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Correlations between patient-specific parameters and dosimetric indices for personalized breast cancer radiotherapy

Ioana-Claudia Costin^{1,2}✉ & Loredana G. Marcu^{3,4}

Treatment planning parameters in radiotherapy are key elements that dictate the success of treatment outcome. While some parameters are commonly evaluated irrespective of cancer type, others are site-dependent and strongly patient specific. Given the critical influence of planning parameters on personalized therapy, the aim of this study was to evaluate the correlations between the dosimetric indices (conformity, homogeneity and mismatch indices) related to tumor coverage and the patient-specific parameters which encompass parameters pertaining to organs at risk (widths and lengths of heart and ipsilateral lung included in treatment fields, mean/maximum doses to heart, ipsilateral lung, left anterior descending aorta and contralateral breast) and tumor volume. Forty breast cancer patients were divided into two groups according to tumor location: twenty with left-sided (group A) and twenty with right-sided breast cancer (group B). Conformal (3DCRT), intensity modulated (IMRT) and volumetric arc modulated (VMAT) radiotherapy techniques were used for plan creation. Moderate to strong correlations were found for ipsilateral lung parameters for both groups of patients regardless of the treatment technique. Moderate to strong correlations were found for heart parameters in group A patients, while no correlations were observed in group B. The mismatch index presented moderate to strong correlations with tumor volume for all treatment techniques ($r = -0.861$ 3DCRT, $r = -0.556$ IMRT, $r = -0.533$ VMAT) particularly in group A. The evaluated correlations indicate the role of dosimetric indices in personalized treatment planning.

Keywords Treatment planning, Dosimetric parameters, Organs at risk, Conformal radiotherapy, Intensity modulated techniques

Based on global population incidence, breast cancer is among the first cancers leading to mortality and its occurrence is predicted to increase with over 7.00% in the future. Furthermore, female breast cancer has lately become the most commonly diagnosed malignancy (11.70%) thus slightly exceeding lung cancer incidence (11.40%)¹. Radiotherapy plays a key role in the multidisciplinary approach of breast cancer. In order to increase survival, minimize tumor recurrence and reduce treatment-related toxicities, the focus of breast cancer radiotherapy must be balanced between tumor control and normal tissue protection. The most commonly used treatment techniques in breast cancer radiotherapy are still the linear accelerator-based ones: 3D conformal radiotherapy (3DCRT) and intensity modulated techniques (intensity modulated radiotherapy - IMRT and volumetric modulated arc radiotherapy - VMAT)². Accurate treatment delivery is multifactorial dependent and involves a personalized approach, that besides the choice of treatment technique, of the immobilization board or the position on treatment couch, takes into account patient-related parameters (such as body mass index, comorbidities, tumor volume, the volume and position of the organs at risk (OARs) relative to the target) as well as the quality of dose distribution conformed to target volume geometry³.

Several factors have been reported in the literature to influence the final outcome of a treatment plan: the number of fields and field geometry⁴, tumor volume - depending on lymph nodes involvement⁵, irradiated healthy tissue areas⁴, overdosed and underdosed regions of tumor volume⁴, dosimetry of organs at risk⁴, the number of monitor units, and so on⁴. Given the association between the conformity and homogeneity indexes

¹Faculty of Physics, West University of Timisoara, 300223 Timisoara, Romania. ²Bihor County Emergency Clinical Hospital, 410167 Oradea, Romania. ³Faculty of Informatics and Science, University of Oradea, 410087 Oradea, Romania. ⁴UniSA Allied Health and Human Performance, University of South Australia, Adelaide, SA 5001, Australia. [✉]email: ioanaclaudiacostin@yahoo.com

(CI and HI) and the quality of a treatment plan, their evaluation in regards to target and OARs dosimetry should be a key aspect of quality assurance. Also, the evaluation of mismatch index (MI) helps identify the differences between conformal and modulated intensity techniques regarding the percentage of prescribed dose outside the tumor volume.

In addition to target indices, for a more comprehensive assessment of the treatment plan, the evaluation of different OARs-related parameters should be taken into account in a quantitative manner. The importance of these parameters is given by the organs at risk located nearby the tumor volume, which in breast cancer irradiation are represented by the heart and ipsilateral lung. In view of the above, there are studies in the literature that evaluated heart and lung parameters depending on their inclusion in the irradiation field based on digitally reconstructed radiographs (DRR)^{6,7} or treatment field^{8–10}. These parameters (maximum heart length - MHL, maximum heart distance - MHD, maximum ipsilateral lung length - MLL and maximum ipsilateral lung distance - MLD) showed an influence on dose and irradiated OAR volume, but also a correlation with a series of treatment-related side effects, such as dermatitis¹¹, incidence of poor cosmesis (modifications in breast volume, scars and skin changes)¹² or fat necrosis¹³. A key factor in breast cancer irradiation is tumor location. Left- and right-sided breast cancer patients are exposed to different radiation-induced risks, owing to differences in the anatomical location of critical organs. Therefore, evaluation of dosimetric indicators for each patient category and their correlation with patient-related parameters can offer important information regarding optimization of breast cancer radiotherapy.

A variety of parameters were examined in the literature, which, in the current context, can be divided in patient-related parameters: (1) OAR (heart and ipsilateral lung volume inclusion in treatment field, heart and ipsilateral lung mean dose, mean and maximum dose of left anterior descending aorta - LAD and contralateral breast) and target volume-specific variables (planning target volume - PTV) and (2) dosimetric parameters (CI, HI and MI). A number of studies aimed to identify the influence of irradiation conditions (under free breathing or deep inspiration breath hold - DIBH) by looking for correlations between tumor volume and OARs dosimetry¹⁴ or by evaluating treatment planning-specific parameters (heart volume, lung volume, heart chest wall length, heart height, chest depth, central lung distance, heart chest wall distance, maximum heart depth, lung orthogonal distance) versus OARs dosimetric parameters (heart and LAD mean and maximum dose and contralateral and ipsilateral lung dose volumes)¹⁵ showing that the treatment outcome is better under DIBH technique due to reduced dose to OARs. Also, the influence of treated volume on OAR dosimetry was debated through correlations concluding that larger irradiated volumes increase heart and ipsilateral lung dosimetry (for OARs located in the proximity of the target)¹⁶.

However, the number of studies that evaluated the possible associations between patient-specific parameters (tumor volume, MHD, MHL, MLL, MLD and mean/maximum dose to OARs) and dosimetric indices (CI, HI, MI) that might influence the outcome of radiotherapy is scarce. Therefore, the purpose of this study was to assess through correlations analysis, the factors that lead to target coverage alterations for three radiotherapy techniques: (1) field-in-field tangential 3DCRT, (2) 6 fields IMRT and (3) 2 semiarcs VMAT. Anatomic distances included in the treatment field (MHD, MHL, MLL, MLD) were assessed given their known impact on setup errors³. Thus, another goal of this work was to determine the extent these parameters influence dosimetric indices (CI, HI and MI). This analysis was conducted, comparatively, in both left-sided and right-sided breast cancer patients.

Methods and materials

Patient selection and characteristics

Forty female patients with breast cancer (20 left-sided = Group A and 20 right-sided = Group B) were enrolled in this study. All patients were treated in our center between 2021 and 2023 using 6 and/or 15 MV photon beams from an Elekta Synergy Platform with Agility multi-leaf collimator (MLC). In addition to the original 3D conformal treatment, intensity modulated (IMRT) and volumetric modulated arc radiotherapy (VMAT) plans were also simulated on Monaco treatment planning system (TPS) version 6.1.2 for comparative purpose.

Patients were enrolled in this study regardless of age, tumor size or volume irradiated (presence/absence of positive lymph nodes). An exclusion criterion was the presence of tumor bed (boost) irradiation.

The study was carried out in accordance with relevant guidelines and regulations. The research was approved by the Bihor County Emergency Clinical Hospital ethics committee. Informed consent was waived because the research did not enroll patients for this retrospective study. This work analyzed the data of patients that have been treated as per the normal medical protocol without any change induced by this study.

Computed tomography simulation

Computed tomography (CT) simulation was performed on a Siemens Somatom Definition AS 20 in supine position on an inclined Quest breast board. Patients were positioned supine with hands raised above the head resting on hand and arm supports provided by the breast board. Also, the head was turned to the opposite side of the irradiated breast.

The scanning protocol for breast cancer was performed with 5 mm slices from the middle of the liver up to the mandible. Additionally, the isocenter was marked between the last two ribs.

Treatment planning

The prescribed dose for breast and supraclavicular lymph nodes (mean volume for group A of 115.82 cc and 84.96 cc for group B, respectively) irradiation was 50 Gy in 25 fractions. Target volume and organs at risk were contoured by each patient's attending physician according to the RTOG consensus¹⁷. The OARs of interest were the heart, LAD, ipsilateral lung and contralateral breast.

3D conformal plans were calculated with Collapsed Cone Convolution (CCC) algorithm in Monaco 6.1.2 treatment planning system (TPS). Two opposite tangential fields (medial and lateral) were used for OARs sparing and field-in-field (FIF) technique for dose optimization in target volume. Lymph node irradiation was performed using 2 anterior and 1 posterior fields with FIF technique (Fig. 1).

The Monte Carlo algorithm was used for IMRT and VMAT plan calculations in Monaco 6.1.2 TPS. IMRT technique was performed using 6 fields for breast conformation and 2 anterior fields for lymph node irradiation (Fig. 1). VMAT technique was executed using 2 medial 45° (1 clockwise and 1 anti-clockwise) and 2 lateral 45° semiarcs with a region of avoidance (region without treatment field arrangements for lung sparing). Lymph node irradiation was performed using 1 anterior 45° semiarcs. Cost functions were employed for plan optimization applied to organs at risk and target volume; for mean dose control: $D_{mean} = 4$ Gy for heart and $D_{mean} = 20$ Gy for ipsilateral lung, and for volume control: $V_{25} < 10\%$ for heart and $V_{20} < 30\%$ for ipsilateral lung¹⁸. Target volume was optimized obtaining a coverage $> 95\%$ of the prescribed dose and a maximum dose $< 107\%$ of the prescribed dose. Same dose constraints for organs at risk and dose optimization in target volume were used in conformal plan calculations.

Patient-related parameters: planning target volume

Target volume was defined by outlining the clinical target volume (CTV) for breast area and/or lymph node irradiation according to the RTOG consensus¹⁷. Planning target volume (PTV) delineation was achieved by adding 5 mm margins to the CTV in all directions (except the anterior - the volume was withdrawn 3 mm from the skin) to exclude the heart and ipsilateral lung from the contoured volume¹⁹.

The size of target volume differs from patient to patient, therefore, the contoured volume (tumor volume - TV) was considered a variable parameter influencing dosimetric indices.

Patient-related parameters: organs at risk

Patient's characteristics and OAR geometrical indices are summarized in Table 1.

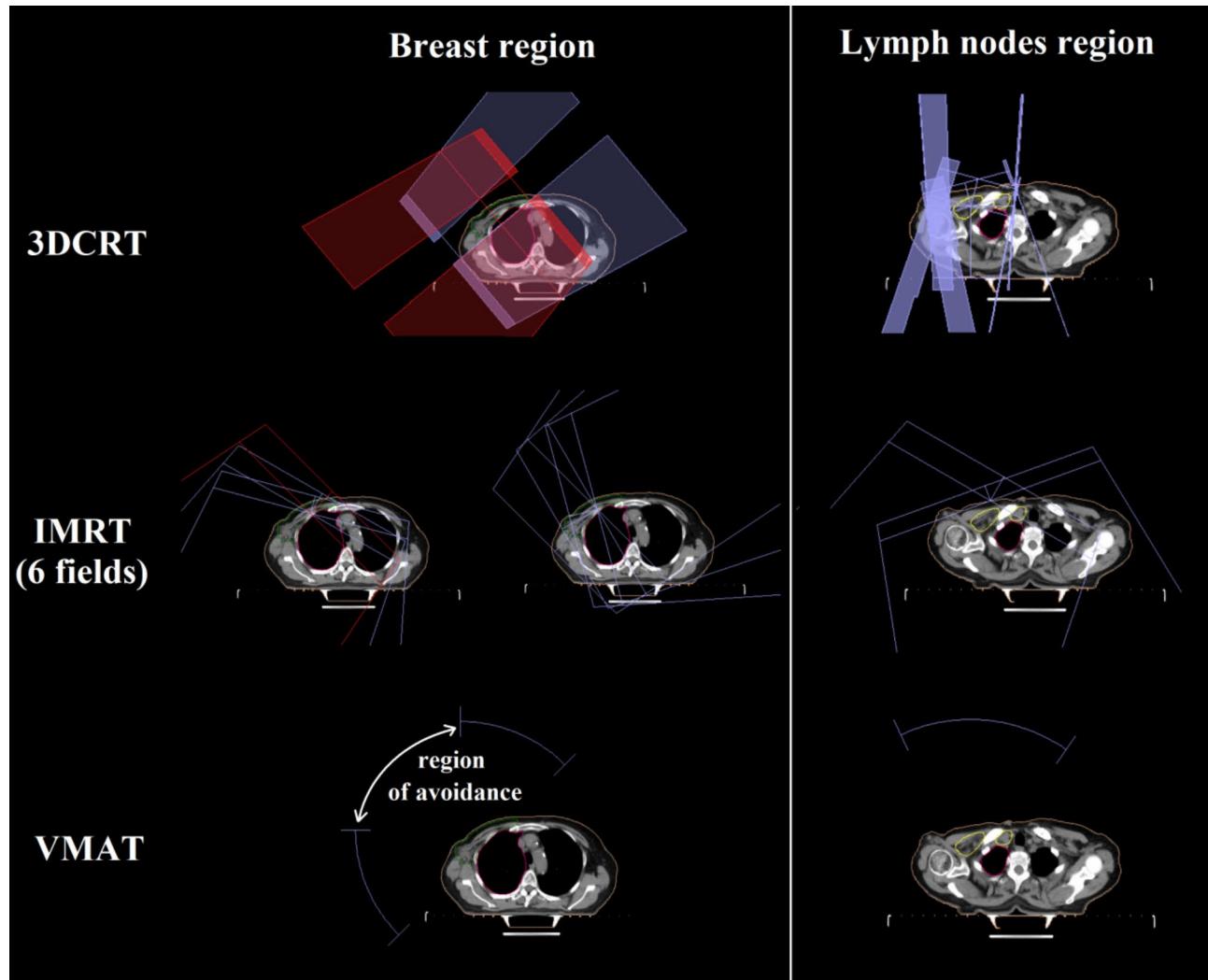


Fig. 1. Field geometry for conformal and intensity modulated plans represented in Monaco TPS 6.1.2.

Patients	Age	TV (cc)	MHD (mm)	MHL (mm)	MLD (mm)	MLL (mm)
Group A - left-sided breast irradiation						
1	53	1219.04	31.00	73.00	39.00	138.20
2	61	1100.07	6.20	50.20	32.20	141.20
3	53	993.51	21.10	55.30	35.30	120.00
4	65	827.06	-	-	23.40	110.30
5	56	906.62	6.50	58.00	34.00	176.10
6	37	1485.27	8.03	60.30	23.20	130.00
7	68	914.47	30.60	69.10	32.40	88.50
8	69	3005.64	22.20	63.50	45.20	144.50
9	52	1691.33	23.10	86.70	24.60	172.20
10	67	1008.29	18.00	79.10	40.20	178.60
11	51	721.73	34.20	75.60	39.70	192.10
12	66	1573.90	29.10	94.00	30.20	165.40
13	68	2018.91	33.00	67.10	35.70	107.30
14	60	383.61	30.30	56.70	44.10	134.50
15	51	363.39	-	-	18.60	148.20
16	78	2977.07	30.40	80.60	20.30	91.50
17	69	1489.68	23.00	44.20	29.70	132.90
18	82	276.27	23.20	91.60	22.90	137.30
19	75	818.08	8.30	70.20	23.20	118.30
20	42	928.91	28.30	85.90	40.60	142.80
Mean \pm SD / median (range)	61.15 \pm 1.70 / 63 (37–82)	1235.14 \pm 749.56 / 1000.90 (276.27–3005.64)	20.33 \pm 9.52 / 23.15 (6.20–34.20)	63.06 \pm 14.45 / 69.65 (44.20–94.00)	31.73 \pm 8.24 / 32.30 (18.60–45.20)	138.50 \pm 28.34 / 137.75 (88.50–192.10)
Group B - right-sided breast irradiation						
1	69	255.72	-	-	25.00	109.10
2	74	1204.41	-	-	35.50	140.50
3	69	543.55	-	-	49.50	170.30
4	58	496.28	-	-	39.00	176.70
5	72	1229.09	-	-	48.90	157.20
6	65	1021.07	6.20	19.20	45.20	115.10
7	79	746.313	-	-	28.90	158.20
8	52	1028.26	6.40	25.20	46.20	169.20
9	61	1396.28	-	-	42.00	158.60
10	40	1587.64	-	-	50.10	210.80
11	77	995.14	20.20	90.20	33.00	189.10
12	67	1561.99	-	-	28.00	156.30
13	78	553.15	-	-	27.10	185.40
14	74	571.37	-	-	32.00	113.60
15	74	1236.30	-	-	30.10	130.30
16	63	532.84	-	-	40.20	149.10
17	62	323.67	-	-	22.30	160.30
18	63	581.84	-	-	51.50	147.40
19	76	463.42	-	-	25.00	134.70
20	48	581.83	-	-	45.30	161.90
Mean \pm SD/median (range)	66.05 \pm 10.52 / 68 (40–79)	845.51 \pm 414.81 / 664.08 (255.72–1587.64)	10.93 \pm 8.03 / 6.40 (6.20–20.20)	44.87 \pm 39.37 / 25.20 (19.20–90.20)	37.24 \pm 9.67 / 37.25 (22.30–51.50)	154.69 \pm 26.11 / 157.70 (109.10–210.80)

Table 1. Patient's characteristics and OAR geometrical indices. TV = tumor volume, MHD = maximum heart distance, MHL = maximum heart length, MLD = maximum ipsilateral lung distance, MLL = maximum ipsilateral lung length. “-” the heart was not included in tangent fields (heart width and length = 0.00 mm), therefore the measurement of maximum heart distance and length was not possible.

Organs at risk-related parameters were calculated using the medial tangent field for heart and ipsilateral lung. The evaluated parameters were the following: maximum heart distance (MHD), maximum heart length (MHL), maximum ipsilateral lung distance (MLD) and maximum ipsilateral lung length (MLL). Maximum heart and ipsilateral lung distances were calculated as the maximum width of heart and lung included in the tangent fields. Maximum heart and ipsilateral lung lengths were calculated as the maximum length of heart and lung, respectively, included in the radiation fields (Fig. 2)^{6,8}.

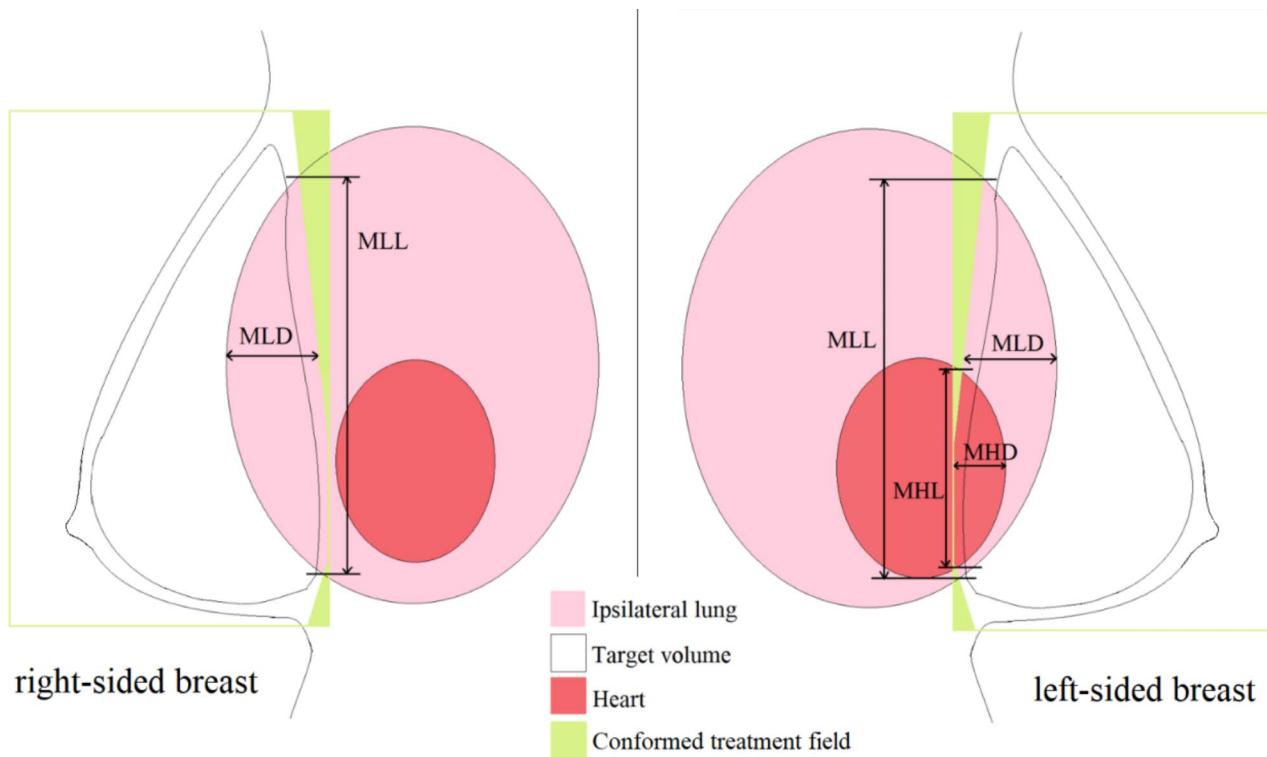


Fig. 2. Organs at risk-related parameters represented in beam eye view mode (MHD = maximum heart distance, MHL = maximum heart length, MLD = maximum ipsilateral lung distance, MLL = maximum ipsilateral lung length). The green square is the medial tangent field with collimation on breast target volume.

In addition, mean dose (D_{mean} ; heart, ipsilateral lung, LAD and contralateral breast), maximum dose (D_{max} ; heart, LAD and ipsilateral lung) and the dose to 1 cc of OAR volume ($D_{1\text{cc}}$; heart) were also evaluated.

Dosimetric indices

Dosimetric indices were evaluated for both target dose distribution conformity and OARs statistics.

Dosimetric indices: planning target volume

Homogeneity index (HI) identifies the absorbed dose uniformity distribution regarding the target volume with an optimal value close to 1^{20,21}. The following formula was used for HI calculation:

$$HI = \frac{D_{5\%}}{D_{95\%}},$$

where $D_{5\%}$ represents the dose (Gy) received by 5% of the target and $D_{95\%}$ is the dose (Gy) received by 95% of the target.

The conformity index (CI) characterizes the optimization of high-dose regions applied to the target volume with an optimal value close to 1^{20,21}. The following formula was used for CI calculation:

$$CI = \frac{V_{95\%}}{V_{\text{target}}},$$

where V_{target} represents the volume (cc) of target and $V_{95\%}$ is the volume (cc) of the 95% isodose of the prescribed dose (in our study, the isodose of 47.50 Gy).

The mismatch index (MI) was calculated to assess the percentage of prescribed dose outside the target volume^{22,23}. The following formula was used for MI calculation:

$$MI = \frac{V_{95\%-\text{target}}}{V_{95\%}},$$

where the $V_{95\%-\text{target}}$ represents the volume outside the target, calculated by extracting the target volume from the volume of 95% isodose ($V_{95\%}$).

Dosimetric indices: organs at risk

For further consolidation of correlations between the parameters pertaining to organs at risk (MHD, MHL, MLD and MLL) and dosimetric indices (CI, HI and MI), heart dosimetry (V_{25} , D_{mean} , D_{max} , D_{1cc}), ipsilateral lung (V_{20} , D_{mean}), contralateral breast (D_{mean} , D_{max}) and LAD (D_{mean} , D_{max}) were evaluated. As all plans fulfil the corresponding constraints (heart $V_{25} < 10\%$; ipsilateral lung $V_{20} < 30\%$), the percentage of patients with dosimetry laying in the proximity of constraints was assessed, i.e. patients with $5\% < V_{25} < 10\%$ for heart and $25\% < V_{20} < 30\%$ for ipsilateral lung.

Statistical analysis

To identify factors that influence target conformity and homogeneity, correlations were calculated between dosimetric indices vs. patient-related parameters.

Furthermore, MI was used to identify the factors that influence the increase of reference isodose (95% of the prescribed dose) percentage laying outside target volume. The correlation between MI and both dosimetric indices (CI, HI) and OAR-specific parameters (MHD, MHL, MLD, MLL, D_{mean}/D_{max} heart, ipsilateral lung, contralateral lung and LAD) was tested.

For right-sided breast cancer patients, the correlations between heart parameters (MHD and MHL) with CI, HI and MI were not possible due to the exclusion of the heart from the initial tangent fields.

Pearson correlation statistical test was used for evaluating the association between two variables. For moderate to strong correlation, results higher than $r = \pm 0.500$ were taken into account (Pearson correlation coefficient: $r > \pm 0.500$)²⁴.

Student's t-distribution test was employed to evaluate the statistical significance between differences among the 2 groups for CI, HI and MI. P-value threshold was set to 0.05 for statistical significance.

Results

Only for 3 patients in group B (right-sided breast cancer localization) the heart was present in treatment field projection. Therefore, heart parameters (MHD and MHL) were calculated only for 3 patients out of 20.

Dosimetric evaluation of heart for group A and B are presented in Fig. 3. Mean heart dose was higher than 4.00 Gy for all treatment techniques in group A (left-sided breast cancer patients): 4.99 ± 1.81 Gy for 3DCRT; 5.26 ± 1.15 Gy for IMRT and 5.09 ± 1.10 Gy for VMAT plans, and below 4.00 Gy for group B (right-sided breast cancer patients): 1.27 ± 0.66 Gy for 3DCRT; 2.66 ± 0.83 Gy for IMRT and 2.68 ± 0.59 Gy for VMAT plans. It is observed that D_{max} and D_{1cc} are below 30.00 Gy for group B and above 30.00 Gy for group A for all treatment techniques.

Dosimetric evaluations of the ipsilateral lung for groups A and B are presented in Fig. 4. Mean ipsilateral lung dose was smaller for 3DCRT plans in both groups (11.23 ± 3.10 Gy and 11.21 ± 3.12 Gy, $p\text{-value} = 0.984$) compared to IMRT (13.58 ± 2.26 Gy and 13.94 ± 1.41 Gy, $p\text{-value} = 0.607$) and VMAT plans (13.05 ± 2.61 Gy and 13.87 ± 1.46 Gy, $p\text{-value} = 0.267$).

LAD maximum and mean doses are represented in Fig. 5. Conformal plans presented higher mean (27.14 ± 10.91 Gy) and maximum doses (44.68 ± 12.18 Gy) than IMRT ($D_{mean} = 17.32 \pm 5.55$ Gy, $D_{max} = 34.78 \pm 8.10$ Gy) and VMAT ($D_{mean} = 16.28 \pm 6.29$ Gy, $D_{max} = 34.18 \pm 8.70$ Gy) in left-sided breast cancer patients (Group A). In group B, LAD was better spared with conformal plans ($D_{mean} = 1.00 \pm 0.42$ Gy, $D_{max} = 1.25 \pm 0.611$ Gy) than with modulated techniques (IMRT: $D_{mean} = 2.19 \pm 0.85$ Gy, $D_{max} = 3.48 \pm 1.60$ Gy; VMAT: $D_{mean} = 2.48 \pm 0.99$ Gy, $D_{max} = 3.81 \pm 2.20$ Gy).

Figure 6 shows similar mean and maximum doses for the contralateral breast between the two groups for conformal plans (D_{mean} $p\text{-value} = 0.468$, D_{max} $p\text{-value} = 0.414$), while modulated plans presented statistically significant differences regarding mean and maximum doses (IMRT: D_{mean} $p\text{-value} < 0.001$, D_{max} $p\text{-value} = 0.001$; VMAT: D_{mean} $p\text{-value} = 0.019$, D_{max} $p\text{-value} = 0.014$).

CI and HI are summarized in Table 2. Significant differences ($p\text{-value} < 0.05$) between the 2 groups were observed for CI in modulated treatment techniques and for HI only in IMRT plans.

The percentage of healthy tissue receiving 95% of the prescribed dose is represented in Fig. 7, through the mean MI for each group and for all treatment techniques. P-values are also indicated for statistical significance of differences between the 2 groups ($p\text{-value} = 0.249$ for 3DCRT, $p\text{-value} = 0.904$ for IMRT and $p\text{-value} = 0.692$ for VMAT).

Pearson correlation results (and p-values) are summarized in Table 3. Tumor volume positively correlated with CI in VMAT plans ($r = 0.506$, $p\text{-value} = 0.022$) for group A and in IMRT plans ($r = 0.502$, $p\text{-value} = 0.023$) for group B, while no correlation with HI was observed for conformal and modulated plans for either group. In addition, a moderate/strong negative correlation was found between tumor volume and MI for all treatment techniques ($r = -0.861$, $p\text{-value} < 0.001$ for 3DCRT, $r = -0.556$, $p\text{-value} = 0.010$ for IMRT and $r = -0.533$, $p\text{-value} = 0.015$ for VMAT) in group A and for 3DCRT plans ($r = -0.532$, $p\text{-value} = 0.015$) in group B. Positive correlations between TV and dosimetric indices indicates an increase in dosimetric parameters with an increase in TV.

Contralateral breast dosimetry correlated with HI in conformal plans ($D_{mean} r = 0.516$, $p\text{-value} = 0.019$) and in modulated plans (D_{max} : IMRT $r = 0.506$, $p\text{-value} = 0.022$; VMAT $r = 0.505$, $p\text{-value} = 0.022$) for group A patients (left-sided breast cancer).

MHL showed a moderate correlation only with the MI for conformal plans ($r = -0.522$, $p\text{-value} = 0.003$) for group A, while for group B the associations were not evaluated for heart parameters.

Mean heart dose correlated positively with CI ($r = 0.616$, $p\text{-value} = 0.003$) and with HI ($r = 0.599$, $p\text{-value} = 0.003$) for group A in conformal plans. However, mean ipsilateral lung dose moderately correlated with CI only for modulated plans (group A: $r = 0.511$, $p\text{-value} = 0.020$ IMRT and $r = 0.531$, $p\text{-value} = 0.015$ VMAT; group B: $r = 0.576$, $p\text{-value} = 0.011$ VMAT), while the association with HI was observed for VMAT

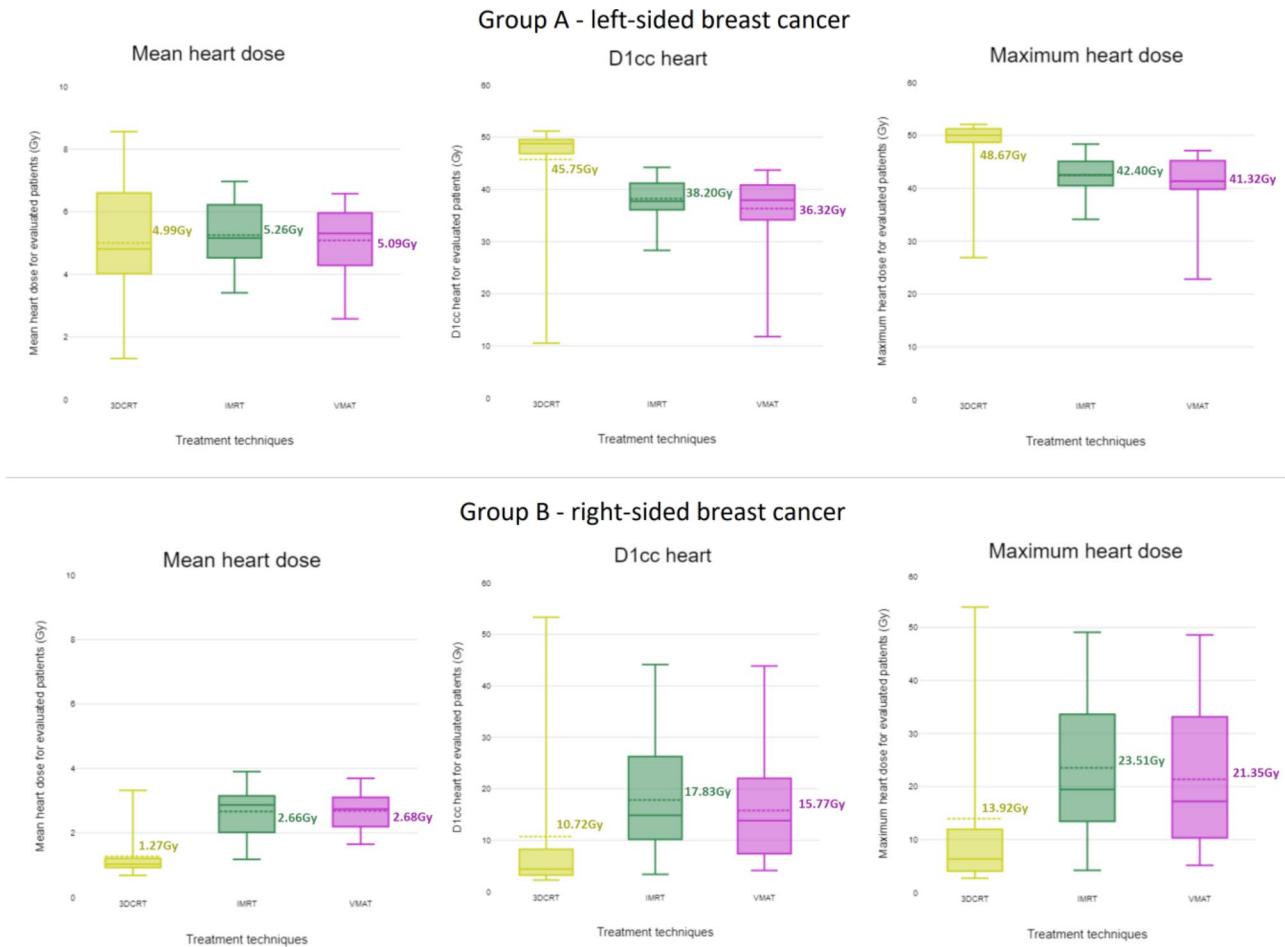


Fig. 3. Mean and median heart dose for both groups. Mean dose (values) represented as dashed line and median dose as solid line (3DCRT = 3D conformal radiotherapy, IMRT = intensity modulated radiotherapy, VMAT = volumetric modulated arc radiotherapy).

plans in group A ($r = 0.687$, p -value < 0.001), and with 3DCRT ($r = 0.573$, p -value $= 0.008$) and IMRT ($r = 0.515$, p -value $= 0.019$) in group B.

In group A, all evaluated parameters correlated with MI for at least one treatment technique. In conformal plans, Pearson correlation coefficient was higher than 0.500 for tumor volume ($r = -0.861$, p -value < 0.001), heart parameters ($r = -0.620$, p -value $= 0.003$ MHD, $r = -0.522$, p -value $= 0.017$ MHL) and ipsilateral lung parameters ($r = -0.660$, p -value $= 0.001$ MLD, $r = -0.582$, p -value $= 0.007$ MLL). The r coefficient presented correlations in intensity modulated plans for tumor volume ($r = -0.556$, p -value $= 0.010$) and MLL ($r = -0.594$, p -value $= 0.005$), while in volumetric modulated plans the coefficient was higher than 0.500 for all evaluated parameters, except for heart ($r = -0.195$, p -value $= 0.409$ MHD and $r = -0.347$, p -value $= 0.132$ MHL).

Mismatch index correlations in group B were observed only in conformal plans for tumor volume ($r = -0.532$, p -value $= 0.015$) and MLL ($r = -0.549$, p -value $= 0.011$) parameters.

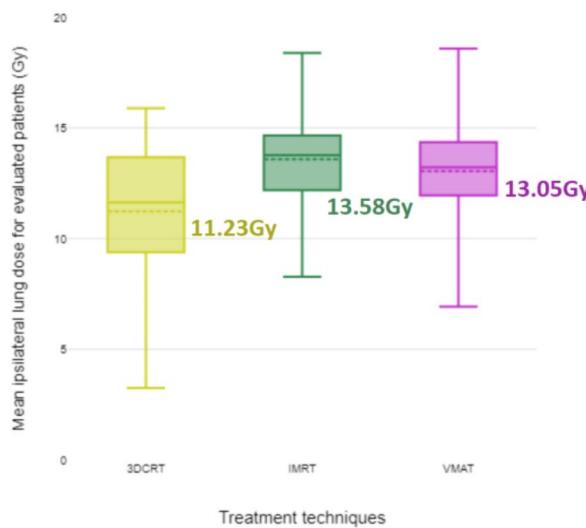
Moreover, mismatch index correlated negatively with conformity and homogeneity indices for both groups. A moderate correlation was observed in modulated plans in group A for CI ($r = -0.543$, p -value $= 0.013$ IMRT and $r = -0.546$, p -value $= 0.012$ VMAT) and for HI ($r = -0.555$, p -value $= 0.010$). Other moderate to strong correlations were found for conformal and intensity modulated plans for CI ($r = -0.608$, p -value $= 0.004$ 3DCRT and $r = -0.656$, p -value $= 0.001$ IMRT) and in modulated plans for HI ($r = -0.542$, p -value $= 0.013$ IMRT and $r = -0.571$, p -value $= 0.008$ VMAT) for group B.

Figure 8 shows mean V_{20} for ipsilateral lung (for whole group A and B) and the percentage of patients exceeding dose constraints, i.e. $V_{20} > 25\%$. A major difference between the 2 groups was observed for VMAT plans with mean $V_{20} = 20.67\%$ in left-sided patients (group A) and 24.82% in right-sided patients (group B).

Mean V_{25} for heart was evaluated only for left-sided breast cancer patients due to heart inclusion in tangent fields (the heart was included in tangent fields for only 3 right-sided patients so the evaluation of V_{25} was not conducted). Mean values represented for whole group A and B and the percentage of patients exceeding dose constraints, i.e. $V_{25} > 5\%$ are presented in Fig. 9. Modulated plans presented smaller values for V_{25} heart (3.74% IMRT and 3.47% VMAT) than conformal plans (5.65%), with more patients exceeding 5% of V_{25} for the latter technique.

Group A - left-sided breast cancer

Mean ipsilateral lung dose



Group B - right-sided breast cancer

Mean ipsilateral lung dose

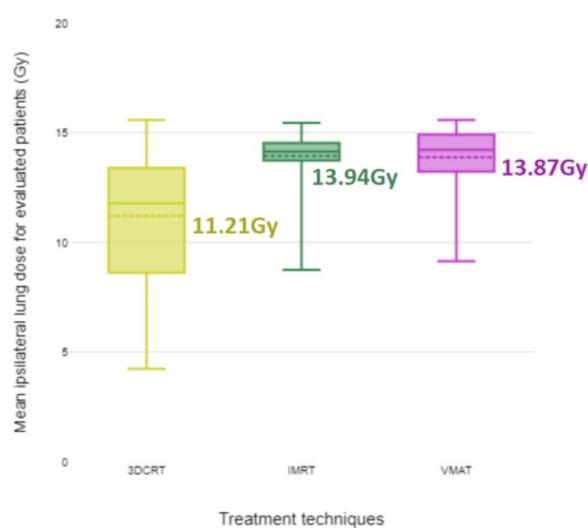


Fig. 4. Mean and median ipsilateral lung dose for both groups. Mean dose (values) represented as dashed line and median dose as solid line (3DCRT = 3D conformal radiotherapy, IMRT = intensity modulated radiotherapy, VMAT = volumetric modulated arc radiotherapy).

Discussion

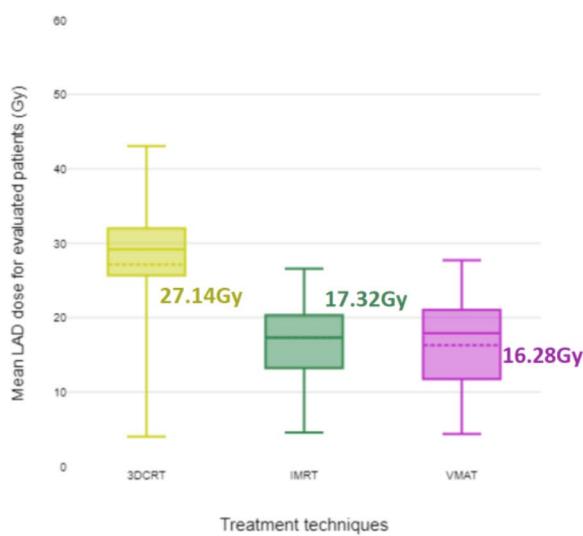
Plan personalization is a key concept in modern radiotherapy. Plan optimization according to the individual patient's tumor characteristics improves treatment efficacy and limits radiation-induced side effects²⁵. In view of this, plan personalization should take into account dosimetric indices pertaining to both target and OARs as an important indicators of treatment outcome. Conformity and homogeneity indices are two main indicators that reflect tumor coverage and dose uniformity within the tumor volume and were assessed in the current study in the context of breast cancer radiotherapy using three different treatment techniques.

Mean values of conformity and homogeneity indices were reported in the literature after analyzing the dosimetry of tumor volume and organs at risk of several treatment techniques²⁶. Liu et al. evaluated right-sided breast cancer patients by using two methods of VMAT technique (continuous partial arc and non-continuous partial arc), IMRT and hybrid 3DCRT/IMRT obtaining CI values of 0.74 for VMAT, 0.64 for IMRT and 0.68 for 3DCRT techniques. The conclusion suggested by Liu et al. regarding the high conformity index obtained by VMAT was that the technique can increase dose modulation in treatment fields which in turn increases the quality of tumor coverage²⁶. Another study evaluated treatment plans according to the CI for 100 plans comparing three treatment techniques: 3DCRT (CI = 0.46), FIF (CI = 0.59) and IMRT (CI = 0.72)²⁷. The study, among others^{28,29}, suggested that IMRT offers better tumor volume coverage than FIF plans and also that FIF has better coverage and fewer hot spots than 3DCRT. As shown by our study, the mean CI value obtained for right-sided patients was 0.78 for 3DCRT, while higher values were reached for IMRT (0.90) and VMAT (0.92), being consistent with the studies employing intensity-modulated techniques²⁶. For left-sided breast cancer patients, the CI values reported by our study were 0.80 for 3DCRT, 0.88 for IMRT and 0.89 for VMAT, showing better conformity compared to the plan characteristics described by Takabi et al. (CI = 0.46 for 3DCRT and CI = 0.72 for IMRT). Their study asserted that changing the treatment technique also changes the dose distribution in target volume²⁷.

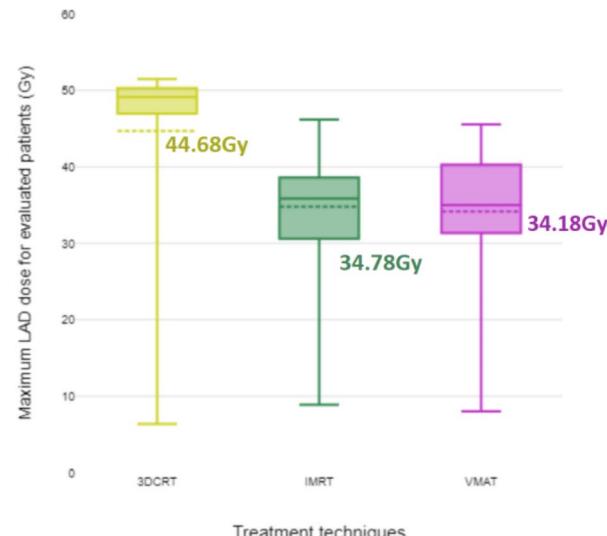
The homogeneity index is a variable that analyzes the uniformity of dose distribution in tumor volume. Petrova et al. evaluated this index for 58 patients with breast cancer using two methods of conformational technique (3DCRT with segments and 3DCRT with standard tangent fields) and obtained HI = 1.08 with segments and 1.09 without segments, showing a significant statistical difference between the two groups (p-value < 0.001)³⁰. Wang et al. evaluated the IMRT technique for 96 left-sided breast cancer patients reporting a mean homogeneity index of 1.095. The finding of the studies showed that although the index would be a good indicator of treatment plan evaluation⁸, the interpretation of the results should not be done from section to section, but based on the gradient and dose distribution in the tumor volume³⁰. However, it was concluded that hot spot reduction by using segments³⁰ or by modulating the intensity⁸, leads to an homogeneous dose distribution. In our study, the mean value of homogeneity index for 3DCRT was 1.10 for left-sided patients and 1.09 for right-sided patients, slightly higher than in modulated intensity plans (1.09 left-sided patients and 1.07 right-sided patients for IMRT; 1.08 left-sided patients and 1.07 right-sided patients for VMAT) although the FIF technique was used to control the hot spots.

Group A - left-sided breast cancer

Mean LAD dose

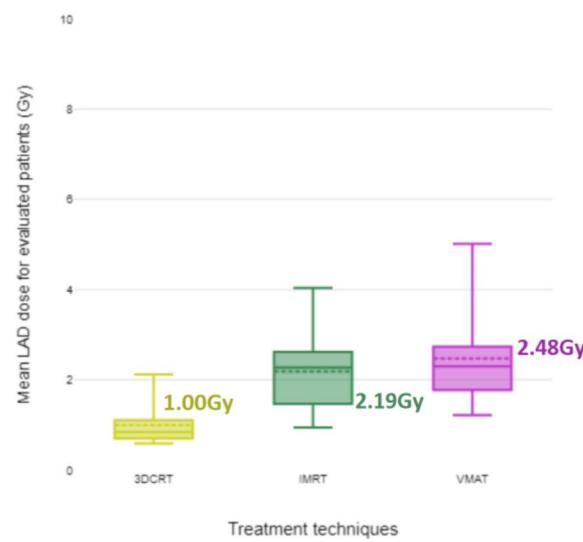


Maximum LAD dose



Group B - right-sided breast cancer

Mean LAD dose



Maximum LAD dose

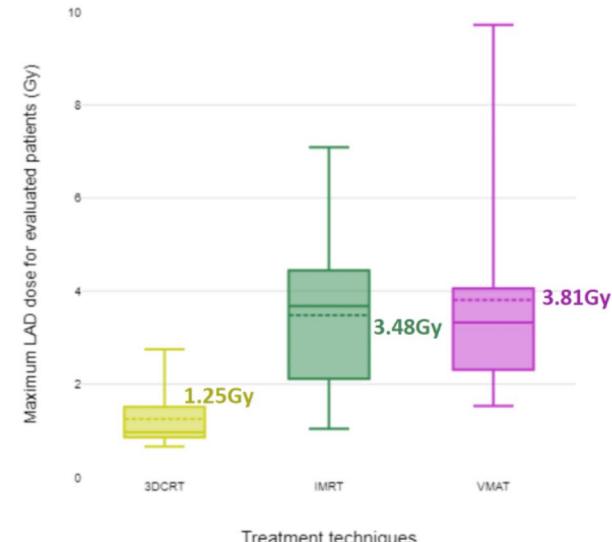
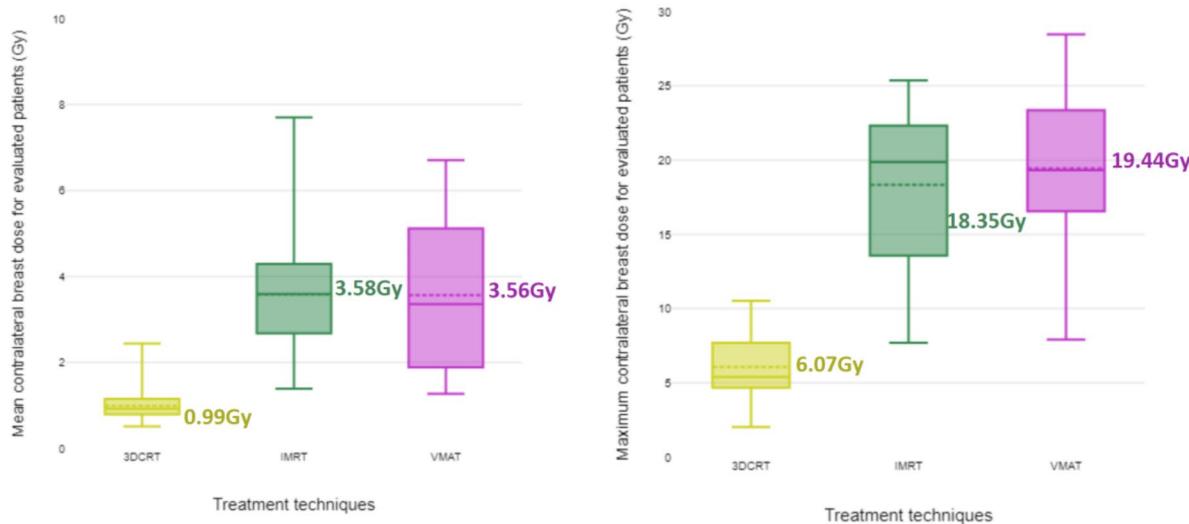


Fig. 5. Mean and median LAD doses for both groups. Mean dose (values) represented as dashed line and median dose as solid line (LAD = left anterior descending aorta, 3DCRT = 3D conformal radiotherapy, IMRT = intensity modulated radiotherapy, VMAT = volumetric modulated arc radiotherapy).

Due to lack of information regarding 3D dose distribution outside target volume, the mismatch index was created to report the influence of a reference isodose (specifically the 95% of the prescribed dose) on healthy tissue²³. Schoepen et al. evaluated the mismatch index for 51 patients divided into 4 groups depending on tumor stage and position (right or left-sided), using four treatment techniques (tangent fields with wedges - W-TF, tangent IMRT, multi-fields IMRT and VMAT) in three positions: supine, prone dive and prone crawl²³. The results of MI in supine position were 46.43% W-TF, 18.94% tangent IMRT, 11.33% multi-fields IMRT and 8.00% VMAT. Also, Mulliez et al. analyzed three treatment techniques (W-TF, tangent IMRT and multi-fields IMRT) in supine and prone position suggesting higher values than Schoepen's study for modulated techniques in supine position: 46.80% W-TF, 34.70% tangent IMRT and 28.50% multi-field IMRT. The conclusions drawn by the studies concerning mismatch index escalation in conformal techniques were related to the concave shape of the breast²² and the longer path lengths through healthy tissue in lateral tangent and axillary/shoulder regions for lymph node irradiation^{22,23}. Mean values of mismatch index in our study were comparable to those in the

Group A - left-sided breast cancer

Mean contralateral breast dose Maximum contralateral breast dose



Group B - right-sided breast cancer

Mean contralateral breast dose Maximum contralateral breast dose

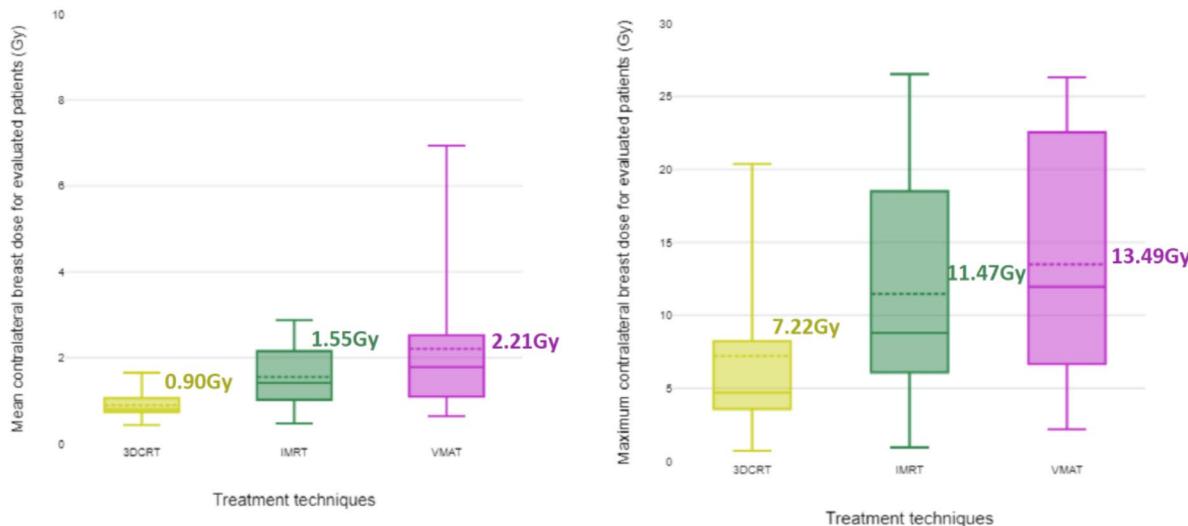


Fig. 6. Mean and median contralateral breast dose for both groups. Mean dose (values) represented as dashed line and median dose as solid line (3DCRT = 3D conformal radiotherapy, IMRT = intensity modulated radiotherapy, VMAT = volumetric modulated arc radiotherapy).

Mean value of indices (SD)	3DCRT			IMRT			VMAT		
	A (left-sided breast)	B (right-sided breast)	p-value	A (left-sided breast)	B (right-sided breast)	p-value	A (left-sided breast)	B (right-sided breast)	p-value
CI	0.80 (0.05)	0.78 (0.06)	0.391	0.88 (0.02)	0.90 (0.03)	0.003	0.89 (0.02)	0.92 (0.03)	0.007
HI	1.10 (0.02)	1.09 (0.01)	0.206	1.09 (0.02)	1.07 (0.01)	0.008	1.08 (0.02)	1.07 (0.01)	0.159

Table 2. Mean conformity and homogeneity index (significant p-value highlighted in bold). A = group A, B = group B, SD = standard deviation, CI = conformity index, HI = homogeneity index, 3DCRT = 3D conformal radiotherapy, IMRT = intensity modulated radiotherapy, VMAT = volumetric modulated arc radiotherapy, p-value = Student's t-distribution coefficient (p-value < 0.05 to be statistically significant).

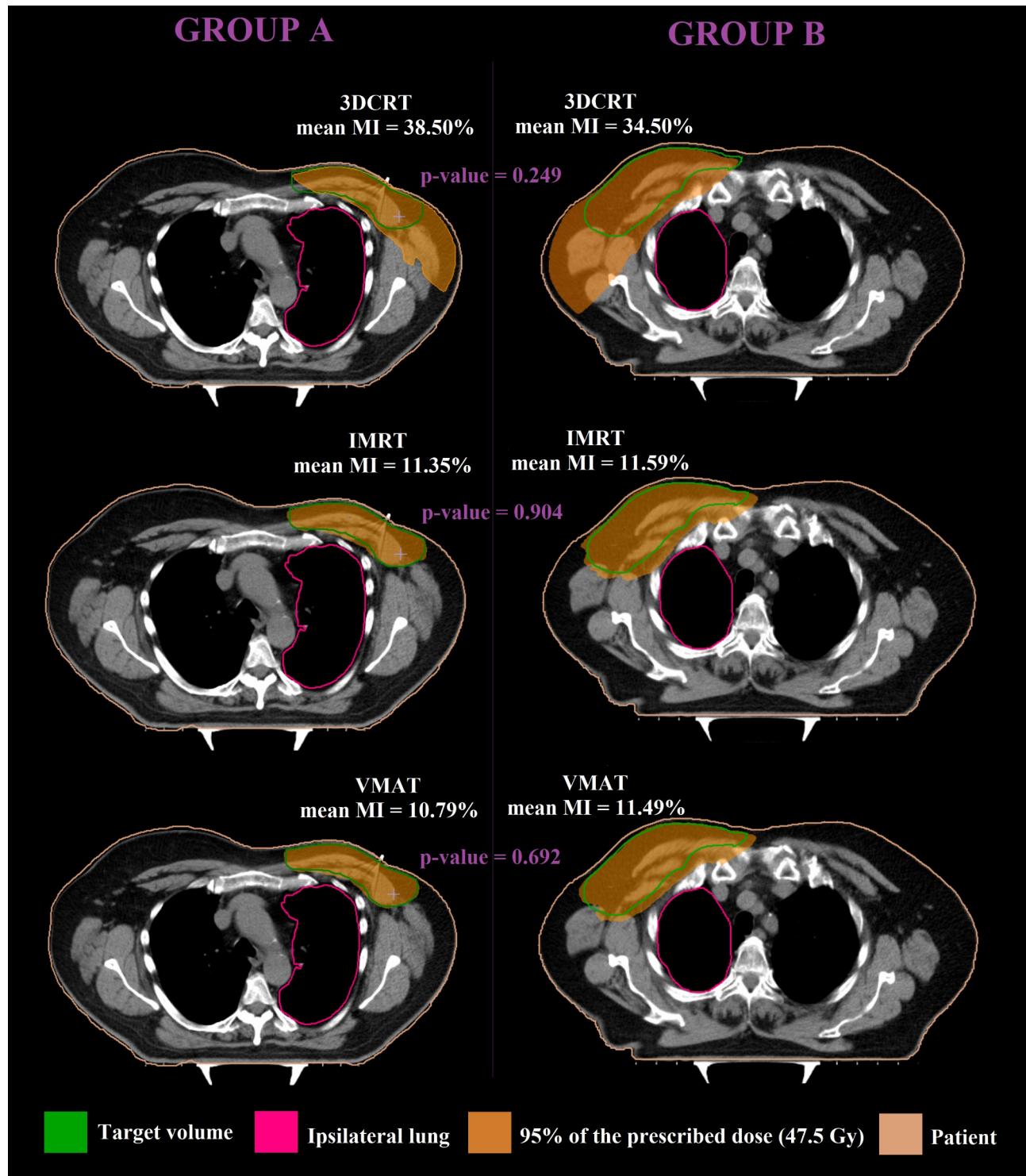


Fig. 7. Mean mismatch index for group A and B (MI = mismatch index, 3DCRT = 3D conformal radiotherapy, IMRT = intensity modulated radiotherapy, VMAT = volumetric modulated arc radiotherapy). The figures are representative examples of patients for each evaluated group.

literature, reporting higher values for 3DCRT (34.50% right-sided patients and 38.50% left-sided patients) and lower for modulated intensity plans for both groups of patients (11.59% right-sided patients and 11.35% left-sided patients for IMRT; 11.49% right-sided patients and 10.79% left-sided patients for VMAT plans).

Owing to the differences of CI, HI and MI among treatment techniques, our study evaluated the correlations between indices and tumor volume and OAR-related parameters for both groups of patients.

r (p-value)	CI			HI			MI		
	3DCRT	IMRT	VMAT	3DCRT	IMRT	VMAT	3DCRT	IMRT	VMAT
Group A: left-sided breast irradiation									
TV	0.358 (0.119)	0.329 (0.155)	0.506 (0.022)	0.352 (0.126)	0.339 (0.142)	0.193 (0.414)	-0.861 (< 0.001)	-0.556 (0.010)	-0.533 (0.015)
MHD	0.563 (0.009)	0.107 (0.654)	0.251 (0.284)	0.213 (0.366)	-0.056 (0.815)	-0.077 (0.745)	-0.620 (0.003)	-0.354 (0.124)	-0.195 (0.409)
MHL	0.205 (0.385)	0.155 (0.514)	0.215 (0.362)	0.104 (0.663)	0.141 (0.552)	0.071 (0.767)	-0.522 (0.017)	-0.252 (0.282)	-0.347 (0.132)
MLD	0.274 (0.241)	0.608 (0.004)	0.641 (0.002)	0.386 (0.091)	0.517 (0.019)	0.623 (0.003)	-0.660 (0.001)	-0.234 (0.320)	-0.507 (0.021)
MLL	0.379 (0.098)	0.142 (0.550)	0.576 (0.007)	0.735 (< 0.001)	0.274 (0.240)	0.247 (0.291)	-0.582 (0.007)	-0.594 (0.005)	-0.554 (0.011)
D_{mean} H	0.616 (0.003)	0.289 (0.215)	0.125 (0.598)	0.599 (0.003)	-0.292 (0.210)	0.002 (0.995)	-0.378 (0.099)	-0.270 (0.249)	-0.526 (0.016)
D_{max} H	0.012 (0.961)	0.214 (0.340)	0.106 (0.657)	0.034 (0.888)	0.225 (0.338)	0.322 (0.164)	-0.162 (0.492)	-0.147 (0.535)	-0.342 (0.138)
D_{1cc} H	0.019 (0.938)	0.180 (0.447)	0.154 (0.517)	0.356 (0.859)	0.152 (0.522)	0.188 (0.426)	-0.159 (0.501)	-0.220 (0.351)	-0.289 (0.216)
D_{mean} LAD	0.076 (0.751)	-0.123 (0.606)	-0.094 (0.694)	0.552 (0.022)	-0.059 (0.806)	-0.058 (0.807)	0.045 (0.850)	0.068 (0.776)	0.004 (0.956)
D_{max} LAD	0.148 (0.533)	0.089 (0.707)	0.098 (0.682)	0.158 (0.504)	0.086 (0.719)	0.152 (0.522)	-0.171 (0.471)	-0.096 (0.688)	-0.184 (0.436)
D_{mean} L	0.077 (0.746)	0.511 (0.020)	0.531 (0.015)	0.162 (0.495)	0.079 (0.737)	0.687 (< 0.001)	0.048 (0.839)	-0.283 (0.225)	-0.559 (0.010)
D_{mean} CB	-0.346 (0.133)	0.032 (0.892)	-0.010 (0.967)	0.516 (0.019)	0.395 (0.083)	0.372 (0.105)	-0.043 (0.857)	-0.039 (0.870)	-0.305 (0.189)
D_{max} CB	0.101 (0.670)	0.350 (0.129)	0.156 (0.509)	0.185 (0.434)	0.506 (0.022)	0.505 (0.022)	-0.657 (0.001)	-0.354 (0.124)	-0.279 (0.232)
MI	-0.230 (0.328)	-0.543 (0.013)	-0.546 (0.012)	-0.359 (0.118)	-0.318 (0.170)	-0.555 (0.010)	-	-	-
Group B: right-sided breast irradiation									
TV	0.322 (0.323)	0.502 (0.023)	0.383 (0.094)	0.292 (0.211)	0.171 (0.471)	0.366 (0.111)	-0.532 (0.015)	-0.259 (0.269)	-0.009 (0.969)
MHD	-	-	-	-	-	-	-	-	-
MHL	-	-	-	-	-	-	-	-	-
MLD	0.279 (0.232)	0.183 (0.439)	0.192 (0.417)	-0.215 (0.364)	0.599 (0.005)	0.017 (0.944)	0.150 (0.526)	-0.135 (0.571)	0.186 (0.432)
MLL	0.077 (0.745)	0.626 (0.003)	0.246 (0.295)	0.675 (< 0.001)	0.118 (0.619)	0.511 (0.020)	-0.549 (0.011)	-0.054 (0.820)	-0.149 (0.530)
D_{mean} H	0.020 (0.934)	0.043 (0.857)	0.183 (0.438)	0.434 (0.054)	0.056 (0.815)	0.192 (0.417)	0.074 (0.758)	0.170 (0.472)	0.246 (0.294)
D_{max} H	-0.094 (0.693)	0.071 (0.765)	0.196 (0.406)	-0.120 (0.614)	0.165 (0.485)	-0.322 (0.165)	0.150 (0.526)	-0.335 (0.147)	0.124 (0.602)
D_{1cc} H	-0.220 (0.351)	0.022 (0.927)	0.114 (0.632)	-0.165 (0.487)	0.048 (0.841)	-0.282 (0.226)	0.213 (0.367)	-0.249 (0.289)	0.162 (0.495)
D_{mean} LAD	0.183 (0.440)	0.422 (0.062)	0.130 (0.584)	0.017 (0.944)	0.038 (0.873)	0.054 (0.821)	-0.052 (0.828)	-0.411 (0.070)	0.056 (0.814)
D_{max} LAD	0.139 (0.559)	0.354 (0.124)	0.105 (0.659)	-0.029 (0.902)	-0.049 (0.834)	0.067 (0.780)	-0.046 (0.847)	-0.379 (0.097)	0.067 (0.778)
D_{mean} L	0.089 (0.852)	0.095 (0.931)	0.576 (0.011)	0.573 (0.008)	0.515 (0.019)	0.030 (0.899)	0.493 (0.044)	0.114 (0.423)	-0.109 (0.324)
D_{mean} CB	0.289 (0.216)	0.336 (0.145)	0.099 (0.678)	-0.026 (0.915)	0.005 (0.985)	-0.193 (0.414)	-0.022 (0.926)	-0.347 (0.132)	0.013 (0.956)
D_{max} CB	0.153 (0.518)	0.403 (0.077)	0.232 (0.326)	-0.169 (0.475)	0.127 (0.594)	-0.310 (0.181)	0.351 (0.128)	-0.288 (0.216)	0.051 (0.832)
MI	-0.608 (0.004)	-0.656 (0.001)	-0.399 (0.079)	-0.136 (0.568)	-0.542 (0.013)	-0.571 (0.008)	-	-	-

Table 3. Correlations between patient-related parameters and dosimetric indices (r coefficients higher than ± 0.500 are highlighted in bold along with p-values in brackets). TV = tumor volume, CI = conformity index, HI = homogeneity index, MI = mismatch index, MHD = maximum heart distance, MHL = maximum heart length, MLD = maximum ipsilateral lung distance, MLL = maximum ipsilateral lung length, D_{mean} H = mean dose of the heart, D_{mean} L = mean dose of the ipsilateral lung, D_{max} H = maximum dose of the heart, D_{1cc} H = dose to 1 cc of the heart, D_{mean} LAD = mean dose of left anterior descending aorta, D_{max} LAD = maximum dose of left anterior descending aorta, D_{mean} CB = mean dose of contralateral breast, D_{max} CB = maximum dose of contralateral breast, r = Pearson correlation parameter, 3DCRT = 3D conformal radiotherapy, IMRT = intensity modulated radiotherapy, VMAT = volumetric modulated arc radiotherapy.

For right sided-breast cancer patients, dose normalization on heart and ipsilateral lung has been presented in the literature under different dosimetric values. Liu et al. evaluated patients with right-sided breast cancer using four radiotherapy techniques (continuous partial arc, non-continuous partial arc, hybrid 3DCRT/IMRT and IMRT) reporting mean heart doses of 1.73 Gy, 3.15 Gy, 1.47 Gy and 4.35 Gy for each of the above-mentioned technique, respectively²⁶. A study conducted by Czeremszynska et al. evaluated 10 patients with right-sided breast cancer comparing three treatment techniques (3DCRT, IMRT and VMAT) showing mean heart doses of 0.85 Gy (3DCRT), 1.30 Gy (IMRT) and 1.70 Gy (VMAT)³¹. In our study, the mean heart dose for right-sided patients was under 3.00 Gy for all evaluated treatment techniques. In addition, the literature reported values between 7.60 and 10.14 Gy in conformal plans, between 8.50 and 12.76 Gy in IMRT and 8.32–9.00 Gy in VMAT plans^{26,31} for ipsilateral lung dosimetry. Our study presented comparative mean values of 11.21 Gy for 3DCRT, 13.94 Gy for IMRT and 13.87 Gy for VMAT plans. These different dosimetric values between studies reinforce the need for treatment personalization, for dose reduction to OARs on an individual basis.

Furthermore, LAD has become an organ at risk of interest in breast cancer treatment, therefore, it is often evaluated in right-sided breast treatments. Gocer et al. selected 40 patients with right and left-sided breast cancer treated with wedged tangent fields in order to evaluate radiotherapy-induced cardiotoxicity³². The study presented comparable values for mean LAD dose (9.76 Gy) and maximum dose (11.19 Gy) for right-sided

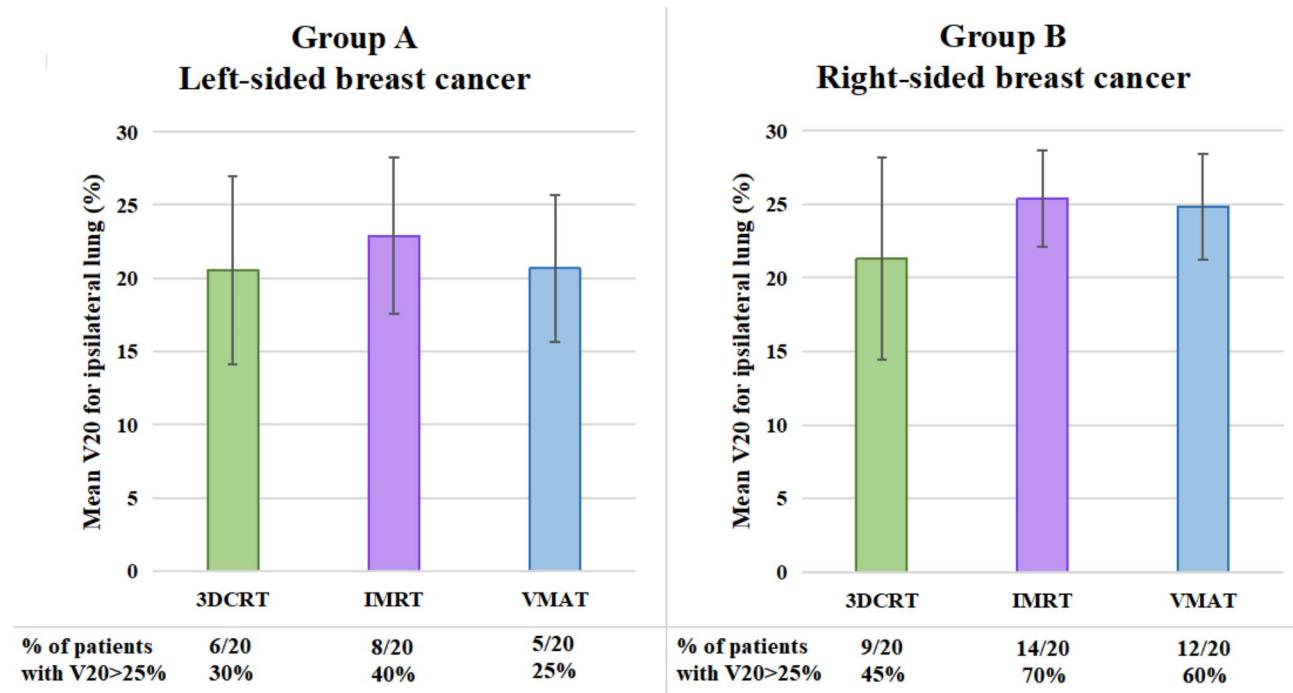


Fig. 8. Mean V_{20} ipsilateral lung parameter calculated for all left (group A) and right-sided (group B) breast cancer patients and for all treatment techniques. (3DCRT = 3D conformal radiotherapy, IMRT = intensity modulated radiotherapy, VMAT = volumetric modulated arc radiotherapy).

patients. In our study, the mean LAD values were 1.00 Gy for 3DCRT, 2.19 Gy for IMRT and 2.48 Gy for VMAT. Maximum dose was 1.25 Gy in conformal plans and 3.48 Gy and 3.81 Gy for IMRT and VMAT, respectively.

Lower doses were also observed on contralateral breast in conformal plans ($D_{mean} = 0.90$ Gy, p-value 3DCRT vs. IMRT/VMAT < 0.01 and $D_{max} = 7.22$ Gy, p-value 3DCRT vs. IMRT/VMAT < 0.01) compared to modulated plans (IMRT $D_{mean} = 1.55$ Gy and $D_{max} = 11.47$ Gy; VMAT $D_{mean} = 2.21$ Gy and $D_{max} = 13.49$ Gy), a trend that was observed by other studies^{31,35,34}. This fact is mainly due to the scattered radiation from the linac head or within the treated breast, as the amount of radiation on contralateral breast increases with the decrease of its distance from the treated breast. Furthermore, this dose difference highlights one of the most important disadvantage of modulated techniques, namely the difficulty of controlling low-dose volumes, mainly because modulated plans were created with multiple fields (contributing to the cumulative dose), while conformal plans were created using two opposite tangent fields^{31,35,36}. Moreover, MU delivered in modulated techniques are higher than conformal plans (IMRT: 471.20 ± 44.40 MU and VMAT: 672.40 ± 126.70 MU vs. 3DCRT: 395.50 ± 84.20 MU, p-value < 0.01) due to modulation complexity and small MLC segments, which increase the scattered radiation, leading to higher low-dose volumes³¹.

Owing to the limited number of reports in the literature regarding the factors influencing tumor volume coverage, this study included correlations between dosimetric indices and patient-specific variables depending on treatment field geometry (MHD, MHL, MLD, MLL, D_{mean} heart, D_{mean} lung) and tumor volume. Our study identified several factors that influence the conformity index, one of them being the tumor volume ($r = 0.502$, p-value = 0.023 IMRT). No correlation between tumor volume and homogeneity index was found for any of the evaluated treatment techniques.

However, correlations were observed between lung parameters and dosimetric indices (CI and HI). The MLL parameter showed correlation with CI for IMRT ($r = 0.626$, p-value = 0.003) and with HI for 3DCRT ($r = 0.675$, p-value < 0.001) and VMAT ($r = 0.511$, p-value = 0.020). Ipsilateral lung dosimetry was evaluated using mean dose ($D_{mean} < 20$ Gy) and volumetric parameters ($V_{20} < 30\%$). Although the mean dose is below the limit imposed by the attending physician for all treatment techniques, the mean values of V_{20} were: 21.30% (6.19 – 29.30%) for 3DCRT, 25.36% (16.54 – 29.67%) for IMRT and 24.82% (16.43 – 28.25%) for VMAT. Values higher than 25% reaching 30% of irradiated volume (being an interval close to dose limit) were extracted for the V_{20} parameter. The results showed better lung sparing in 3DCRT plans, with 9 patients (45%) exceeding the interval in group B, while 14 patients (70%) for IMRT and 12 patients (60%) for VMAT plans were close to dose limits. The large number of patients presented with difficulties in lung sparing indicates the need for correlation with MLL parameter, as OARs dose reduction is detrimental to target volume coverage^{8,37}.

In addition, the correlation between MLD and homogeneity index ($r = 0.599$, p-value = 0.005 IMRT) could be justified by the increased values of irradiated lung volume and the attempt of the calculation algorithm to reduce the dose, by penalizing the tumor volume uniformity dose distribution^{8,37}.

The evaluation of mean and maximum LAD dose indicated the lack of correlations between these parameters and dosimetric indices (CI, HI and MI), suggesting no influence on target coverage and homogeneity due to

Group A

Left-sided breast cancer

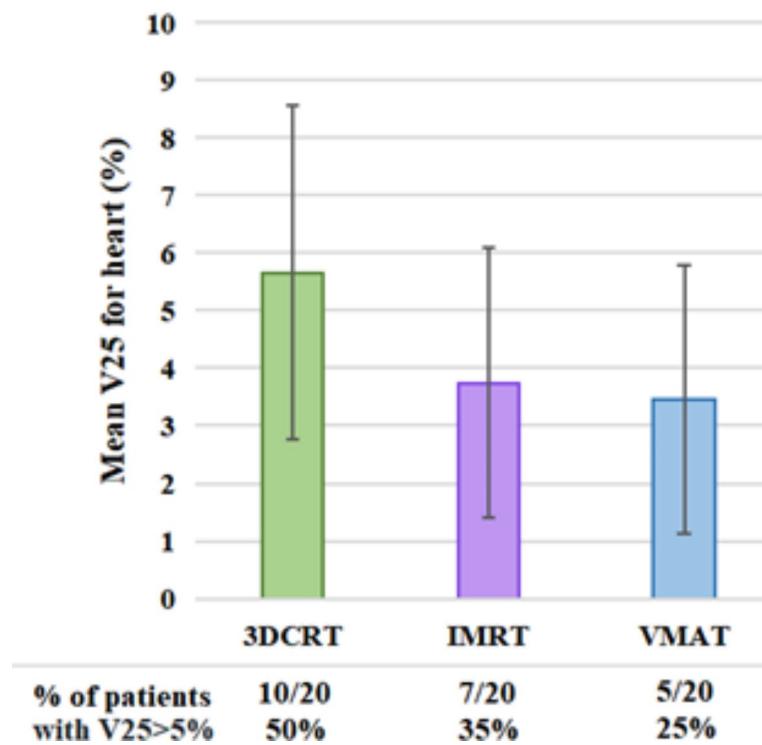


Fig. 9. Mean V_{25} heart calculated for all left-sided breast cancer patients (group A) for all treatment techniques. (3DCRT = 3D conformal radiotherapy, IMRT = intensity modulated radiotherapy, VMAT = volumetric modulated arc radiotherapy).

its anatomical position and distance relative to the target. Likewise, no correlations were observed between the contralateral breast and dosimetric indices.

As stated by Wang et al., CI and HI mean values of intensity modulated plans were affected not only by gantry angle and MLC movement, but also by the OAR dose limitation and spatial distance. The increase in number of OARs and dose constraints would complicate planning optimization. To improve the efficiency of planning design by increasing the conformity index when increasing the subfields or using different gantry angles (factors not specific to patients), low-dose exposure volume of OARs increases as well³⁷.

The mismatch index was evaluated to identify the influence of 95% isodose of the prescribed dose (47.50 Gy) outside the irradiated volume on organs at risk. A moderate correlation was observed between tumor volume and MI ($r = -0.532$, p -value = 0.015), suggesting an increase in the percentage of dose outside the target, especially in 3DCRT plans, which can be confirmed by the geometry used for planning (tangent fields) and dose accumulation in the patient's posterior region (Fig. 7). The fact that there were no correlations with intensity modulated plans may suggest the algorithm's ability to optimize the dose distribution taking into account the increase in target coverage. Also, the percentage escalation might influence OARs dosimetry, a fact that can be asserted by the correlation between MI and MLL parameter ($r = -0.549$, p -value = 0.011) in conformal plans.

In addition, the percentage of 47.50 Gy outside target volume might also influence tumor volume coverage, which is indicated by correlations between MI and CI ($r = -0.608$, p -value = 0.004 3DCRT, $r = -0.656$, p -value = 0.001 IMRT) and HI ($r = -0.542$, p -value = 0.013 IMRT, $r = -0.571$, p -value = 0.008 VMAT).

Mean heart and ipsilateral lung dose were assessed for left-sided breast cancer patients. A number of studies in the literature compared different treatment techniques regarding heart and ipsilateral lung dosimetry. Czeremszynska et al. evaluated 17 left-sided breast cancer patients and found mean heart doses of 3.60 Gy for 3DCRT, 3.70 Gy for IMRT and 3.80 Gy for VMAT techniques³¹. Cardiac dosimetry (mean dose) reported by Das Majumbar et al. for 35 left-sided breast cancer patients for three treatment techniques evaluated were 11.89 Gy for 3DCRT, 14.25 Gy for IMRT and 12.35 Gy for VMAT plans¹⁰. In our study, mean heart dose for left-sided breast cancer patients was approximately 5.00 Gy for all evaluated treatment techniques. Regarding the lung, studies reported values of 18.25 Gy for 3DCRT, 13.66 Gy for IMRT and 12.35 Gy for VMAT plans for mean ipsilateral lung dose^{10,37}. Our study presented comparative mean values of 11.23 Gy for 3DCRT, 13.58 Gy for IMRT and 13.94 Gy for VMAT techniques.

Furthermore, both mean and maximum LAD doses were observed to be higher in conformal plans ($D_{mean} = 27.14$ Gy and $D_{max} = 44.68$ Gy) compared to those from intensity modulated plans (IMRT $D_{mean} = 17.32$ Gy and $D_{max} = 34.78$ Gy; VMAT $D_{mean} = 16.28$ Gy and $D_{max} = 34.18$ Gy), outcome that was also observed by Czeremszynska et al. (3DCRT $D_{max} = 35.70$ Gy, IMRT $D_{max} = 31.00$ Gy and VMAT $D_{max} = 28.90$ Gy)³¹ and by Garg et al. (3DCRT $D_{max} = 48.68$ Gy, IMRT $D_{max} = 48.22$ Gy, p-value = 0.66)³⁸. This is owing to the inclusion of LAD in treatment fields, being located in the anterior part of the heart which receives a higher dose than the whole heart in breast cancer irradiation³².

The mean LAD dose reported in our study is comparable to other studies that used modulated plans (IMRT 11.04 Gy and VMAT 11.09 Gy)²³, forward and inverse IMRT techniques (9.50 Gy forward IMRT and 17.17 Gy inverse IMRT)³² or tangent fields techniques (24.02 Gy)³⁹.

Dosimetry of the contralateral breast showed a reduction in mean and maximum dose in conformal plans ($D_{mean} = 0.99$ Gy and $D_{max} = 6.07$ Gy) compared to IMRT plans ($D_{mean} = 3.58$ Gy and $D_{max} = 18.35$ Gy) and VMAT ($D_{mean} = 3.56$ Gy and $D_{max} = 19.44$ Gy), which is explained by the chosen field geometry (tangent fields for 3DCRT and multi-field arrangement for IMRT/VMAT plans)^{35,36}. Other studies reported mean doses of 1.43–2.39 Gy and maximum doses of 41.13–43.55 Gy for IMRT plans³⁹.

The differences between treatment techniques regarding OARs dosimetry should raise careful consideration towards personalized plans while evaluating factors that suggest possible penalties on tumor volume or organs at risk.

Wang et al. evaluated 4 factors (tumor volume, apex of the heart distance to the field - MHD, lung maximum width - CLD and cardiothoracic ratio - CTR) for 96 left-sided patients using the IMRT technique⁸. The results expressed through linear regression analysis showed that the tumor volume, MHD and CTR appeared to be the factors influencing the conformity index, while the only evaluated parameter that influenced the homogeneity index was the tumor volume.

The correlation between CI and TV of our study was also observed in group A patients using volumetric modulation plans ($r = 0.506$, p-value = 0.022), but no correlation was observed with the homogeneity index for the evaluated treatment techniques.

Correlations with heart parameters were evaluated for this group of patients, being an organ at risk in the vicinity of the tumor volume. A correlation was observed between MHD and conformity index for the 3DCRT technique, a result implied by the 50% of the evaluated patients which had V_{25} values close to the maximum limit (10%) imposed by the attending physician. For the other techniques, V_{25} was 35% in IMRT and 25% in VMAT, without correlations with the conformity or homogeneity index. Other moderate correlations were observed with mean heart dose for both CI ($r = 0.616$, p-value = 0.003) and HI ($r = 0.599$, p-value = 0.003) in conformal technique due to large variations of mean doses: 1.31 – 8.56 Gy.

Ipsilateral lung parameters showed higher number of correlations with CI and HI than those for the heart. Plans with intensity modulation showed correlations between MLD and both indices (CI: $r = 0.608$, p-value = 0.004 IMRT and $r = 0.641$, p-value = 0.002 VMAT; HI: $r = 0.517$, p-value = 0.019 IMRT and $r = 0.623$, p-value = 0.003 VMAT) and between MLL and CI in VMAT plans ($r = 0.576$, p-value = 0.007). These correlations could be justified through the addition of V_{20} constraint on ipsilateral lung, which complicates tumor volume optimization⁸, although a strong correlation was observed in conformal plans with MLL and HI ($r = 0.735$, p-value < 0.001). The percentage of patients who presented values for V_{20} greater than 25% was 30% (6/20) for 3DCRT, 40% (8/20) for IMRT and 25% (5/20) for VMAT.

Correlations were also observed between mean ipsilateral lung dose and CI (for IMRT and VMAT) and HI (for VMAT) being in accordance with weight escalation in planning optimization and OARs dose accumulation^{8,37,40}. Furthermore, LAD showed correlations with HI in conformal plans ($r = 0.552$, p-value = 0.039), suggesting that OAR dose reduction leads to coverage/homogeneity alteration of the target volume.

Significant positive correlations were observed between contralateral breast dosimetry and HI. Mean dose correlated in 3DCRT plans ($r = 0.516$, p-value = 0.019), and maximum dose in IMRT/VMAT plans (IMRT $r = 0.506$, p-value = 0.022; VMAT $r = 0.505$, p-value = 0.022), thus influencing the homogeneity of the tumor volume. In addition, a significant negative correlation ($r = -0.657$, p-value = 0.001) was observed in the 3DCRT plans between MI and the maximum dose of the contralateral breast, indicating that the 95% isodose outside the tumor volume influences the dose to the contralateral breast.

The mismatch index correlated strongly ($r = -0.861$, p-value < 0.001) with tumor volume in 3DCRT plans, due to the increased percentage of 47.50 Gy located outside the tumor volume (38.50%, range 16.21 – 54.44%). Correlations with tumor volume were also observed in intensity modulated techniques ($r = -0.556$, p-value = 0.010 IMRT; $r = -0.533$, p-value = 0.015 VMAT), although the 95% isodose percentages were lower than in conformal plans (11.35%, range 1.97 – 28.84% for IMRT; 10.79%, range 0.57 – 23.46% for VMAT).

Moderate to strong correlations between MI and MHD ($r = -0.620$, p-value = 0.003), MHL ($r = -0.522$, p-value = 0.017), MLD ($r = -0.660$, p-value = 0.001) and MLL ($r = -0.582$, p-value = 0.007) were observed for conformal plans, suggesting heart and lung sparing. Furthermore, moderate negative correlations were observed in VMAT plans for MLD ($r = -0.507$, p-value = 0.021), MLL ($r = -0.554$, p-value = 0.011), D_{mean} heart ($r = -0.526$, p-value = 0.016) and D_{mean} lung ($r = -0.559$, p-value = 0.010) possibly due to the impact of modulation on plan outcome. Also, owing to this reason, conformity and homogeneity indices correlated with mismatch index for modulated techniques, impacting on coverage and dose distribution uniformity.

When comparing the left-sided vs. right-sided breast cancer groups, the mean doses of OARs, especially to the heart, showed lower values in right-sided breast patients (Fig. 3) due to the heart's anatomical position. This difference was also observed by Lamprecht et al. who evaluated 15 patients with left-sided and 15 with right-sided breast cancer using 3DCRT technique and two other VMAT techniques (reduced arc and reduced arc flattening filter free - reduced arc FFF). The values presented by the study for left-sided patients were 1.57 Gy

3DCRT, 1.19 Gy reduced arc VMAT and 1.20 Gy reduced arc FFF VMAT, and for right-sided patients the values were 0.51 Gy 3DCRT, 0.61 Gy reduced arc VMAT and 0.71 Gy reduced arc FFF VMAT⁴¹.

Mean doses to the ipsilateral lung appeared to be similar for both groups of patients between treatment techniques. However, it was ascertained that modulated techniques presented higher values on mean lung dose (left-sided patients: 13.58 Gy IMRT and 13.05 Gy VMAT; right-sided patients: 13.94 Gy IMRT and 13.87 Gy VMAT) compared to 3D plans (left-sided patients: 11.23 Gy; right-sided patients: 11.21 Gy), due to the increased number of fields used in treatment planning. In 3D technique 2 tangent fields were employed while 6 fields were used for IMRT and 2 semi-arcs with region of avoidance for VMAT plans. This conclusion was also drawn by Shafei et al. who evaluated 30 left-sided breast cancer patients comparing tangent 3DCRT with 6 and 9 IMRT fields (6 F IMRT and 9 F IMRT), showing an average dose of 6.80 Gy for 3DCRT, 9.28 Gy for 6 F IMRT and 10.30 Gy for 9 F IMRT⁴².

A major difference between the 2 groups was observed in the V_{20} values for ipsilateral lung dose in VMAT plans, with a mean value of 20.67% in left-sided (group A) and 24.82% in right-sided breast cancer patients (group B). The reduction in ipsilateral lung volume receiving 20 Gy in group A could be due to more dose constraints (extra cost-functions) used to protect the heart in vicinity of the tumor volume⁴³.

Regarding the influencing factors of tumor volume coverage, correlations were found between tumor volume and CI for intensity modulated techniques (left-sided patients: $r=0.506$, $p\text{-value}=0.022$ VMAT; right-sided patients: $r=0.502$, $p\text{-value}=0.023$ IMRT), therefore the size of tumor volume might influence its coverage, and also OARs dosimetry^{43,44}.

Moreover, most of the correlations with homogeneity index were observed for ipsilateral lung parameters, both for conformal and modulated intensity plans. These correlations reinforce the need for treatment plan personalization because the greater the coverage and uniformity of tumor volume (through HI and CI), the greater the dose delivered to OARs. A study conducted by Zhang et al. compared intensity modulated techniques in order to reduce dose to OARs and increase the homogeneity index by taking into account several factors: tumor complexity and shape, monitor unit reduction and organs at risk sparing. As reported in the study, mean heart dose was lower for VMAT (5.20 Gy) than for IMRT plans (6.00 Gy). Furthermore, virtual blocks were used for target homogeneity improvement without increasing the low-dose volumes ($V_5=20.90\%$ VMAT and $V_5=27.90\%$ IMRT). At the same time, the number of monitor units decreased in VMAT compared to IMRT plans (611 MU VMAT vs. 893 MU IMRT, $p\text{-value}<0.001$)⁴⁵.

Another difference between left-sided and right-sided breast cancer patients was observed in terms of contralateral breast dosimetry and HI. Left-sided patients (group A) showed moderate correlations for all treatment techniques evaluated, while right-sided breast cancer patients indicated no correlations. This result can be associated with the increased number of dose constraints (complexity of the treatment plan) applied to the treatment plan optimization (thus reducing the coverage and homogenization of tumor volume)⁴³.

On the same note, the number of mismatch index correlations was higher for left-sided than for right-sided breast cancer patients. Correlations were observed between tumor volume and organs at risk parameters (MHD, MHL, MLD, MLL, D_{mean} heart and lung) for both conformal and intensity modulated techniques in left-sided breast patients, while patients with right-sided breast cancer did not show correlations in intensity modulated techniques for any evaluated parameter. The lack of correlations with the mismatch index could be due to reduced number of dose constraints (the heart was not included in treatment fields, therefore no need for constraints), thus not affecting the healthy tissue in order to decrease the percentage dose outside tumor volume.

Figure 10 is a summary of our findings together with literature-based results, to emphasize the need for breast cancer treatment personalization based on the presented correlations^{42–44}.

The findings of our study suggest a course of action to personalize treatment in patients with unfavorable geometry or in situations when dosimetric indices show suboptimal values. A simple step would be the adjustment of gantry angle to protect organs at risk while maintaining target coverage to 95% of the prescribed dose. Furthermore, an increased number of fields could lead to an improved target homogeneity and conformality; to limit doses to OARs, more complex techniques can be employed, such as the use of virtual blocks to increase tumor homogeneity and decrease low-dose volumes to OARs. Increasing cost functions to OARs and limiting monitor units to avoid complicated treatment plans should also be considered^{37,45}.

Our study has certain limitations. One shortcoming is the limited number of patients evaluated for each group, which should be taken into account when transposing the results. However, similar other studies with small number of patients were reported in the literature which, nevertheless, presented valuable information regarding treatment techniques comparison from a dosimetric perspective^{10,31}. Another limitation would be the lack of heart parameters in right-sided breast cancer patients to serve for comparative purpose. Nevertheless, correlations were evaluated for mean heart dose and the comparison of ipsilateral lung parameters between treatment techniques was achieved. Furthermore, while patients were treated with conformal 3DCRT, the plans derived from the intensity modulated techniques were calculated for simulation only.

Conclusions

Most of the moderate/strong correlations in our study were observed in ipsilateral lung parameters for all treatment techniques evaluated, regardless of tumor location, given that both groups of patients (left- and right-sided breast cancer) presented the associations.

The evaluated correlations between dosimetric indices and parameters pertaining to organs at risk suggest the involvement of dose constraints, treatment plan adaptation and field geometry modulation for a more personalized treatment plan. Different dosimetric indices and patient-specific parameters should be considered in left- and right-sided breast cancer patients and the analysis of these parameters should be conducted and interpreted on an individual basis.

Group A (left-sided breast cancer)

MI

TV in 3DCRT => 38.50% of 47.50 Gy outside target - tangent and lymph nodes irradiation

CI, HI in IMRT/VMAT => influencing coverage and dose distribution

MHD, MHL, MLD, MLL in 3DCRT => 50% patients with V25 > 5%, Dmean heart > 4 Gy and 30% patients with V20 > 25%

MLD, MLL, Dmean HEART and LUNG in IMRT/VMAT => Dmean heart > 4 Gy, 40% and 25% patients for IMRT and VMAT with V20 > 25%

CI

TV in VMAT => influencing coverage

MHD, Dmean HEART in 3DCRT => Dmean > 4 Gy, 50% patients with V25 > 5%

MLD, MLL, Dmean LUNG in IMRT/VMAT => higher number of fields, 40% and 25% patients with V20 > 25%

HI

No **TV** correlation

No **MHD, MHL** correlation

MLL, Dmean HEART in 3DCRT => 50% patients with V25 > 5%, Dmean > 4 Gy

MLD, Dmean LUNG in IMRT/VMAT => higher number of fields, 40% and 25% patients with V20 > 25%

Group B (right-sided breast cancer)

MI

TV in 3DCRT => 34.50% of 47.50 Gy outside target - tangent and lymph nodes irradiation

CI, HI in 3DCRT, IMRT, VMAT => influencing coverage and dose distribution

No **HEART parameters** correlation

MLL in 3DCRT => 45% patients with V20 > 25%

CI

TV in IMRT => influencing coverage

No **HEART parameters** correlation

MLL, Dmean LUNG in IMRT/VMAT => 70% and 60% patients with V20 > 25%

HI

No **TV** correlation

No **HEART parameters** correlation

MLL, Dmean LUNG in 3DCRT => 45% patients with V20 > 25%

MLD, MLL, Dmean LUNG in IMRT/VMAT => 70% and 60% patients with V20 > 25%

Fig. 10. Summary of findings regarding the impact of dosimetric indices on target coverage and OARs dosimetry (MI = mismatch index, CI = conformity index, HI = homogeneity index, TV = tumor volume, MHD = maximum heart distance, MHL = maximum heart length, MLD = maximum ipsilateral lung distance, MLL = maximum ipsilateral lung length, Dmean = mean dose, 3DCRT = 3D conformal radiotherapy, IMRT = intensity modulated radiotherapy, VMAT = volumetric modulated arc radiotherapy)⁴²⁻⁴⁴.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

All authors contributed to the study conception and design. Data collection and analysis were performed by ICC, original draft preparation was written by ICC and LGM, review and editing were performed by ICC and LGM. All authors read and approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Informed consent

Patient consent was waived due to the same reason as below by the Bihor County Emergency Clinical Hospital ethics committee.

Institutional review board statement

Ethical review and approval were waived by the Bihor County Emergency Clinical Hospital ethics committee for the research because it did not enroll patients for the said study. This work analysed the data of patients that have been treated as per the normal medical protocol without any change induced by this study.

Additional information

Correspondence and requests for materials should be addressed to I.-C.C.

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