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Anatomical Predictors of Dosimetric Advantages for Deep-inspiration-breath-hold 3D-conformal Radiotherapy Among Women With Left Breast Cancer

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Abstract. *Background/Aim: This study aimed to analyze the dosimetric gain of the deep-inspiration-breath-hold (DIBH) technique over the free-breathing (FB) one in left breast cancer (LBC) 3D-conformal-radiotherapy (3D-CRT), and simultaneously investigate the anatomical parameters related to heart RT-exposure. Patients and Methods: Treatment plans were generated in both DIBH and FB scenarios for 116 LBC patients monitored by the Varian RPM™ respiratory gating system for delivery of conventional or moderately hypofractionated schedules (±sequential boost). For comparison, we considered cardiac and ipsilateral lung doses and volumes. Results: A significant reduction of cardiac and pulmonary doses using DIBH technique was achieved compared to FB plans. Larger clinical target volumes generally need longer distance between medial and lateral entrances of tangent fields at body surface, thus conditioning a worse heart RT-exposure. Conclusion: The DIBH technique reduces cardiac and pulmonary doses for LBC patients. Through easily detectable anatomical parameters, it is possible to predict which patients benefit most from DIBH-RT.*

Despite the reduction of disease-specific mortality, due to an increasingly expanding and promising therapeutic armamentarium, breast cancer is highly frequent in the female population. Indeed, its incidence has increased, as a consequence of a progressively more frequent detection in the early stages thanks to more effective screening programs (1, 2). Such considerations impose the need for a careful analysis of the health risks associated with specific therapies, especially among patients with a long life expectancy. The cardiac risk assessment in patients with left breast cancer, who are candidates for adjuvant radiotherapy (RT) after breast conserving surgery or mastectomy, belongs to this category. The proximity of some cardiac structures [left ventricle, left anterior descending coronary artery (LADCA)] to the radiotherapy target (residual breast tissue or left chest wall) could imply exposure to high doses of radiation, with possible harmful impacts on related functions (3-5). For this reason, numerous strategies are being studied by radiation oncologists to minimize the injurious radiation dose affecting cardiac structures at risk, among which the respiratory-gated breast irradiation technique [deep inspiration breath hold, (DIBH)] appears as particularly promising. In this method the left breast is irradiated during the deep inspiration phase, since in this circumstance the expansion of the lung volume causes the heart to move away from the chest wall by displacing it to a greater or smaller extent into the radiation field. Here, we report our experience with this technique, publishing the dosimetric results compared with the corresponding ones calculated by plans elaborated in free breathing (FB) condition.

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Patients and Methods

From January 2018 to June 2020, we enrolled patients aged less than 80 years, with invasive and ductal in situ variants of left breast carcinoma and stage I-II pN0 who were subjected to quadrantectomy, as candidates for RT to the residual breast parenchyma (Table I). The irradiation of the supra- and infra-clavicular lymph nodes during DIBH, related to the risk of overlap at the junction between Clinical Target Volume (CTV) and Clinical Nodal Volume (CNV) due to the thoracic movement, leads to the exclusion of patients in stage III and/or pN+ from the aforementioned irradiation technique. Another

Table I. *Patient characteristics*.

Feature	N
N. patients	116
Age (years)	
Median	56
Range	34-79
CTV (cc)	
Median	657
Range	145-1,756
Primary RT	
Total dose (Gy), fractions	
50, 25	44
40.05, 15	72
Boost	
Total dose (Gy), fractions	
None	12
10, 5	40
9, 3	62
12,4	2

Table II. *Patient inclusion criteria*.

Inclusion criteria
Age <80 years
Left breast carcinoma
Quadrantectomy
Stage I-II according to 8th TNM classification
Ability to hold your breath for at least 15-20 s

essential inclusion criterion for the feasibility of this technique was patients' ability to hold their breath for at least 15-20 sec (Table II). Two CT-scans with 3 mm slice thickness were acquired for each patient: one in free breathing, the other in deep inspiration. The latter was co-recorded with the patient's respiratory track, acquired through a system that integrates an infrared tracking camera that registers the anteroposterior motion of a reflective marker placed midway between the xiphoid process and umbilicus. The CT scan was acquired once the patient was able to hold her breath within a gating window, whose thresholds were established during the initial training phase, in order to define the most reproducible and stable breathing amplitude during DIBH. We were equipped with Varian RPM™ Respiratory Gating System (Varian Medical Systems, Palo Alto, CA, USA), version 1.7. Two treatment plans were developed for each patient, one for each CT-scan. The CTV contouring was carried out according to the clinical-instrumental evidence of the breast parenchyma, using, when available, preoperative imaging (*i.e.* magnetic resonance). In doubtful cases, we referred to the ESTRO consensus guideline on target volume delineation, whose landmarks are represented by the medial perforating mammarian vessels and the lateral thoracic artery (6). The adequate CTV coverage was obtained with 3D conformal radiation therapy (3DCRT) using two opposite tangent fields and dynamic wedges, considering as acceptable a dose inhomogeneity confined within 95% to 107% of the prescribed dose, according to ICRU recommendations (7). However, forward planning field-in-field technique was often used to improve dose coverage and dose homogeneity (8). The prescribed doses were 50 Gy in 25 fractions of 2 Gy/day or, alternatively, the hypofractionated schedule adopted in the START-B trial consisting of 40.05 Gy in 15 daily fractions (9), with or without an additional boost to the primary tumor bed (2 Gy × 5 daily fractions in conventionally fractionated radiotherapy, 3 Gy × 3 daily fractions in hypofractionated schedule or 4 Gy × 3 daily fractions). The DVHs generated by both plans (FB and DIBH) for each patient were compared. If the dosimetric evaluation showed a gain from the delivery of the treatment in DIBH, the patient was invited to perform controlled breath-hold radiotherapy, in the same conditions as in CT simulation. The evaluated dosimetric parameters were: the mean heart dose (Dmean_heart), the mean LADCA dose (DmeanLADCA), the maximum heart dose (Dmax_heart), the maximum LADCA dose (DmaxLADCA), the volume of LADCA circumscribed by the 20 Gy isodose line (V20_LADCA) in the conventionally fractionated schedule and by the 19 Gy isodose line (V19_LADCA) in the hypofractionated schedule; moreover, volumes receiving more than 20 Gy (V20_lung) and 30 Gy (V30_lung), mean dose (Dmean_lung) and volume (V_lung) were evaluated for the ipsilateral lung. On the Beam's Eye View digitally reconstructed for both FB and DIBH plans of each patient we extrapolated the maximum distance between the anterior cardiac contour and the posterior edge of the tangent fields (Maximum Heart Distance, MHD). On the axial projection of the CT performed in FB we also measured the distance between the medial limit of the CTV and the marginosternal line (Marginosternal CTV Distance, MCD), the distance between the lateral limit of the CTV and the midaxillary line (Midaxillary CTV Distance, MACD) and the distance between the medial and lateral entrances at body surface of the two tangent fields [tangent fields distance (TFD)] (for a clearer understanding of these measurements, refer to Figures 1 and 2). This study was approved by local ethics committee (reference number of ethical approval: report n. 52/2018/CETC2).

Statistical analysis. The treatment planning system allowed to derive the values of the planned dose distribution for the heart, its substructures and lung, by means of dose-volume histograms calculation. A quantitative evaluation of the statistical significance of the differences found between the DIBH and FB techniques was performed. The two-tailed paired *t*-test was used for the analysis, with the statistical level of significance was defined at *p*-values less than 0.05.

Correlations between the mean cardiac dose difference in FB and DIBH plans with MHD and between CTV and TFD were assessed by means of a linear regression model. The strength of these linear correlations and the prediction of future outcomes were determined by the Bravais-Pearson's correlation coefficient (R) and the coefficient of determination (R^2), respectively. The significance of correlation was evaluated using the *t*-test with n-2 degrees of freedom.

Results

The medical records of 116 patients judged eligible for the purpose of the present study were collected and analysed. Dose to organs at risk (OAR) was measured and compared between the two breathing techniques. In Table III and Table IV, we report an update of the results obtained in our

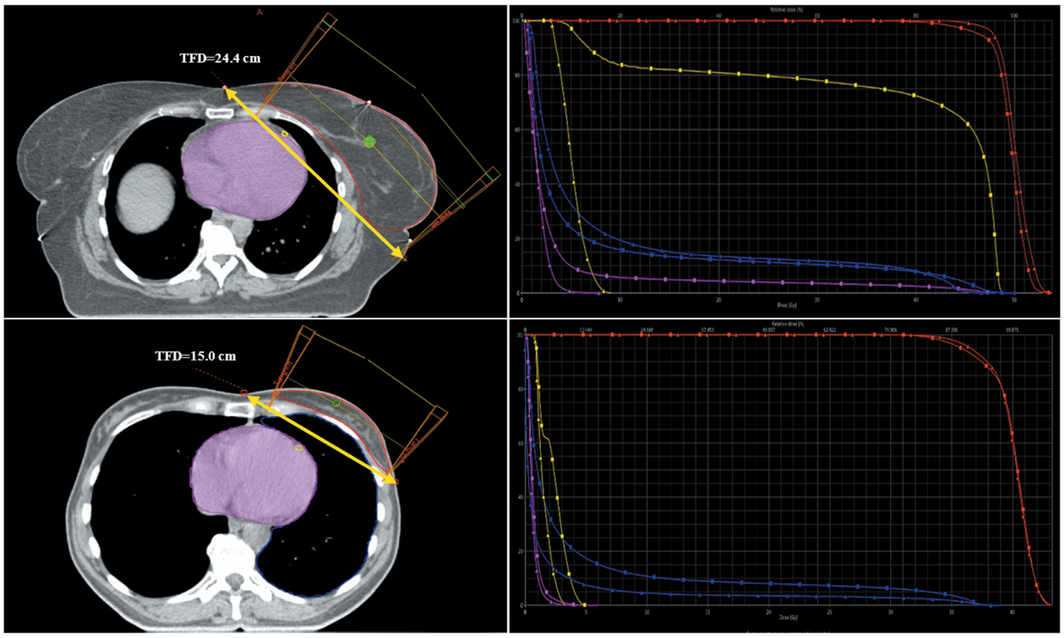

Figure 1. *Impact of tangent fields distance (TFD) on dose to organs at risk for two representative patients. (Left) The yellow arrows, drawn on the axial projection of the free breathing CT scan, show the distance between the medial and lateral entrances at body surface of the tangent fields for two typical patients included in the study. (Right) Corresponding comparison of dose-volume histograms (DVH) in which, together with the CTV (red), the main organs at risk are shown: the heart (magenta), the LADCA (yellow) and the ipsilateral lung (blue). Squares indicate free breathing (FB) plans and triangles indicate deep inspiration breath hold (DIBH) plans. It is possible to note that the larger the CTV (1518 ml for the first patient and 254 ml for the second patient) the greater the TFD (24.4 cm versus 15.0 cm, respectively) and this results in a significant reduction, with DIBH technique (triangles), of the dose to the heart and to the LADCA for the first patient compared to the second.*

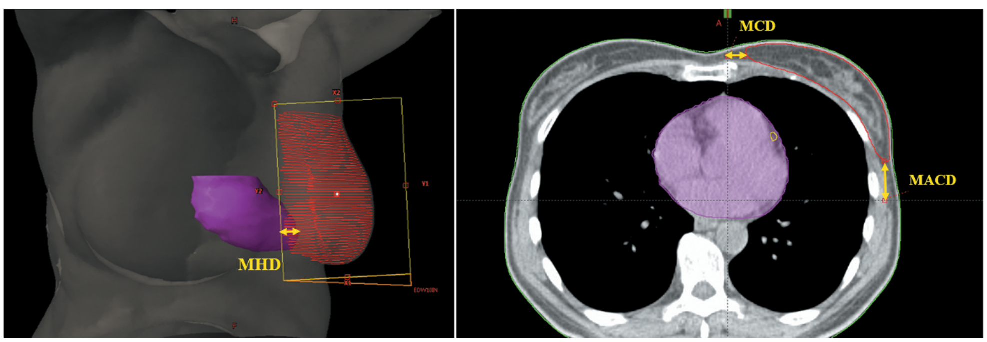

Figure 2. *Representations of maximum heart distance (MHD), marginosternal CTV distance (MCD) and the midaxillary CTV distance (MACD). (Left) Beam's eye view of the medial tangential field for a typical patient, in which the MHD, defined as the maximum distance between the anterior cardiac contour (magenta) and the posterior tangential field edges, is indicated. This distance was calculated for both free breathing (FB) and deep inspiration breath hold (DIBH) plans. (Right) Axial projection of the CT scan in FB in which the distance between the medial limit of the CTV contour (red) and the MCD and the distance between the lateral limit of the CTV and the MACD are shown.*

previous publication on the first 40 patients treated with the DIBH technique at our center (10). A statistically significant reduction of cardiac and pulmonary doses using the DIBH technique was achieved compared to FB plans, maintaining an equal coverage of CTV.

Average Dmean_heart reduced from 2.52 Gy to 1.32 Gy in FB and DIBH, respectively, with an average relative reduction of 47.7% (p<0.0001). Average Dmax_heart relative reduction was 48.4% (p<0.0001). Average DmeanLADCA reduced from 15.27 Gy to 5.55 Gy with a statistically significant mean dose

Table III. *Organs at risk Dmean and Dmax in free breathing (FB) versus deep inspiration breath hold (DIBH) techniques.*

	Technique	Mean dose (Gy)	SD	Mean dose difference (Gy)	Mean dose reduction (%)	*p*-Value
Dmean_heart	FB	2.52	1.55	1.20	47.7	0.0000
	DIBH	1.32	0.60			
Dmax_heart	FB	39.09	11.16	18.92	48.4	0.0000
	DIBH	20.17	15.23			
DmeanLADCA	FB	15.27	10.18	9.72	63.7	0.0000
	DIBH	5.55	5.49			
DmaxLADCA	FB	35.99	12.92	18.28	50.8	0.0000
	DIBH	17.71	14.25			
Dmean_lung	FB	7.44	2.76	1.01	13.5	0.0017
	DIBH	6.43	2.01			

SD: Standard deviation.

Table IV. *Ipsilateral lung volumes receiving more than 20 Gy (V20_lung) and 30 Gy (V30_lung) in FB versus DIBH. LADCA volumes receiving more than 20 Gy and 19 Gy for the conventional and the hypofractionated schedules, respectively. Total ipsilateral lung volumes (V_lung).*

	Technique	Mean volume (%)	SD	Mean volume difference (%)	Mean volume reduction (%)	*p*-Value
V20_lung	FB	13.06	6.25	2.34	17.9	0.0013
	DIBH	10.71	4.56			
V30_lung	FB	10.98	5.87	2.10	19.1	0.0018
	DIBH	8.88	4.12			
V20_LADCA	FB	28.89	26.96	24.19	83.7	0.0000
	DIBH	4.71	14.10			
V19_LADCA	FB	33.72	28.58	26.99	80.1	0.0000
	DIBH	6.73	15.12			
	Technique	**Mean volume (cc)**	**SD**	**Mean volume difference (cc)**	**Mean volume increase (%)**	***p*-value**
V_lung	FB	1286.8	337.0	932.3	72.4	0.0000
	DIBH	2219.1	462.7			

SD: Standard deviation.

Table V. *Maximum heart distance (MHD) in free breathing (FB) versus deep inspiration breath hold (DIBH) techniques.*

	Technique	Mean (cm)	SD	N. patients with MHD=0	Mean difference (cm)	Mean reduction (%)	*p*-Value
MHD	FB	1.04	0.74	11 (9.5%)	0.83	80.0	0.0000
	DIBH	0.21	0.38	71 (61.2%)			

SD: Standard deviation.

reduction of 63.7% ($p<0.0001$). Average DmaxLADCA decreased from 35.99 Gy to 17.71 Gy ($p<0.0001$) and an average relative reduction of 50.8% was recorded. In the conventional schedule, average V20_LADCA was 28.89% in the FB plans and 4.71% in the DIBH plans ($p<0.0001$) with an average relative volume decrease of 83.7%. In 68% of the patients, a 100% reduction in V20_LADCA was observed. In the hypofractionated schedule, average V19_LADCA was reduced from 33.72% to 6.73% in FB and DIBH, respectively ($p<0.0001$). The average relative volume reduction of V19_LADCA was 80.1% and a 100% decrease was obtained in 57% of the patients treated with this schedule.

On average, also pulmonary doses reduced and the ipsilateral lung volumes significantly increased with DIBH

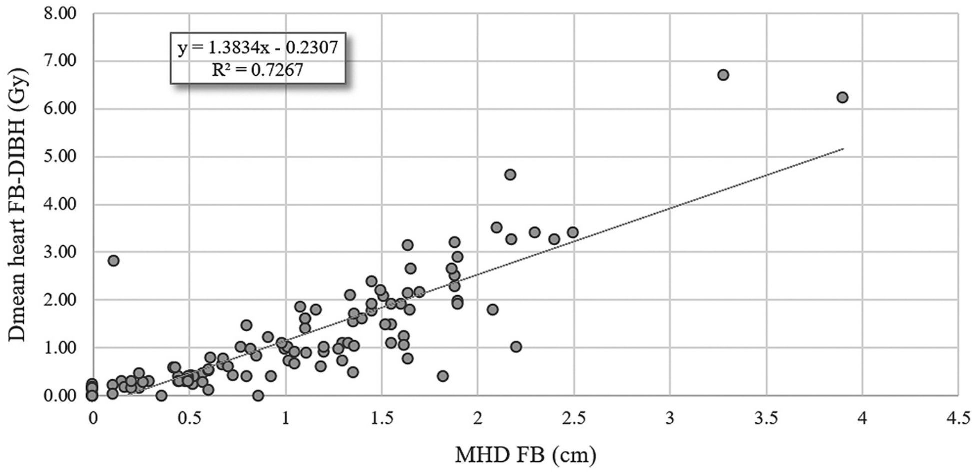

Figure 3. *Correlation of maximum heart distance (MHD) with cardiac mean dose difference in free breathing (FB) versus deep inspiration breath hold (DIBH).*

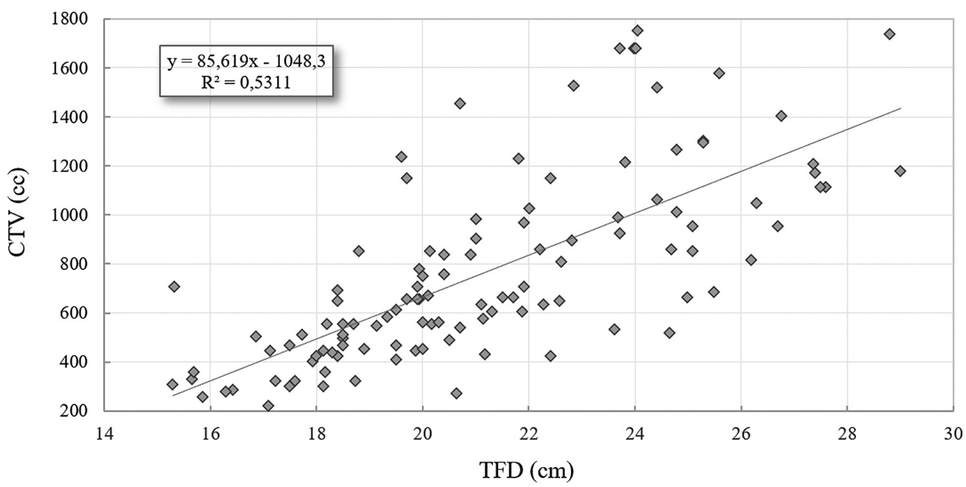

Figure 4. *Correlation between clinical target volume (CTV) and tangent fields distance (TFD).*

compared to the FB technique. A mean dose reduction of 13.5% in Dmean_lung was observed (p=0.0017). V20_lung was reduced from 13.06% (FB) to 10.71% (DIBH), with an average relative reduction of 17.9% (p=0.0013). Similarly, average V30_lung was 10.98% and 8.88% in the FB plans and DIBH plans, respectively, with an average relative reduction of 19.1% (p=0.0018).

As reported in Table V, average MHD decreased from 1.04 cm (FB) to 0.21 cm (DIBH) with an average relative reduction of 80% (p<0.0001). More than two-thirds of patients showed a reduction greater than 90% in MHD. Except for 11 patients (9.5%), all the treatment plans based on FB included heart tissue within the beam tangential fields. On the other hand, in the DIBH plans the heart was outside the beam fields for 71 of the 116 patients (61.2%). Furthermore, as has been previously shown (10), the data analysis confirmed that 73% of the mean dose difference to the heart between FB and DIBH techniques is related to the MHD measured in the FB CT scans. In fact, a statistically significant positive correlation (R=0.85, R^2=0.73) was found between the MHD and the mean cardiac dose difference in FB and DIBH plans (Figure 3).

In the present study, based on a larger sample size, we also investigated possible correlations between TFD, CTV and the percentage of reduction of MHD in FB compared with DIBH plans. Linear regression analysis identified a

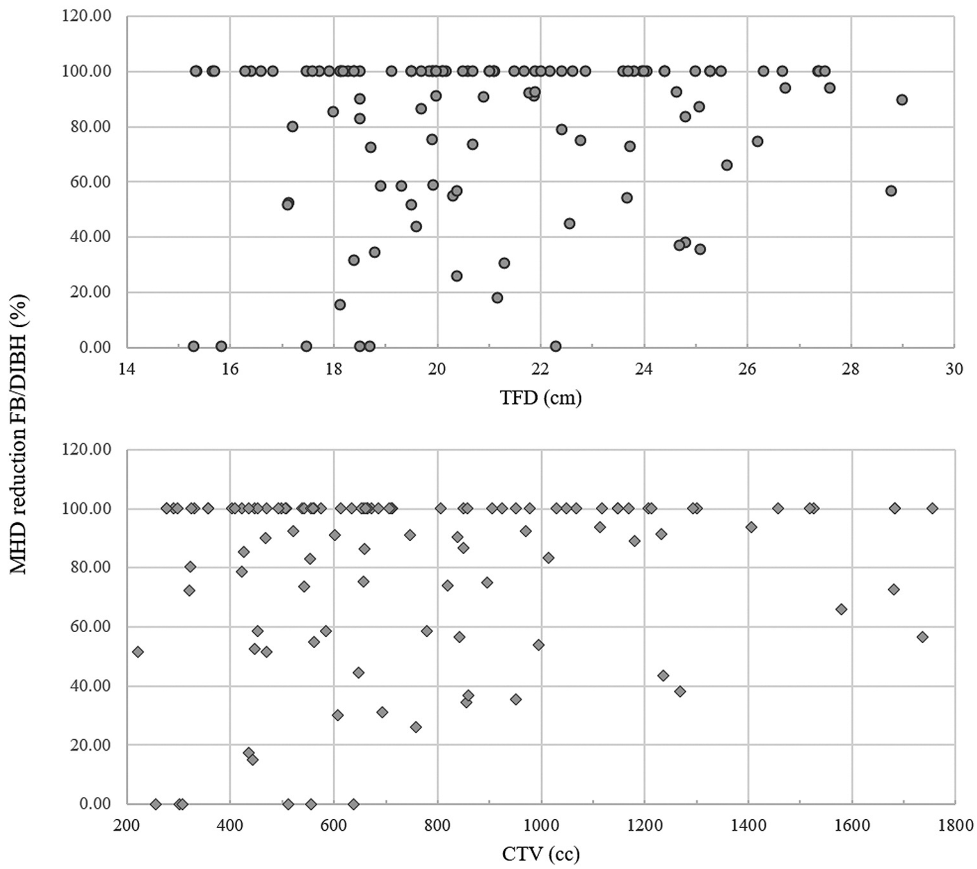

Figure 5. *Reduction of maximum heart distance (MHD) in free breathing (FB) versus deep inspiration breath hold (DIBH) techniques as a function of tangent fields distance (TFD) and clinical target volume (CTV): from a TFD greater than 22.4 cm there is a reduction of MHD greater than 35.5% as well as from a breast volume of 647 cc there is a reduction of MHD greater than 26%.*

positive correlation between CTV and TFD (R=0.73, R^2=0.53) (Figure 4): increasing the CTV requires generally a greater TFD (Figure 1). Moreover, starting from a breast volume of 647 cc we recorded a reduction of MHD constantly greater than 26%, and starting from a TFD greater than 22.4 cm we found a reduction of MHD systematically greater than 35.5% (Figure 5). This results in a reduction in the mean heart dose due to the previously mentioned correlation.

Lastly, we did not find any correlation between the dose to the heart in the two breathing techniques and the MCD and MACD distances.

Discussion

This study focused on the dosimetric comparison of OAR, with particular attention to cardiac structures, between the FB and DIBH irradiation techniques for patients suffering from left breast cancer and treated with 3DCRT, while pursuing an optimal dose coverage of the target. We also investigated whether it is possible to predict, at least approximately, what patient-specific and easily obtainable parameters mostly correlate with heart dose reduction.

The need to reduce the dose impact on heart during irradiation of the left breast has been suggested by previous studies such as those by Darby *et al*. (5), who reported a Hazard Ratio of 1.13 (95%CI=1.03-1.25, p<0.01) for cardiac mortality for over 10 years after radiotherapy among patients irradiated in the left breast compared to those treated on the right one. The same authors have fixed, in subsequent studies, the rate of risk of major coronary events at 7.4% per Gy of the mean heart dose, without an apparent threshold dose, which appears already within the first 5 years after treatment and persists even after the third subsequent decade (11, 12). Similarly, van de Bogaard *et al*. have found a relative increase in the cumulative incidence of acute coronary events of 16.5% per Gy of Dmean_heart (11). Paszat *et al*. likewise have documented a relative risk of 2.10

of fatal myocardial infarction by comparing 1,555 women irradiated for left-sided breast cancer and 1,451 for right-sided one (13). Since this risk can be further increased by exposure to cardiotoxic chemotherapy drugs such as anthracyclines (14), it is of fundamental importance to adopt all those technical precautions that allow maximum saving for cardiac structures. Merchant *et al.*, for example, have examined the dosimetric advantages of irradiation of the left breast in a prone position (15) and confirmed the long-term clinical results reported by Stegman *et al.* (16). However, this technique could compromise patient comfort and is not as widespread as supine treatment. An alternative option could be the use of a cardiac block in the tangential field to shield left ventricle from radiation port. However, this would result in an underdosing of a significant portion of the medial inferior region of the left breast. In this case the application of an "electron patch" on the medial side of the radiotherapy target may be required to exploit the lower penetration of the electron beam with consequent reduced exposure to radiation dose of the cardiac structures (17). A similar result, but with a different method, has been reported by Kong *et al.* that proposes the implementation of an additional combined photon/electron (with a dose ratio equal to 1/3) medial radiation port to two shallower than conventional tangential fields, in an effort to minimize the lung and heart volumes within the treatment fields (18). Such ploys are cumbersome, not so common and not always so effective in reaching the ideal dosimetric goal. For this reason, in case you are dealing with fully compliant patients and you have the necessary equipment, you could consider the irradiation of the left breast with the DIBH technique, whose advantages have been shown as early as 20 years ago by Lu *et al.* (19). Our experience highlights these and other similar findings published later (10, 20, 21). Furthermore, the irradiation in DIBH minimizes the dosimetric uncertainties attributable to the variability of the respiratory breast movement and daily error setup, especially for compensation tangential fields techniques (22, 23). In order to improve the dose homogeneity to the target and reduce the high heart doses, the intensity modulated radiotherapy techniques were effectively tested, although with the unavoidable drawback of increasing low doses to the contralateral lung and breast due to the greater number of treatment fields (24). The same problem has been highlighted with helical tomotherapy which, in the face of improved PTV dose homogeneity and conformity indices, entails a greater volume of OAR, including the heart, exposed to low doses, harbinger of a greater risk of radiation-induced secondary malignancies (25). A good compromise could hence be tangential volumetric modulated arc therapy (tVMAT) with restricted range of gantry rotation (50-60˚), which has actually been shown to improve target dose coverage and reduce heart dose without increasing the dose to contralateral breast or lung, placing itself as the best technique between standard tangential field-in-field (FinF), tangential intensity modulated radiotherapy (tIMRT) and continuous VMAT (cVMAT) (26). However, this technique, which can also be applied in DIBH setting, is burdened by a greater V5 in both right breast and heart as compared to tIMRT (27). The latter method is in fact considered the best if compared with all the other techniques, as shown in the dosimetric report published by Jin *et al.* (28), without prejudice to the already excellent performance of the forward planning field-in-field technique (29). For such a reason we consider and demonstrated that this technique is sufficient and effective in most cases.

The work conducted by Kapanen *et al.* reported a systematic intrafractional error of at least 2 mm adding to a systematic setup error in the longitudinal direction of the same order in 38% of the women irradiated for the whole breast and supraclavicular lymph nodes (30). Since our center could not count on the intra-breath-hold stability and extreme accuracy of a true Surface Guided Radiotherapy (31), we were forced to manually fix the inspiratory excursion range along the vertical y axis (the one monitored by the infrared tracking camera positioned high at the caudal extremity of the treatment couch and the reflective marker placed on patient's abdomen) within which to activate the beam; this range was maximum 1 cm wide, as suggested by a gating device specialist. Due to the difficulty of an accurate estimation of the corresponding craniocaudal shift along the z axis (the one where the junction between breast and lymph nodes fields was), we duly excluded from DIBH radiotherapy the enrollment of patients that needed to be treated in regional draining lymph nodes (for disease stage) (32), whose proven movement caused by deep inspiration (33) would further complicate the matter and justifies our worries about overlap between the contiguous treatment fields.

The hypothesis that the degree of benefit from DIBH may vary with patient characteristics was investigated by Yamauchi *et al.* (34), who demonstrated higher advantages for patients with low body mass index (BMI), refuting what was observed by Mkanna *et al.* (35) who, on the contrary, reported a positive correlation between mean heart dose reduction and increasing BMI comparing the DIBH technique and the FB one. Our results better agree with those reported by the second author than the first one. Indeed, although we have not measured BMI in our cohort, it can be reasonably hypothesized that women with larger breast, for which we noted a greater saving of heart dose with the DIBH technique, generally have a greater BMI, according to Coltman's findings (36). The lack of this body parameter, however, does not allow us to endorse the above likely assumption as definitive statement, being a limitation of the present study. There is no doubt that the dose received by the heart is influenced by various anatomical factors, such as thorax shape, breast size, and heart volume. It can also be easily guessed that a higher inspiratory reserve volume usually results in a greater distance between tangential fields and the heart with better dosimetric results. Among patient-specific parameters related to radiation exposure of the heart we reported the distance between the two tangential fields, that increases as the breast volume increases or in certain anatomical conditions, *i.e.* pendulous breast. It is noteworthy that neither the distance between the CTV medial limit and the marginosternal line nor the distance between the CTV lateral limit and the mid-axillary line affects the dose to the heart but only the distance between the tangent fields. Based on our results, in addition to the MHD (which, however, can be inferred only from an imaging post-hoc analysis but not clinically), we can therefore propose a breast volume so large that a greater tangential fields distance is necessary for adequate CTV coverage as a tool of rapid and effective applicability in the clinical setting for an approximate prediction of the magnitude of heart dose reduction with the DIBH technique. We showed that the percentage of MHD reduction between CT scans in DIBH compared to that in FB is always greater than 26% for breast volumes greater than 647 cc (median CTV: 657 ml) (Figure 5).

These findings indicate that our clinical practice has to stick to clinical-instrumental landmarks for the CTV contouring, since we consider that the anatomical limits suggested by the RTOG atlas (marginosternal line for the medial limit and mid-axillary line for the lateral limit) are undue, not applicable to all cases and often responsible for excessive exposure of a large proportion of healthy tissues (contralateral breast, skin, ipsilateral lung, heart) to the radiation dose.

In addition to the dosimetric gain obtained with the DIBH technique on the cardiac structures, we have reported a significant reduction of the ipsilateral lung dose. Such effect was probably due to three different factors: 1) an organ expansion that implies more favourable dose-volume relationships (*i.e.* Dmean_lung, V20_lung, V30_lung), 2) a thorax motion that reduces the most pronounced convexities and consequently the lung volume therein contained and 3) a target contouring more clinical and imaging-oriented than suggested by some atlases (*i.e.* RTOG). Moreover, since Gagliardi *et al.* have demonstrated a lung volume effect in determining the incidence of radiation pneumonitis after breast irradiation (37), such a dose reduction could involve a minor decrease in the forced vital capacity and forced expired volume in 1 second early after radiotherapy than described by Lund *et al.* (38), although these findings are rarely of clinical relevance.

Finally, our results, with regard to dose reduction in both heart and lung, are in agreement with those previously reported by Vikstrom *et al.* and Lawler *et al.* (39, 40), further confirming the effectiveness of the deep inspiration breath hold technique for left breast cancer radiotherapy, as recently summarized by Duma *et al.* (41).

Conclusion

The irradiation of the left breast with tangent fields and the DIBH technique could lead to a significant saving of cardiac structures in almost all patients, whilst still allowing an optimal dose coverage to the target. This therapeutic gain becomes even more evident in patients with a large breast volume. The DIBH technique is easy to perform, does not scatter excessive low doses to organs at risk unlike some arc and tomotherapy techniques. The only limitation to extending its application to the entire female population affected by left breast cancer is the poor compliance of some patients that leads to the application of other techniques, such as tIMRT, where available. Cardiac risk assessment is a priority when planning a radiotherapy treatment for left breast cancer. However, it is necessary to evaluate how much of these and other technological efforts are actually clinically advantageous with respect to FB 3D-CRT, which is still the most widespread standard of adjuvant treatment for breast cancer.

Conflicts of Interest

The Authors report no conflicts of interest in relation to this study.

Authors' Contributions

GF and GRB conceived the study. GF, AT and VV recruited the patients. GRB collected the data and performed the statistical analysis. GF wrote the manuscript with support from LM and GRB. GRB, VAM and SII performed the calculation of treatment plans. GF, GRB, IRC, AT and VV contributed to the interpretation of the results. GRB was in charge of overall direction and planning.

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