Predictors of Heart and Lung Dose in Left-sided Breast Cancer Treated with VMAT Relative to 3D-CRT：A Retrospective Study

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Research

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Abstract

Background

Before radiotherapy for breast cancer patients, the choice of three-dimensional conformal radiation therapy (3D-CRT) and volumetric modulated arc therapy (VMAT) should be made. This study investigates the performance of two structural metrics in aiding the choice of 3D-CRT and VMAT plans in women undergoing left-sided whole breast radiotherapy.

Materials and methods

119 patients previously treated with left-sided breast radiotherapy (61 3D-CRT treatments and 58 VMAT treatments) from a single institution were retrospectively studied. Two structural metrics, which are cardiac intersetion (CI) index and pulmonary intersection (PI) index, were defined and the relationship between these metrics and dose of organs at risk (OARs) were evaluated. Two-tailed Student's t-test was performed to compare patient characteristics between 3D-CRT and VMAT. Linear regressions were calculated to investigate the association between structural metrics and absorbed dose of heart and left lung, including MHD, V_5, V_{30} of heart, and MLLD, V_5, V_{10}, V_{20}, V_{30}, V_{40} of left lung.

Results

The CI index was strongly correlated with the mean dose of heart (MHD) in 3D-CRT group and VMAT group, the linear regression formulas were MHD = 4826.59 ×CI Index + 310.48 (R = 0.857, F = 163.77, P = 0.000) in 3D-CRT plans and MHD = 1789.29×CI Index + 437.50 (R = 0.45, F = 14.23, P = 0.000) in VMAT plans, the intercept of these formulas was CI index = 4.2% and MHD = 512.33 cGy. The PI index demonstrated a strongly positive correlation with mean dose of left lung (MLLD) in 3D-CRT group and VMAT group as well, the linear regression formulas were MLLD = 2879.54×PI Index + 999.79 (R = 0.697, F = 55.86, P = 0.000) in 3D-CRT plans and MLLD = 1411.79×PI Index + 1091.88 (R = 0.676, F = 47.11, P = 0.000) in VMAT plans, the intercept of these formulas was PI index = 6.3% and MLLD = 1180.46 cGy.

Conclusions

CI index and PI index could serve as a practical tool of choosing either 3D-CRT or VMAT before the plan was generated. We recommend that VMAT plan is preferable when CI index is greater than 4.2% and PI index is greater than 14.6%, while 3D-CRT plan is the first choice in the opposite.

1. Introduction

Postmastectomy radiation therapy (PMRT), which significantly improves local tumor control and increase 5-year overall survival for breast cancer patients, is an effective and well-established adjuvant treatment

for breast cancer patients with modified radical mastectomy[1–5].

However, the heart and lungs are routinely exposed to incidental ionizing radiation during adjuvant radiotherapy of breast cancer. It can result in increasing cardio-toxicity and cardiovascular mortality especially in left sided breast cancer patients[6]. Radiation induced heart disease generally occurs when patient follow-up is over 10 years even with modern therapy [7]. Clinical study had shown that rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per Gy, the increase started within the first 5 years after radiotherapy and continued at least 20 years[8]. While another research demonstrated that the cumulative acute coronary event rate increased by 16.5% per Gy[9]. Except for cardio-toxicity, radiation related lung toxicity is also a concern in left-sided breast radiotherapy. Studies suggested that the incidence of symptomatic radiation pneumonitis could range from 3.7% to almost 20% in different studies[10, 11]. Grantzau et al. conducted a research indicated that the risk of second non-breast cancer after radiotherapy of the breast cancer patients, including the lung, esophagus, thyroid and connective tissues progressively increased over time, peaking at 10–15 years following breast cancer diagnosis[12].

Conventionally, the three-dimensional conformal radiation therapy has been widely applied for breast cancer. Due to the concave shape of the thoracic wall, a novel plan technique known as the volumetric modulated arc therapy has also been extensively utilized in clinic recently. Researches indicated that VMAT plans spares the OAR from high-dose volume at the cost of increasing their low-dose volume[13–15], especially in patients with axillary and supraclavicular lymph node areas. In the ipsilateral lung, the VMAT plans demonstrated lower V_{20}, V_{30}, while higher V_5, V_{10} compared to 3D-CRT plans[15]. In the heart, the VMAT plans had lower V_5, V_{20} and V_{30} than the 3D-CRT plans[14].

Given the radiotherapy of breast cancer is a localized treatment, the clinical consequences of its induced injury are in part due to the location and volume of OAR exposed to radiation from the treatment technique used. To date, few studies have identified specific anatomical features that influence the heart and lung dose distribution and how these “undesirable” characteristics impact on these OARs. In clinic, radiation plans are time consuming. Often, we are confused whether to choose 3D-CRT plan or VMAT plan before work started. In this study, we propose two novel and practical structural metrics which associated with dose distribution of heart and left lung in women undergoing either 3D-CRT or VMAT left-sided whole breast radiotherapy. We hypothesized that these structural metrics could be used as predictors for heart and left lung dose, and would help to choose the plan style before the plan was actually produced.

2. Materials And Methods

2.1. Patient population

A retrospective review study, approved by the Ethics Committee of the First Affiliated Hospital of Xiamen University and performed in accordance with the Declaration of Helsinki, was performed to quantitatively

assess 119 consecutive women with left-sided breast cancer. And informed consent of all patients was obtained. All patients were treated with adjuvant whole breast RT after modified radical mastectomy at our institution from 2019 to 2020 using Varian TrueBeam or Unique or 23EXlinear accelerator with 6-MV photon energy (Varian Medical Systems, Palo Alto, CA). The prescription for the whole breast RT was 50.4 Gy (1.8 Gy/fraction).

2.2. Contouring and treatment planning

All patients received computer tomography (CT) (GE Lightspeed 16, GE HealthCare) scans. CT images were acquired with patients in supine position lying on a breast-board, at a 0.5 mm slice thickness. Clinical target volume (CTV) was delineated in accordance to the Radiation Therapy Oncology Group (RTOG) guidelines, including the whole ipsilateral chest wall and lymph node region around collar bone, using the Eclipse treatment planning system (Eclipse 11.0, Varian Medical Systems, Palo Alto, CA, USA). The planning target volume (PTV) was generated by expanding the CTV with a 5 mm margin in all directions, subsequently retracted 0.1 cm and 0.5 cm from the body surface in the chest wall section and supraclavicular section, respectively.

All treatment plans were generated using 6MV photon beam in Eclipse V.11.0 (Varian, USA). The VMAT plans with 6 partial arcs was generated, while the 3D-CRT plans with 5 field-in-field fields including two tangential fields in the chest wall region were obtained. Tissue equivalent compensator was placed over the surface of the chest wall to ensure sufficient target coverage near the chest wall surface with thickness of 1 cm for the volumetric modulated arc therapy, and 0.3 cm for the 3-dimensional conformal radiotherapy. Dose metrics were calculated based on the cumulative DVH, including V_5, V_{10}, V_{20}, V_{30}, V_{40}, as well as the mean dose of the left lung (MLLD), and V_5, V_{30}, as well as the mean dose of the heart (MDH). All plans were reviewed by two physicists and being approved by a radiation oncologist.

2.3. Tangential field of PTV and cardiac and pulmonary intersections

The tangential field (TF) of PTV was defined as the area bounded by the posterior tangent line of the PTV and the chest wall, from the layer above the apex of left lung to the bottom of PTV (Fig. 1). For this work, we drew one layer of TF every two CT slices and utilized the interpolate tool in the Eclipse V.11.0 to form the whole contour of TF. The cardiac intersection (CI) was determined as the region where the heart and the TF intersect as illustrated in Fig. 1. The pulmonary intersection (PI) was defined as the region where the left lung and the TF intersect. Then the volume of CI and PI was measured for the calculation of CI and PI index, which depicted the ratio of CI to the heart and ratio of PI to the left lung, respectively. In this study, the relationship between CI index and the absorbed dose of heart, as well as the association of PI index to the absorbed dose of left lung were investigated.

2.4. Statistical analysis

Descriptive statistics were summarized for all doses and structural metrics. Two-tailed Student's t-test was performed to compare patient characteristics between 3D-CRT and VMAT. Linear regressions were

calculated to investigate the association between structural metrics and absorbed dose of heart and left lung, including MHD, V_5, V_{30} of heart, and MLLD, V_5, V_{10}, V_{20}, V_{30}, V_{40} of left lung. Statistical significance was defined at the $p = 0.05$ significance level, and data was presented in a mean ± SD manner. The IBM SPSS Statistics V22 software was used for all statistical analysis.

Table 1
Characteristics of patients treated using 3D-CRT and VMAT

Characteristics	**3D-CRT** **N = 61, mean ± SD**	**VMAT** **N = 58, mean ± SD**	***P-Value***
Age (year)	46.0 ± 10.6	48.0 ± 9.3	0.278
Heart Volume (cc)	521.36 ± 92.75	535.63 ± 76.89	0.364
CI Volume (cc)	30.63 ± 20.55	37.78 ± 22.34	0.099
CI Index (%)	5.8 ± 3.7	6.9 ± 3.3	0.099
Left Lung Volume (cc)	996.90 ± 268.54	1041.07 ± 227.44	0.336
PI Volume (cc)	146.26 ± 53.50	194.82 ± 61.16	0.000
PI Index (%)	14.6 ± 3.2	18.8 ± 4.3	0.000
Linac			
TrueBeam	1	8	
Unique		50	
23EX	60		

3. Results

One hundred and nineteen patients with modified radical mastectomy were included in this study. Patient clinical and treatment characteristics of each cohort and their structural parameters are summarized in Table 1. No significant differences were observed between the 3D-CRT and VMAT patient cohorts with respect to patient age, heart volume, CI volume, and left lung volume. However, significant differences were noted between 3D-CRT and VMAT patient cohorts with respect to the PI volume. The measured CI volume and PI volume in each cohort were highly variable. The CI volume was 30.63 ± 20.55 cc in 3D-CRT compared to 37.78 ± 22.34 cc in VMAT. The PI volume was 146.26 ± 53.50 cc and 194.82 ± 61.16 in 3D-CRT and VMAT, respectively. The PI volume was 48.56 cc larger in VMAT relative to 3D-CRT. CI index was 0.058 ± 0.037 and 0.069 ± 0.033 in 3D-CRT and VMAT, respectively. PI index was 0.146 ± 0.032 and 0.188 ± 0.043 in 3D-CRT and VMAT, respectively.

The MHD was similar in the 3D-CRT and VMAT cohort ($p = 0.368$), which were 589.43 ± 209.82 cGy and 560.19 ± 132.38 cGy, respectively (Table 2). The V_5 of heart was dramatically larger in the VMAT plans

than the 3D-CRT plans, suggesting 3D-CRT may reduce low-dose spread of radiation to intact heart, relative to the VMAT method. Nevertheless, the dosimetry of V30 of heart shown an opposite fashion in 3D-CRT and VMAT plans, with 5% larger in 3D-CRT plans (Table 2).

The CI index was strongly correlated with the MHD (r = 0.857, p<0.01) in 3D-CRT, so was V_5 of heart (r = 0.814, p<0.01) and V_{30} of heart (r = 0.869, p<0.01) in 3D-CRT (Fig. 2). There was weak correlation between CI index and the MHD(r = 0.45, p<0.01), V_5 of heart (r = 0.328, p<0.01), as well as V_{30} of heart (r = 0.431, p<0.01) in VMAT (Fig. 2).

The MLLD was 1420.31 ± 133.65 cGy in 3D-CRT plans as opposed to 1356.09 ± 89.93 cGy in VMAT plans (Table 2), demonstrating statistically significant difference between these plans. As expected, 3D-CRT plans produced less low-dose radiation (V_5 and V_{10}) to left lung than VMAT plans, while increased high-dose radiation (V_{20}, V_{30} and V_{40}) to the organ at risk (Table 2).

For the VMAT plans, the PI index demonstrated a strongly positive linear correlation with MLLD (r = 0.676, p<0.01), and V_{20} of left lung (r = 0.6, p<0.01), and V_{30} of left lung (r = 0.578, p<0.01), as well as V_{40} of left lung (r = 0.594, p<0.01)(Fig. 3). Similarly, there was statistics significance in the correlation between PI index and the absorbed dose parameters of left lung in 3D-CRT plans, the correlation was found to be strongly between PI index and MLLD (r = 0.697, p<0.01), V_5 (r = 0.568, p<0.01), V_{10} (r = 0.663, p<0.01), V_{20} (r = 0.659, p<0.01), V_{30} (r = 0.66, p<0.01), and V_{40} (r = 0.691, p<0.01) of left lung, respectively (Fig. 3).

Linear regression formulas were generated for mean dose of heart and left lung in both 3D-CRT and VMAT plans. The formulas for MHD were MHD = 4826.59×CI Index + 310.48 (R = 0.857, F = 163.77, P = 0.000) in 3D-CRT plans and MHD = 1789.29×CI Index + 437.50 (R = 0.45, F = 14.23, P = 0.000) in VMAT plans, which produced intercept of CI index (0.042) and MHD (512.33 cGy), implying that when CI index exceeded 4.2% the mean dose of heart in 3D-CRT plans would be larger than in VMAT plans. The formulas for MLLD were MLLD = 2879.54×PI Index + 999.79 (R = 0.697, F = 55.86, P = 0.000) in 3D-CRT plans and MLLD = 1411.79×PI Index + 1091.88 (R = 0.676, F = 47.11, P = 0.000) in VMAT plans, which generated intercept of PI index (0.063) and MLLD (1180.46 cGy).

Table 2
Dosimetric parameters of heart and left lung

Absorbed dose	3D-CRT n = 61, mean ± SD	VMAT n = 58, mean ± SD	*p*-Value
Heart			
Mean dose (cGy)	589.43 ± 209.82	560.19 ± 132.38	0.368
V_5 (%)	16.46 ± 6.25	28.17 ± 8.02	<0.01
V_{30} (%)	7.65 ± 3.87	2.35 ± 1.65	<0.01
Left lung			
Mean dose (cGy)	1420.31 ± 133.65	1356.09 ± 89.93	<0.01
V_5 (%)	45.34 ± 3.80	56.17 ± 3.73	<0.01
V_{10} (%)	32.92 ± 3.09	39.98 ± 3.55	<0.01
V_{20} (%)	26.56 ± 2.90	25.31 ± 2.43	0.013
V_{30} (%)	23.58 ± 2.88	16.70 ± 1.76	<0.01
V_{40} (%)	19.56 ± 2.80	9.68 ± 1.60	<0.01
Right lung			
Mean dose (cGy)	78.25 ± 27.80	439.50 ± 84.97	<0.01
V_5 (%)	2.25 ± 1.91	29.85 ± 8.85	<0.01
V_{20} (%)	0.01 ± 0.05	0.55 ± 0.60	<0.01
Right breast			
Mean dose (cGy)	75.32 ± 46.44	450.96 ± 92.33	<0.01
V_5 (%)	0.77 ± 1.81	28.25 ± 10.64	<0.01
HI (%)	0.16 ± 0.03	0.10 ± 0.17	<0.01

4. Discussion

In this study, we identified two structural metrics on CT scans of left-sided breast cancer patients with modified radical mastectomy and investigated the relationships between these metrics and the heart and left lung absorbed dose, including the mean dose of heart and left lung, V_5, V_{30} of heart and V_5, V_{10}, V_{20},

V_{30}, V_{40} of left lung. To the best of our knowledge, this study was the first research, evaluated these structural metrics and relationship between them and the heart and left lung dose, to present.

According to the results, CI index was associated strongly with all of the dose metrics of heart in 3D-CRT plans, the correlation coefficients were 0.857 (p<0.01), 0.814 (p<0.01), and 0.869 (p<0.01) of MHD, V_5, and V_{30} of heart, respectively. Recently, Cao et al. indicated that the cardiac contact distance (CCD_{ps}) showed a positive linear correlation with the MHD (r = 0.63, p<0.01) in their study[16]. They also suggested that the lateral heart-to-chest distance (HCD) demonstrated a negative linear correlation with the MHD (r=-0.65, p<0.01). Similarly, Mendez et al. investigated predictors (4th Arch and 5th Arch) in another study, involved a simple linear line drawing to the 4th or 5th costal arch level (4th Arch, 5th Arch), from the left edge of the sternum to the anterior portion of the left lung[17]. The previous study shown that the correlation coefficient of 4th Arch and MHD was 0.61 (p<0.05), while 4th Arch and V_{25} of heart was 0.57 (p<0.05). Despite its reasonable prediction capacity, it was not clear if the CT scan would accurately acquire slice at the level of the 4th costal arch because the thickness of the 4th costal arch is well beyond the range of the thickness of CT scans. In our research, we acquired the structural metrics through the entire range of the organs at risk, so we could ignore the CT slice thickness. Other studies had also shown that the maximum heart distance to the chest wall correlates with mean dose of heart[18–20]and can reliably estimate cardiac exposure in patients treated with breast RT. In line with the previous studies, our results implied that the dose distribution of heart greatly dependent on the proximity of the heart to the irradiation fields. Nevertheless, we only observed moderate correlation between CI index and the dosimetry of heart in VMAT plans. We hypothesized that the dose delivered by the arc of radiation fields would render less high dose to the heart in a nonlinear fashion, thus the correlation was weaker in VMAT compared to 3D-CRT.

Interestingly, the intercept of the two formulas for MHD in 3D-CRT and VMAT plans was when CI index equaled 0.042, the MHD equaled 512.33 cGy, which was slightly less than the mean dose of heart in both plans. Considering the slop of formulas of 3D-CRT plans was steeper than formulas of VMAT plans, the MHD of 3D-CRT plans would surpass the one of VMAT plans when CI index was more than 4.2% (Fig. 2.). Therefore, we recommend that VMAT plan is preferable when CI index is greater than 4.2%, and 3D-CRT plan is the first consideration when CI index is less than 4.2%.

In this study, we examined the influence of PI index on dose metrics of left lung as well. There were strongly positive associations between PI index and absorbed dose parameters in 3D-CRT and VMAT plans as illustrated in Fig. 3. Although the linear regression formulas for MLLD in both 3D-CRT and VMAT plans intercepted at PI index equaled 0.063 and MLLD equaled 1180.46 cGy, we supposed this is not significantly clinically meaningful, for the reason that breast cancer with supraclavicular region would produce PI index more than 6.3% for most of the time. Since the slops of formulas in 3D-CRT plans are steeper than those of VMAT plans, the greater the PI index the greater the absorbed does to the left lung in 3D-CRT plans compared to VMAT plans as a result. In addition, the MLLD of 3D-CRT plans was 1420.31 cGy, and its corresponding PI index was 14.6%. Thus, we suggest that when PI index is greater than 14.6%, we could choose VMAT plan firstly, yet we may choose 3D-CRT plan in the opposite.

We also found that VMAT plans exhibited advantageous dosimetry in high-dose compared with the 3D-CRT plans in the current study. The V_{30} of heart and V_{30}, V_{40} of the ipsilateral lung were considerably lower in VMAT plans than in 3D-CRT plans (p 0.01). Moreover, the mean dose of ipsilateral lung in VMAT plans were less than in 3D-CRT plans as well, in accordance with the studies of Liu et al. and Mo et al[14, 15], but opposite to the results of Bogue's study[13]. Incidentally, we discovered that the PI were larger in the VMAT plans than in 3D-CRT plans. Although we observed a similar mean dose of heart in either cohort plans in our research, the larger PI in VMAT may indicated that VMAT plans played an important role in sparing the heart from redundant doses. However, the V_5 of heart, V_5, V_{10} of ipsilateral lung, and V_5, V_{20} and mean dose of contralateral lung, as well as the V_5 and mean dose of contralateral breast were higher in the VMAT plans due to the low dose spread of VMAT in our study, the results agreed with many studies comparing the dose of VMAT and 3D-CRT plans[13–15].

There are several limitations in this planning study. First, we recognize that the prediction of heart and lung dose is sophisticated and using only structural metrics may be incomplete. Second, there is no standard VMAT, and the dose in OAR depend on widely varying technology, beam setup, OAR constraints et al. Thus, the relation between structural metrics and dose distributions may lack of generalizability. Third, although CI index is similar between groups, it should be noted that the PI index is different between these cohorts, suggesting that the groups are not completely matched, the VMAT group may have larger or longer target.

Conclusion

we propose two structural metrics which were found to be associated with the dose distribution of heart and left lung. These easily implementable and low-cost metrics are potential candidates for aiding the decision making for the use of 3D-CRT plan or VMAT plan before the plans were generated. We recommend that VMAT plan is preferable when CI index is greater than 4.2% and PI index is greater than 14.6%, while 3D-CRT plan is the first choice in the opposite. Our hypothesis require validation in the future papers.

Abbreviations

3D-CRT
three-dimensional conformal radiation therapy
VMAT
volumetric modulated arc therapy
CI
cardiac intersection
PI
pulmonary intersection
OAR
organ at risk

MHD
the mean dose of heart
MLLD
the mean dose of left lung
PMRT
Postmastectomy radiation therapy
CT
computer tomography
CTV
Clinical target volume
RTOG
Radiation Therapy Oncology Group
PTV
planning target volume

Declarations

Ethics approval and consent to participate

This study has been approved by ethics committee board.

Consent for publication

This study has no individual data.

Availability of data and materials

Please contact author for data requests

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceived study: Zheng Kang, Sijia Chen. Data analysis: Yipeng He, Xiang Gao. Statistical analysis: Liwan Shi, Zheng Kang. All authors participated in the writing, and manuscript edition. All authors read and approved the final manuscript.

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References

1. Wang H, Kong L, Zhang C, Chen D, Zhu H, Yu J: **Should all breast cancer patients with four or more positive lymph nodes who underwent modified radical mastectomy be treated with postoperative radiotherapy? A population-based study**. *Oncotarget* 2016, **7**(46):75492-75502.
2. Stecklein SR, Shen X, Mitchell MP: **Post-Mastectomy Radiation Therapy for Invasive Lobular Carcinoma: A Comparative Utilization and Outcomes Study**. *Clin Breast Cancer* 2016, **16**(4):319-326.
3. Rusthoven CG, Rabinovitch RA, Jones BL, Koshy M, Amini A, Yeh N, Jackson MW, Fisher CM: **The impact of postmastectomy and regional nodal radiation after neoadjuvant chemotherapy for clinically lymph node-positive breast cancer: a National Cancer Database (NCDB) analysis**. *Ann Oncol* 2016, **27**(5):818-827.
4. Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, Cutter D, Davies C, Ewertz M, Godwin J *et al*: **Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials**. *Lancet* 2011, **378**(9804):1707-1716.
5. McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T *et al*: **Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials**. *Lancet* 2014, **383**(9935):2127-2135.
6. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, Godwin J, Gray R, Hicks C, James S *et al*: **Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials**. *Lancet* 2005, **366**(9503):2087-2106.
7. Demirci S, Nam J, Hubbs JL, Nguyen T, Marks LB: **Radiation-induced cardiac toxicity after therapy for breast cancer: interaction between treatment era and follow-up duration**. *Int J Radiat Oncol Biol Phys* 2009, **73**(4):980-987.
8. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, Correa C, Cutter D, Gagliardi G, Gigante B *et al*: **Risk of ischemic heart disease in women after radiotherapy for breast cancer**. *N Engl J Med* 2013, **368**(11):987-998.
9. van den Bogaard VA, Ta BD, van der Schaaf A, Bouma AB, Middag AM, Bantema-Joppe EJ, van Dijk LV, van Dijk-Peters FB, Marteijn LA, de Bock GH *et al*: **Validation and Modification of a Prediction Model for Acute Cardiac Events in Patients With Breast Cancer Treated With Radiotherapy Based on Three-Dimensional Dose Distributions to Cardiac Substructures**. *J Clin Oncol* 2017, **35**(11):1171-1178.
10. Jeba J, Isiah R, Subhashini J, Backianathan S, Thangakunam B, Christopher DJ: **Radiation Pneumonitis After Conventional Radiotherapy For Breast Cancer: A Prospective Study**. *J Clin Diagn Res* 2015, **9**(7):XC01-XC05.

11. Wen G, Tan YT, Lan XW, He ZC, Huang JH, Shi JT, Lin X, Huang XB: **New Clinical Features and Dosimetric Predictor Identification for Symptomatic Radiation Pneumonitis after Tangential Irradiation in Breast Cancer Patients**. *J Cancer* 2017, **8**(18):3795-3802.
12. Grantzau T, Overgaard J: **Risk of second non-breast cancer among patients treated with and without postoperative radiotherapy for primary breast cancer: A systematic review and meta-analysis of population-based studies including 522,739 patients**. *Radiother Oncol* 2016, **121**(3):402-413.
13. Bogue J, Wan J, Lavey RS, Parsai EI: **Dosimetric comparison of VMAT with integrated skin flash to 3D field-in-field tangents for left breast irradiation**. *J Appl Clin Med Phys* 2019, **20**(2):24-29.
14. Mo JC, Huang J, Gu WD, Gao M, Ning ZH, Mu JM, Li QL, Pei HL: **A dosimetric comparison of double-arc volumetric arc therapy, step-shoot intensity modulated radiotherapy and 3D-CRT for left-sided breast cancer radiotherapy after breast-conserving surgery**. *Technol Health Care* 2017, **25**(5):851-858.
15. Liu H, Chen X, He Z, Li J: **Evaluation of 3D-CRT, IMRT and VMAT radiotherapy plans for left breast cancer based on clinical dosimetric study**. *Comput Med Imaging Graph* 2016, **54**:1-5.
16. Cao N, Kalet AM, Young LA, Fang LC, Kim JN, Mayr NA, Meyer J: **Predictors of cardiac and lung dose sparing in DIBH for left breast treatment**. *Phys Med* 2019, **67**:27-33.
17. Mendez LC, Louie AV, Moreno C, Wronski M, Warner A, Leung E, Sakuraba R, Helito JK, Rezende A, Carvalho IT *et al*: **Evaluation of a new predictor of heart and left anterior descending artery dose in patients treated with adjuvant radiotherapy to the left breast**. *Radiat Oncol* 2018, **13**(1):124.
18. Coon AB, Dickler A, Kirk MC, Liao Y, Shah AP, Strauss JB, Chen S, Turian J, Griem KL: **Tomotherapy and multifield intensity-modulated radiotherapy planning reduce cardiac doses in left-sided breast cancer patients with unfavorable cardiac anatomy**. *Int J Radiat Oncol Biol Phys* 2010, **78**(1):104-110.
19. Taylor CW, McGale P, Povall JM, Thomas E, Kumar S, Dodwell D, Darby SC: **Estimating cardiac exposure from breast cancer radiotherapy in clinical practice**. *Int J Radiat Oncol Biol Phys* 2009, **73**(4):1061-1068.
20. Hiatt JR, Evans SB, Price LL, Cardarelli GA, Dipetrillo TA, Wazer DE: **Dose-modeling study to compare external beam techniques from protocol NSABP B-39/RTOG 0413 for patients with highly unfavorable cardiac anatomy**. *Int J Radiat Oncol Biol Phys* 2006, **65**(5):1368-1374.

Figures

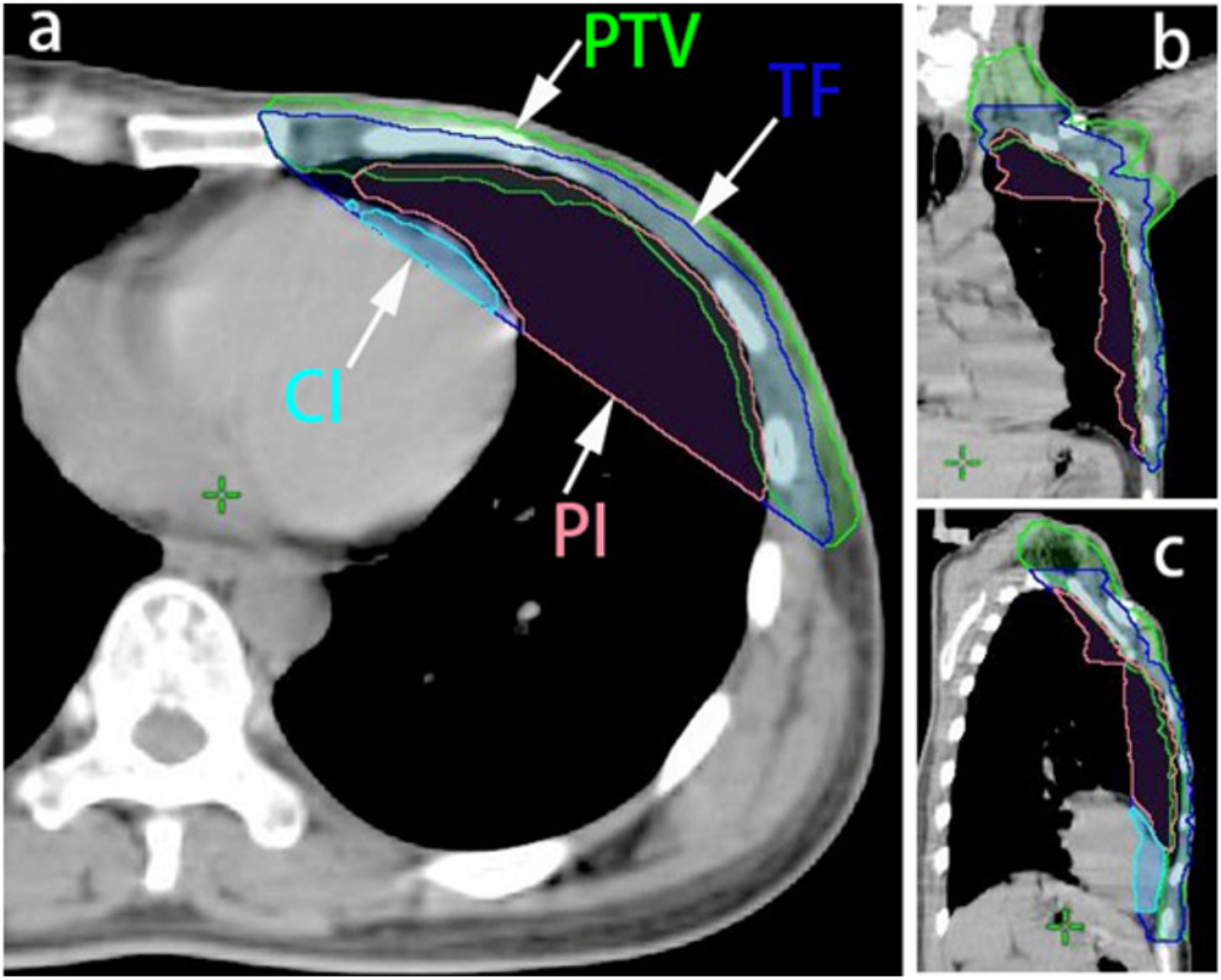

Figure 1

Structural metrics displayed in axial (a), coronal (b) and sagittal (c) slices. The green, blue, cyan and pink contours were PTV, TF, CI and PI, respectively.

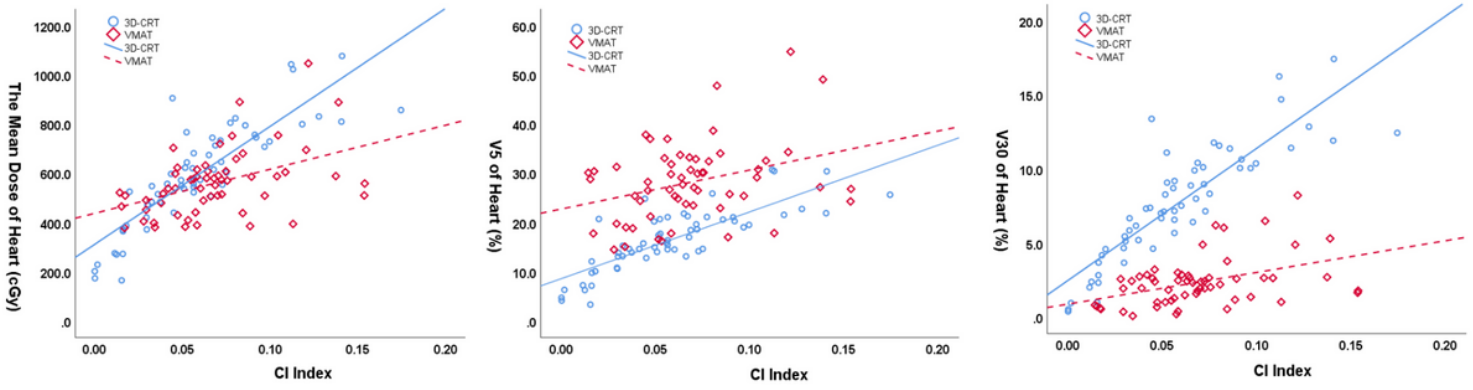

Figure 2

Correlation between CI index and mean dose of heart in 3D-CRT and VMAT (a: r=0.857 for 3D-CRT, p□0.01□r=0.45 for VMAT, p□0.01); CI index and V5 of heart (b: r=0.814 for 3D-CRT, p□0.01; r=0.328 for VMAT, p□0.01); CI index and V30 of heart(c: r=0.869 for 3D-CRT, p□0.01; r=0.431 for VMAT, p□0.01)

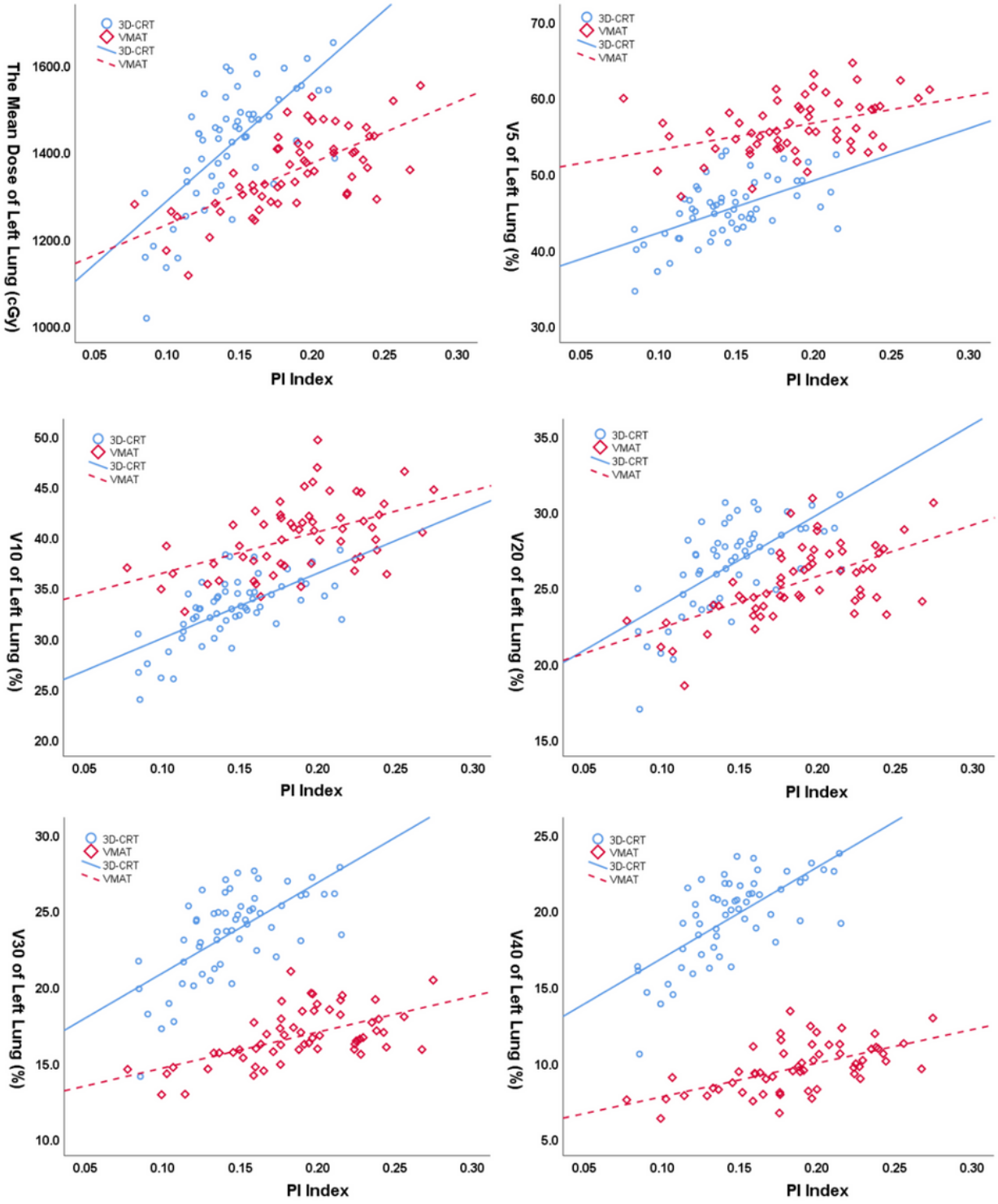

Figure 3

Correlation between PI index and dose metrics of left lung in 3D-CRT and VMAT. (a. MLLD: r=0.697 for 3D-CRT, p□0.01□r=0.676 for VMAT, p□0.01); (b. V5 of left lung: r=0.568 for 3D-CRT, p=0.1; r=0.407 for

VMAT, p□0.01); (c. V10 of left lung: r=0.663 for 3D-CRT, p□0.01; r=0.495 for VMAT, p□0.01); (d. V20 of left lung: r=0.659 for 3D-CRT, p□0.01; r=0.6 for VMAT, p□0.01); (e. V30 of left lung: r=0.66 for 3D-CRT, p□0.01; r=0.578 for VMAT, p□0.01); (f. V40 of left lung: r=0.691 for 3D-CRT, p□0.01; r=0.594 for VMAT, p□0.01).