Volume 20, No 4 | International Journal of Radiation Research, October 2022

Assessment of vital organ dose in volumetric intensity modulated arc therapy for left and right breast cancer

H. Zhang[1*], H. Yin[2*], W. Shao[3]

[1]*Department of Breast Surgery, Harbin Medical University Cancer Hospital, Harbin, China*
[2]*Department of Radiation Oncology, Harbin Medical University Cancer Hospital, Harbin, China*
[3]*Department of Radiation Physics, Harbin Medical University Cancer Hospital, Harbin, China*

► ***Original article***

***Corresponding authors:**
Wencheng Shao, Ph.D. &
Hongtao Yin, M.D. Ph.D.,
E-mail:
wenchengshao@outlook.com,
yinhongtao1982@outlook.com

Received: August 2021
Final revised: March 2022
Accepted: March 2022

Int. J. Radiat. Res., October 2022; 20(4): 761-765

DOI: 10.52547/ijrr.20.4.5

Keywords: *Left breast cancer, right breast cancer, VMAT, heart dose, lung dose.*

ABSTRACT

***Background*:** Breast cancer (BC) is a global threat to women's health. Volumetric intensity modulated arc therapy (VMAT) is effective for the local control of BC. This study evaluated the pulmonary and cardiac radiotherapeutic dosage to provide information for estimating normal tissue complication probability (NTCP) once malignant tumors appear in patients' left and right breasts. ***Materials and Methods*:** We conducted a retrospective analysis of VMAT regimen of 40 patients with BC, among whom 20 patients (group 1) were diagnosed with right BC and 20 patients (group 2) with left BC. The pulmonary and cardiac dose volume histogram (DVH) parameters were acquired and compared between patients with left and right BC treated with VMAT. ***Results*:** Generally, the pulmonary and cardiac dosages in patients with right BC were larger than in those with left BC. For the lung, the V_{20} and V_5 of right BC patients were significantly higher, relative to the left BC patients ($P<0.05$). For the heart, the V_5 and V_{10} of right BC patients were significantly lower, compared to left BC patients, with differences of up to 20% and 10%, respectively (both $P<0.05$). V_{20}, V_{30}, and V_{40} as low as zero were observed for right BC patients. ***Conclusions*:** When treating left BC, image guidance and respiratory management techniques should be applied to limit radiotherapy complications that occur in the heart because of patient positioning and respiratory movement.

INTRODUCTION

Breast cancer (BC) is a life-threatening malignant tumor affecting women worldwide [1,2]. The main factors related to BC incidence include alcohol consumption, premature menarche, advanced menopause, obesity in postmenopausal women, and elevated body estradiol levels [3-6]. The exploration of effective BC therapy methodologies is beneficial to prolonging life and improving quality of life for BC- suffering women.

Radiotherapy is a promising therapeutic methodology for achieving better regional modulation and survival rate; thus, it is recommended by the Early BC Trialists' Collaborative Group (EBCTCG) [7]. During radiotherapy, ionization beams are used to irradiate the breast tumor, which introduces an extra radiation to the cardiac and pulmonary zones of BC patients. Ionization beam irradiation results in normal tissue complication possibility (NTCP) [8-10]. Compared to traditional three-dimensional conformal radiotherapy (3D-CRT), volumetric intensity modulated arc therapy (VMAT) can achieve a reduced dosage in healthy tissues without sacrificing the target dose because of its inverse dose optimization algorithm [11-13]. It is necessary to evaluate the VMAT dose in BC patients in terms of reducing heart and lung dose.

In terms of BC patients treated with VMAT radiotherapy, the radiation dosage to organs at risk (OARs) is the most important factor for damage to OARs. According to a previous study [14], the death rate due to cardiovascular disease in left BC patients is considerably increased, compared to right BC patients after radiotherapy. A previous study [15] show that left BC patients experience a higher risk of cardiac damage due to radiotherapy. Till now, most investigations concentrated on the vital organ dose of patients with right or left BC receiving VMAT radiotherapy [16-19]. However, few studies have compared vital organ doses between left and right BC patients who underwent VMAT radiotherapy. Unlike existing studies, this study aimed to quantify the difference in VMAT radiotherapy dosage to the cardiac and pulmonary zones between left and right BC patients. This study serves as a beneficial reference for future studies assessing radiation complications from VMAT radiotherapy in BC patients.

[DOI: 10.52547/ijrr.20.4.5]

MATERIALS AND METHODS

BC patient selection

Forty BC patients who underwent VMAT were selected to evaluate the VMAT dosage to the cardiac and pulmonary zones of left and right BC patients. Among the 40 BC patients, 20 patients were diagnosed with right BC (group 1) and the other 20 with left BC (group 2). The (mean age ± standard deviation) is 48.9±8.5 for all the 40 patients, 48.2±7.8 for group 1, and 49.7±9.2 for group 2. The VMAT-treated region included the whole breast and supraclavicular regions. The serial number of the institutional Ethical approval is KY2019-17 registered on November 15, 2019.

Computed tomography (CT) imaging and organ segmentation

The 40 patients with BC were scanned with a Philips Brilliance Big Bore CT simulator. For each patient, the region between the mandible and diaphragm was scanned using CT and included the entire region treated with VMAT. The clinical target volume (CTV) was segmented into the whole breast using a malignant tumor and the corresponding supraclavicular region. The OARs, including the heart, lung, trachea, esophagus, and spinal cord, were also segmented by radiation oncologists.

Treatment planning and VMAT machines

The CT images and contours of 40 patients (target and OARs) were transferred to the VMAT treatment planning system (TPS). The Pinnacle TPS from Philips was adopted to generate VMAT plans for the 40 patients, and a Varian IX linac was used to irradiate BC patients. The prescribed dosage of 50 Gy in 25 fractions was applied to the 96% dose line covering more than 95% of the CTV. The OAR dose constraints from the AAPM TG101 report were used: double-lung V_{20}<10% and heart D_{max}<30 Gy [20]. A VMAT plan with four arcs was generated using the Pinnacle TPS for each patient with BC.

Dose volume histogram (DVH) parameters and statistical analysis

In terms of the cardiac and pulmonary zones, the DVH parameters of V_5, V_{10}, V_{20}, V_{30}, and V_{40} were defined as the volumes that received over 5, 10, 20, 30, and 40 Gy dosage. All DVH parameters were obtained from the DVHs of the VMAT treatment plans. In this study, the data analysis was processed with SPSS 21.0 software from IBM Company. The DVH parameters for left and right BC patients were normally distributed based on a normality test, and expressed as mean ($\bar{x}$) of a specific DVH parameter and standard deviation (SD) of the mean. A paired sample t-test was carried out comparing DVH parameters in the left and right BC cases. Statistical significance of the dose comparison was defined as P-values less than 0.05.

RESULTS

This section aims to compare the DVH parameters (i.e., V_5, V_{10}, V_{20}, V_{30}, and V_{40}) between groups 1 and 2 using box plots and paired sample t-tests. For each DVH parameter, the mean, SD, t-value, and P-value were computed and are listed in tables 1 and 2 for groups 1 and 2, respectively.

Table 1. Comparison of DVH parameters for the whole lung between groups 1 and 2.

Organ	Parameter	Group 1	Group 2	*t*	*P*
Whole lung	V_5 (%)	48.38 ± 5.96	45.94 ± 4.29	2.921	0.010
	V_{10} (%)	45.37 ± 3.30	34.02 ± 3.56	-1.154	0.263
	V_{20} (%)	25.52 ± 3.43	23.92 ± 0.39	3.811	0.001
	V_{30} (%)	18.85 ± 3.11	18.34 ± 3.34	-0.162	0.86
	V_{40} (%)	13.05 ± 3.16	12.12 ±2.93	1.446	0.167

Table 2. Comparison of DVH parameters between groups 1 and 2.

Organ	Parameter	Group 1	Group 2	*t*	*P*
Heart	V_5 (%)	3.16 ± 3.22	24.19 ± 7.43	17.722	7.675E-13
	V_{10} (%)	0.29 ± 0.60	11.67 ± 4.39	10.782	2.768 E-9
	V_{20} (%)	0.00 ± 0.00	5.90 ± 2.64	9.749	1.317 E-8
	V_{30} (%)	0.00 ± 0.00	3.52 ± 1.76	8.689	7.400 E-8
	V_{40} (%)	0.00 ± 0.00	1.84 ± 1.06	7.543	5.601 E-7

DVH parameters comparison for lung

Figure 1 compares the DVH parameters of the whole lung between groups 1 and 2. As illustrated in Figures 1a and 1b, the lung volume receiving a low dose <5 Gy in group 1 is significantly increased, compared to group 2, which suggests that right BC patients are likely to have a larger region with a lower dose than those with left BC when receiving VMAT treatment. For DVH parameters except V_5 and $V_{20,}$ patients in group 1 had larger variation than group 2 patients. This indicates that the lung dose in right BC patients has a closer relationship with patients' chest anatomies. When evaluating clinical VMAT treatment plans, V_{20} is the top concern of clinical radiation oncologists. As seen in table 1, the V_{20} of group 1 was significantly larger, compared to group 2 (P=0.001, P<0.05), which suggests that patients with right BC experience an enhanced prevalence of radiation complications, compared to left BC patients, from the viewpoint of clinical radiotherapy.

DVH parameters comparison for heart

Figure 2 compares the DVH parameters of the heart between groups 1 and 2. As illustrated in figures 2a and 2b, the V_5 and V_{10} of the heart in group 1 were significantly less than those in group 2 by up to 20% and 10%, respectively, which suggests that the hearts of right BC patients are likely to have a

[DOI: 10.52547/ijrr.20.4.5]

larger region with a low dose than that of patients with left BC for VMAT treatment. Relative to group 2, group 1 showed more severe variations in V_5 and V_{10} among different patients. This implies that the low-dose region in patients with right BC varies more with chest anatomy.As listed in table 2, the mean and SD for V_5, V_{10}, V_{20}, V_{30}, and V_{40} in group 2 were markedly larger, compared to group 1 ($P<0.05$). The hearts of patients with right BC are likely to undergo less photon irradiation than those of left BC patients while undergoing VMAT therapy. V_{20}, V_{30}, and V_{40} as low as zero were observed in group 1, which reveals that the hearts of patients with right BC receive almost no high-dose irradiation from VMAT beams. Thus, patients with right BC have a much lower incidence of radiation-induced side effects from VMAT than patients with left BC.

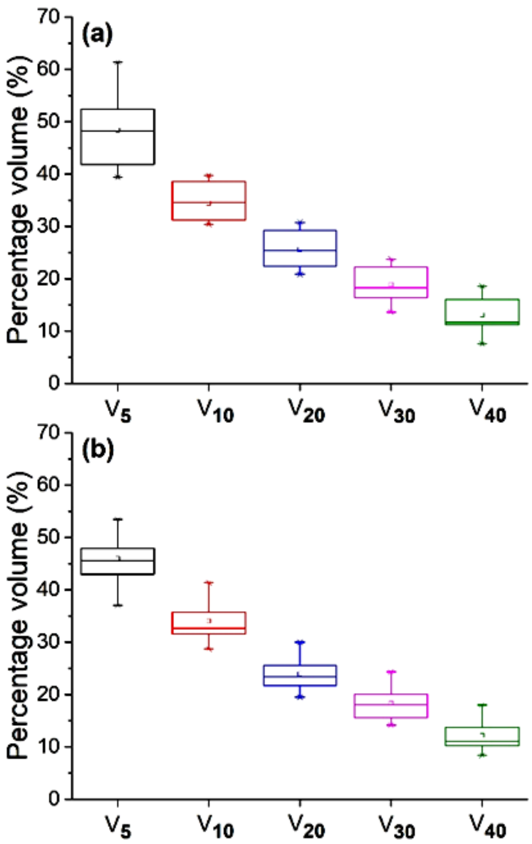

Figure 1. Box plots of lung DVH parameters for **(a)** 20 patients with right breast cancer (group 1) and **(b)** 20 patients with left breast cancer (group 2).

Two-dimensional dose comparison between groups 1 and 2

Two patients were selected from each of groups 1 and 2. Figure 3 compares the two-dimensional planned doses between the selected patients from groups 1 and 2. As seen in figures 3a and 3b, none of the five dose lines (5000 cGy, 4000 cGy, 3000 cGy, 2000 cGy, and 1000 cGy) passed through the heart in both selected right BC patients, suggesting that the heart is almost not affected by VMAT irradiation. In right BC patients, the incidence of radiation-related complications in the heart is very low. As shown in Figures 3c and 3d, all dose lines except for the 5000 cGy dose line passed through the heart ventricle in the selected left BC patients. This means the left ventricle of left BC patients undergoes high-dose irradiation and has an enhanced risk of radiation-related complications, compared to right BC patients during or after VMAT. The geometric relationship between the treated region and heart determines the heart irradiation dose from VMAT. For a patient with right BC, the heart is far away from the treated region. This means the heart receives a relatively low dose. But, in left BC patients, the left heart ventricle is very close to the treated region. Therefore, the heart dose is high.

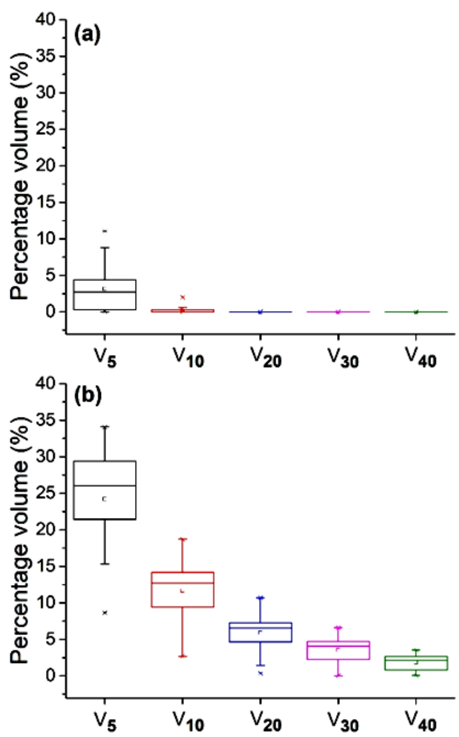

Figure 2. Box plots of lung DVH parameters for **(a)** 20 patients with right breast cancer patients (group 1) and **(b)** 20 patients with left breast cancer (group 2).

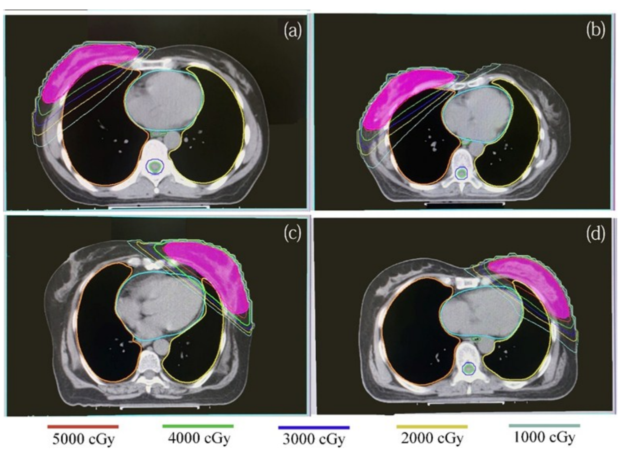

Figure 3. Two-dimensional dose distributions for two patients with left breast cancer **(a, b)** and two patients with right breast cancer **(c, d)**.

[DOI: 10.52547/ijrr.20.4.5]

DISCUSSION

High BC prevalence is common in postmenopausal women. The mortality rate of patients with in situ BC is relatively low. However, the health of women is threatened when breast carcinoma cells spread throughout the body via the blood [21, 22]. To date, radiotherapy after radical surgery is the first in line intervention for BC. Thus, radiotherapy could reduce recurrence and death rates and increase combined treatment efficacy for BC. During BC radiotherapy, the lung is very sensitive to VMAT irradiation, and normal lung tissues within the treated region experience photon radiation damage. Radiotherapy-related complications include pulmonary edema, alveolitis, and pulmonary fibrosis. These complications seriously reduce lung function. Radiotherapy-related pneumonia is not reversible; however, there are few effective treatment methods. Most patients die within two months after radiotherapy-related pneumonia seizures. At present, the incidence of radiation-related pneumonia is reduced by administering a lower dose during radiotherapy.

Radiation-triggered cardiac disease is a complication of BC patients who underwent radiotherapy. Left BC patients have a much higher heart dose than right BC patients because a larger heart volume is involved when treating left BC with radiotherapy. A prior study [23] reported that 40% of BC patients who receive radiotherapy experience a decrease in myocardial perfusion, and the degree of decrease is closely related to the irradiated heart volume. Schultz-Hector et al. verified that the prevalence of radiotherapy-triggered cardiac disease in left BC patients is markedly increased, compared to right BC patients, since left BC patients receive a larger cardiac dosage [24]. The results of this study also show that left BC patients have a remarkably larger irradiated cardiac volume and higher heart dose than those of right BC patients ($P<0.05$).

In clinical BC radiotherapy, many factors affect the incidence of radiotherapy-related pneumonia. Normal lung tissue volume receiving over 20 Gy (V_{20}) is one of the main independent factors related to lung damage from radiotherapy. VMAT, an advanced radiotherapy technique, is frequently applied after BC surgery. During VMAT, the high-dose prescription is confined to the treated breast region. Thus, the dose to surrounding tissues is increased without sacrificing the target dose. The severity of radiation pneumonia is closely related to lung V_{20}. Larger lung V_{20} is associated with more serious radiation damage. Thus, this study evaluated lung V_{20} in radiotherapy for left and right BCs. The results of this study show that patients with left BC and those with right BC experience similar radiation damage to the lung when VMAT is applied.

Photon irradiation of the heart during BC treatment can induce damage to the cardiac substructure. Kaidar-Person *et al*. found that perfusion defects in the anterior wall of the heart depended on the heart dose (HD) and irradiated heart volume (IHV) using single-photon emission CT (SPECT) in BC patients after radiotherapy [25]. However, the relationship between IHV and severity of post-radiotherapy myocardial damage remains unclear and varies among BC patients receiving radiotherapy. In clinical radiotherapy, the HD and IHV should be reduced as much as possible when the prescribed target dose is sufficient. The results of this study show that the HD and IHV in patients with left BC were much higher, compared to right BC patients following VMAT ($P<0.05$). The specificity of clinical manifestations of myocardial damage from radiotherapy is low. Thus, compared to right BC patients, left BC patients need to pay close attention when an abnormal cardiac state occurs after VMAT. For left BC patients, image guidance techniques (i.e., gating and active breath coordination [ABC]) and image-guided techniques (IGRT) are necessary to prevent increased radiation dosage to the heart because of respiratory movements during VMAT.

CONCLUSIONS

In this study, the lung and heart doses following VMAT for left and right BC were evaluated by analyzing DVH parameters. The findings showed that the lung dose of left BC patients was similar to that of the right BC patients following VMAT ($P>0.05$). Compared with right BC patients, the hearts of left BC patients hearts received more photon irradiation and had a higher heart dose and IHV ($P<0.05$). Thus, effective methods (i.e., ABC and IGRT) need to be adopted to reduce the discrepancy between the planned and clinically delivered doses and to prevent serious myocardial damage from happening to the hearts of left BC patients.

ACKNOWLEDGMENTS

The authors would like to thank Prof. Dr. Min Xiao because he provided beneficial guidance when performing comparison between vital organ dose of left breast cancer patients and that of right breast cancer patients.

Conflicts of interest: The authors have no relevant conflicts of interest to disclose.

Ethical consideration: The study was conducted in accordance with the principles of the Declaration of Helsinki. All diagnostic and therapeutic procedures were performed according to the current standard-of-care and after receiving the patients' informed consent. No diagnostic or therapeutic acts were performed for the purpose of research. This is only a retrospectives study based on radiotherapy dose data, thus patient consent for inclusion was waived.

Funding: This study was supported in part by

[DOI: 10.52547/ijrr.20.4.5]

National Cancer Centre (NCC201808B020).

Author contribution: Hongxu Zhang analyzed the DVH data and contributed in writing the manuscript; Hongtao Yin analyzed the DVH data and contributed in writing the manuscript; Min Xiao contributed in revising the manuscript; Wencheng Shao contributed in writing and revising the manuscript.

REFERENCES

1. Waks AG and Winer EP (2019) Breast Cancer Treatment: A Review. *JAMA*, 22; ***321****(3)*: *288-300*.
2. Momenimovahed Z and Salehiniya H (2019) Epidemiological characteristics of and risk factors for breast cancer in the world. *Breast Cancer*, ***11****: 151-164*.
3. Lei S, Zheng R, Zhang S, *et al.* (2021) Global patterns of breast cancer incidence and mortality: A population-based cancer registry data analysis from 2000 to 2020. *Cancer Communications*, ***41****(11): 1183-1194*.
4. Chlebowski RT, Anderson GL, Aragaki AK, Manson JE, Stefanick ML, Pan K, *et al.* (2020) Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the women's health initiative randomized clinical trials. *JAMA*, ***324****(4)*: *369-380*.
5. Katalinic A, Eisemann N, Kraywinkel K, Noftz MR, Hübner J (2020) Breast cancer incidence and mortality before and after implementation of the German mammography screening program. *Int J Cancer*, ***147****(3)*: *709-718*.
6. Mubari S, Malik SS, Wang Z, Li C, Fawad M, Yu C (2019) Recent insights into breast cancer incidence trends among four Asian countries using age-period-cohort model. *Cancer Manag Res,* ***11***: *8145–8155*.
7. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2011) Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10801 women in 17 randomised trials. *Lancet*, ***378****(9804): 1707–1716*.
8. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, *et al.* (2002) Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*, ***347****(16): 1227-1232*.
9. Veronesi U, Luini A, Vecchio M D, Greco M, Galimberti V, Merson M, *et al.* (1993) Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N Engl J Med*, ***328****(22): 1587-1591*.
10. Cuzick J, Stewart H, Rutqvist L, Houghton J, Edwards R, Redmond C, *et al.* (1994) Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol*, ***12****(3): 447-453*.
11. Wolff D, Stieler F, Welzel G, Lorenz F, Abo-Madyan Y, Mai S, *et al.* (2009) Volumetric modulated arc therapy (VMAT) vs. serial tomotherapy, step-and-shoot IMRT and 3D-conformal RT for treatment of prostate cancer. *Radiother Oncol*, ***93****(2): 226-233*.
12. . Rao M, Yang W, Chen F, Sheng K, Ye J, Mehta V, *et al.* (2010) Comparison of Elekta VMAT with helical tomotherapy and fixed field IMRT: plan quality, delivery efficiency and accuracy. *Med Phys*, ***37****(3): 1350-1359*.
13. Hardcastle N, Tomé WA, Foo K, Miller A, Carolan M, Metcalfe P (2011) Comparison of prostate IMRT and VMAT biologically optimised treatment plans. *Med Dosim*, ***36****(3): 292-298*.
14. Chao PJ, Lee HF, Lan JH, Guo SS, Ting HM, Huang YJ, *et al.* (2017) Propensity-score-matched evaluation of the incidence of radiation pneumonitis and secondary cancer risk for breast cancer patients treated with IMRT/VMAT. *Sci Rep*, ***7****(1): 13771*.
15. Saiki H, Moulay G, Guenzel AJ, Liu W, Decklever TD, Classic KL, *et al.* (2017) Experimental cardiac radiation exposure induces ventricular diastolic dysfunction with preserved ejection fraction. *Am J Physiol Heart Circ Physiol,* ***313****(2): H392-H407*.
16. Ahn SH, Kim E, Kim C, Cheon W, Kim M, Lee SB, *et al.* (2021) Deep learning method for prediction of patient-specific dose distribution in breast cancer. *Radiat Oncol,* ***16****: 154*.
17. Qiu J, Zhang S, Lv B, Zheng X (2021) Cardiac dose control and optimization strategy for left breast cancer radiotherapy with non-uniform VMAT technology, *Technol Cancer Res Treat*, ***20***: 15330338211053752.
18. Finazzi T, Nguyen VT, Zimmermann F, Papachristofilou A (2019) Impact of patient and treatment characteristics on heart and lung dose in adjuvant radiotherapy for left-sided breast cancer, *Radiat Oncol*, ***14****(1)*: 153.
19. Ren W, Sun C, Lu N, Xu Y, Han F, Liu Y, *et al.* (2020) Dosimetric comparison of intensity-modulated radiotherapy, volumetric modulated arc therapy and hybrid three-dimensional conformal radiotherapy/intensity-modulated radiotherapy techniques for right breast cancer, *J Clin Med*, ***9****(12): 3884*.
20. Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, *et al.* (2010) Stereotactic body radiation therapy: The report of AAPM Task Group101, *Med Phys*, ***37****(8): 4078-4101*.
21. Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD (2016) Cardiovascular disease mortality among breast cancer survivors. *Epi-demiology*, ***27****(1):* 6-13.
22. Wijsman R, Dankers FJWM, Troost EGC, Hoffmann AL, van der Heijden EHFM, de Geus-Oei LF, *et al.* (2017) Inclusion of incidental radiation dose to the cardiac atria and ventricles does not improve the prediction of radiation pneumonitis in advanced-stage non-small cell lung cancer patients treated with intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys*, ***99****(2): 434-441*.
23. Correa CR, Das IJ, Litt HI, Ferrari V, Hwang WT, Solin LJ, *et al*. (2008) Association between tangential beam treatment parameters and cardiac abnormalities after definitive radiation treatment for left-sided breast cancer. *Int J Radiat Oncol Biol Phys*, ***72****(2)*: 508 -516.
24. Schultz-Hector S and Trott KR (2007) Radiation-induced cardiovascular diseases: is the epidemiologic evidence compatible with the radiobiologic data [J]. *Int J Radiat Oncol Biol Phys*, ***67****(1)*: *10-18*.
25. Kaidar-Person O, Zagar TM, Oldan JD, Matney J, Jones EL, Das S, *et al.* (2017) Early cardiac perfusion defects after left-sided radiation therapy for breast cancer: is there a volume response. *Breast Cancer Res Treat*, ***164****(2): 253-262*.

[DOI: 10.52547/ijrr.20.4.5]