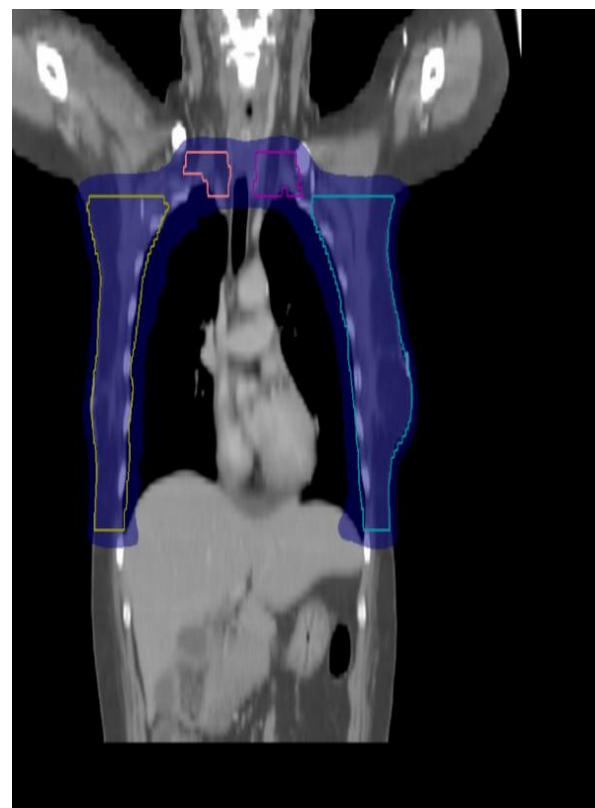


Figure4. Coronal view showing the 50% isodose line for the dual-isocenter plan

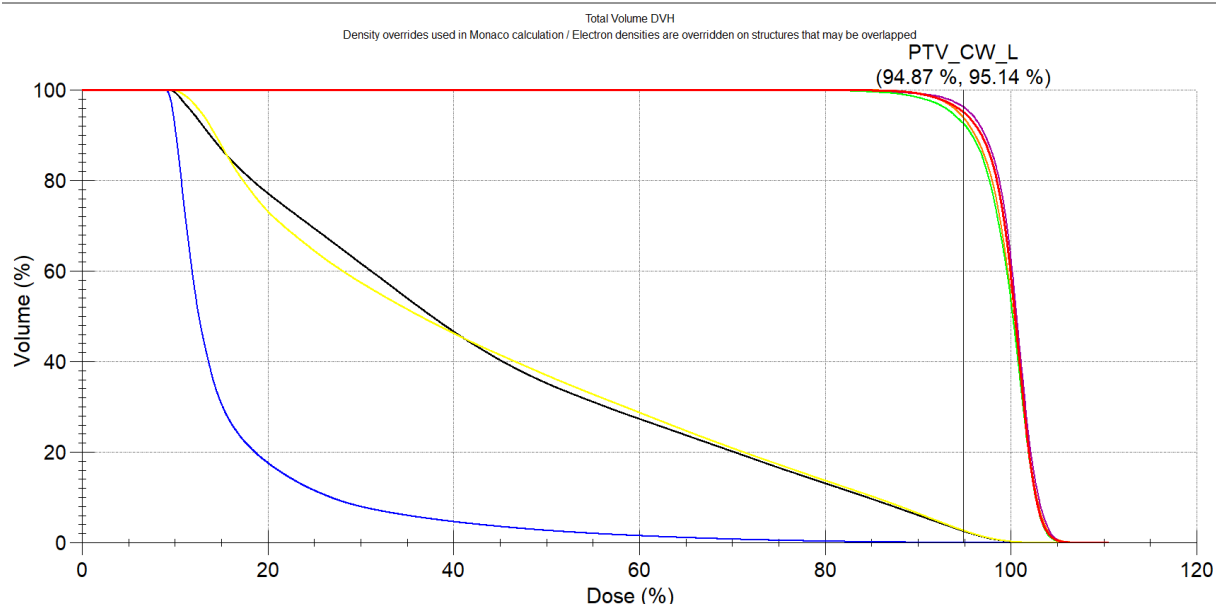


Figure5. Dose–Volume Histogram (DVH) for the monoisocenter plan

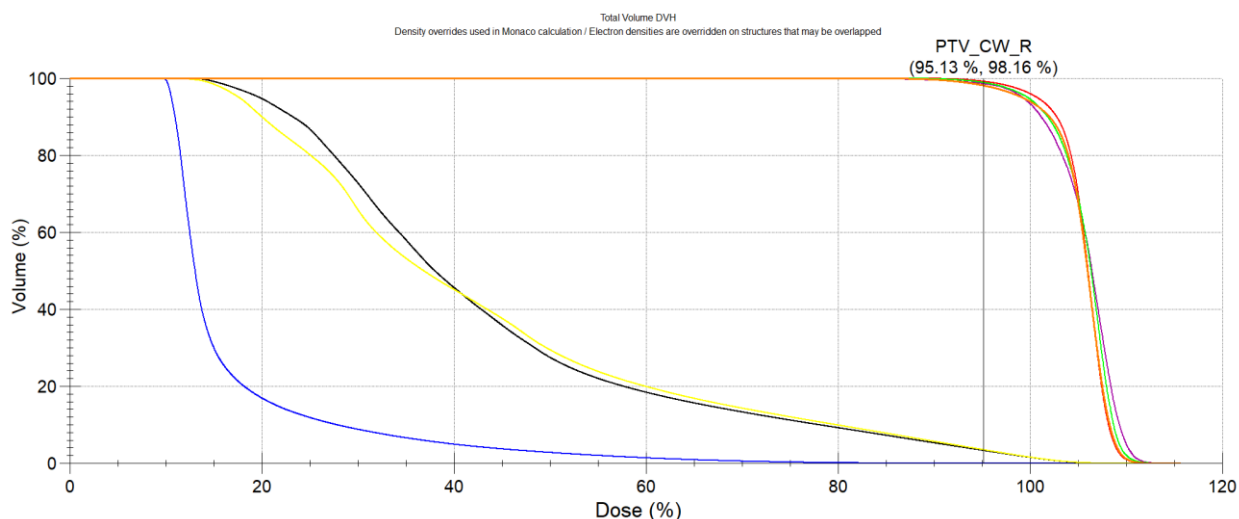


Figure6. Dose Volume Histogram (DVH) for Dual isocentre plan. Colour -coded representation of the selected structures : Heart(Blue), Left Lung (Black), Left chest wall PTV (red),right chest wall PTV (orange), left SCF(purple),right SCF (green),total lung (yellow)

	ISO1	ISO2	P-value
V95	96.7±0.78	97.3.44±1.01	0.228
V105	2.2±1.26	0.97±0.04	0.0001
RT Lung			
Dmean	12.89±2.8	10.2±3.6	0.0003
V5	63.5±5.22	59±4.3	0.0011
V20	23.4±4.8	21±5.7	0.0001
LT Lung			
Dmean	13.54±3.8	11±4.18	0.0005
V5	65.5±8.45	61.48±7.5	0.0004
V20	25.±4.75	22.2±5.23	00006
Heart			
Dmean	5.67±2.3	3.8±2.62	0.0001
V10	4.5±0.9	2.8±1.65	0.0009
V30	0.9±0.2	0.5±0.3	0.0001
CI	0.82±0.27	0.84±0.09	0.0313

HI	1.04±0.05	1.05±0.05	0.0154
MU	702±49	850±31	0.1679

Table 1. Dosimetric comparison of mono-isocentric (ISO1) and dual-isocentric (ISO2) VMAT plans, including target coverage, bilateral lung and heart dose parameters, conformity and homogeneity indices, and monitor units in hypofractionated bilateral breast radiotherapy.

RESULTS

Dosimetric evaluation of the mono-isocentric (ISO1) and dual-isocentric (ISO2) VMAT plans confirmed that the two methods ensured equivalent target coverage as V95 values were similar ($96.7 \pm 0.78\%$ and $97.3 \pm 1.01\%$ for ISO1 and ISO2, correspondingly; $p = 0.228$). On the other hand, ISO2 method ensured a reduction of high-dose hotspots as V105 values for ISO1 and ISO2 were $2.2 \pm 1.26\%$ and $0.97 \pm 0.04\%$, respectively ($p = 0.0001$), suggesting improvement in dose homogeneity of planning target volume. Lung dosimetry showed that ISO2 resulted in more efficient organ sparing. In case of the total lung volume, mean dose for ISO2 was significantly lower than that for ISO1 – 10.2 ± 3.6 and 12.89 ± 2.8 Gy, correspondingly ($p = 0.0003$) which was associated with decrease in both V5 and V20 ($59 \pm 4.3\%$ and $63.5 \pm 5.22\%$, correspondingly; $p = 0.0011$; $21 \pm 5.7\%$ and $23.4 \pm 4.8\%$, correspondingly; $p = 0.0001$). Improvement of lung sparing was also noted in the left lung with the use of ISO2. ISO2 was associated with significantly decreased mean dose and volume parameters in comparison with ISO1. Similar tendency to the decrease in doses was observed for the cardiac tissue. Mean dose for ISO2 was significantly lower than that for ISO1 (3.8 ± 2.62 and 5.67 ± 2.3 Gy, respectively; $p = 0.0001$). Low and medium-dose volumes were also significantly decreased for ISO2. Evaluation of plan quality metrics demonstrated slight but significant increase for ISO2 in conformity index (0.84 ± 0.09 and 0.82 ± 0.27 , respectively; $p = 0.0313$) and homogeneity index (1.05 ± 0.05 and 1.04 ± 0.05 , correspondingly; $p = 0.0154$). Although ISO2 required significantly more monitor units (850 ± 31 vs 702 ± 49), it was not statistically significant ($p = 0.1679$).

DISCUSSION

In the current study, the dosimetric advantages of mono-isocentric (ISO1) and dual-isocentric (ISO2) VMAT approaches have been assessed in hypofractionated adjuvant radiotherapy of synchronous bilateral breast cancer. ISO1 and ISO2 approaches showed a similar level of target coverage with PTV V95 of $96.7 \pm 0.78\%$ for ISO1 and $97.3 \pm 1.01\%$ for ISO2 ($p = 0.228$). This result suggests that the application of two isocenters does not lead to any loss of target coverage. However, V105 was significantly smaller for ISO2 approach than for ISO1 one ($0.97 \pm 0.04\%$ vs. $2.20 \pm 1.26\%$, $p = 0.0001$).

This is supported by the studies carried out by Boman et al. [16,17] on split-arc and dual-isocenter VMAT plans used in treating patients with breast cancer combined with regional nodal irradiation, and bilateral lymph-node positive breast cancer. They found out that VMAT technology can be able to offer target coverage together with doses within an acceptable range. In the dual-isocenter setup, there is individual optimization of the two treatment areas; this could be beneficial in the treatment of bilateral breast cancer, as a result of the larger and complex treatment area. The decrease in V105 in our results could be due to this factor.

The first notable result obtained in the current study is the considerable reduction in bilateral lung dose using ISO2. The average dose of right lung dropped from 12.89 ± 2.8 Gy using ISO1 to 10.2 ± 3.6 Gy using ISO2. Similarly, the mean dose of left lung reduced from 13.54 ± 3.8 Gy to 11.0 ± 4.18 Gy. There was also a significant decrease in V5 and V20 in both lungs. This result is clinically significant since the irradiation of bilateral breasts leads to exposure of the whole bilateral lungs to radiation as opposed to unilateral breast irradiation. Also, other researchers who have investigated VMAT for bilateral breast cancer have found favorable pulmonary doses [16–20].

Another major benefit seen with ISO2 was the sparing of the heart. While the mean heart dose had been 5.67 ± 2.3 Gy for ISO1, this figure fell to 3.8 ± 2.62 Gy with ISO2 ($p = 0.0001$). Moreover, there was significant sparing of heart V10 and V30. Sparing of the heart is especially crucial in breast cancer radiotherapy, as the patients might survive even after radiotherapy. It is thus important to reduce any radiation to the heart during the process of planning. Cardiac sparing has also been highlighted as one of the advantages of VMAT for the treatment of synchronous bilateral breast cancer in various other dosimetric studies [19–21].

There was a statistically significant but slight increase in the conformity index after ISO2 from 0.82 ± 0.27 to 0.84 ± 0.09 ($P = 0.0313$). While there is a statistically significant difference in the HI between the two techniques, the actual difference is insignificant. It is evident that the large decrease in V105 is another indication of a better dose distribution with ISO2. Such observations in regard to VMAT's capabilities in maintaining target coverage while improving dose distribution have been reported before in other bilateral breast radiotherapy studies [18–20].

The results obtained in the current study are also in line with those from Wu et al. [18], who investigated postmastectomy radiotherapy plans for synchronous bilateral breast cancers with regional nodal irradiation and found that VMAT plans can achieve sufficient target coverage with acceptable doses to the organs at risk (OARs). In a similar way, VMAT was found to be feasible for bilateral regional nodal irradiation by Bernstein et al. [19]. The possible advantages of VMAT in terms of providing favorable cardiac and pulmonary doses were pointed out by Salim et al. [20] in their comparison of VMAT, IMRT, and 3D-CRT in patients with synchronous bilateral breast cancer.

Despite the fact that the number of monitor units for ISO2 is more than for ISO1 (850 ± 31 vs. 702 ± 49), there was no statistical difference between them ($p = 0.1679$). Possibly, the higher numerical value of MU can be associated with modulation of two different treatment areas and independent optimization of each region. However, planning time and delivery time have not been analyzed in the current work and should be taken into account in further studies.

Setup robustness is one of the main concerns for dual-isocenter VMAT. Specifically, Boman et al. [17] studied robustness of dual-isocenter VMAT in case of bilateral breast cancer and emphasized the role of relative setup errors between two isocenters. As the setup uncertainties and its effects on the dose distribution have not been examined in the current study, the necessity of proper image guidance and quality assurance remains highly relevant.

There are some limitations of this current study. First of all, the sample size is relatively small because there were only ten patients, and the retrospective planning approach restricts the generalization of results. In addition, only dosimetric indices were used without taking into account such factors as treatment time, setup uncertainty, and possible acute or late toxicities of the heart and lungs. The effect of the active breathing control may have an impact on doses to the heart and lungs; therefore, it is necessary to consider it when comparing the results of this current research with the research that is done without using the active breathing control.

In conclusion, the mono-isocentric VMAT and dual-isocentric VMAT showed acceptable target coverage in hypofractionated bilateral breast radiotherapy. However, ISO2 showed a significant decrease in the high dose-volume and lower doses to the bilateral lungs and heart, as well as improvement in conformity. It is in line with the previous studies on the use of the advanced VMAT and dual-isocenter techniques for bilateral breast irradiation [16-21]. In the framework of the limitations of the current study, it can be said that the dual-isocentric VMAT had good dosimetric properties, especially related to normal tissue sparing, while having comparable target coverage.

CONCLUSION

Both ISO1 and ISO2 had good target coverage, as seen in the similar values of V95 between both plans. However, ISO2 showed a statistically significant increase in dose conformity (CI) and a slight improvement in homogeneity (HI), and reduction in high dose volume (V105). In addition, ISO2 also showed a decrease in the doses received by the organs at risk. It included the statistically significant reduction in mean doses and low and intermediate volume doses (V5 and V20) received by the right and left lungs, and the mean dose and V10 and V30 received by the heart. MU for ISO2 was slightly increased, but not statistically significant.

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