



Role of Hybrid Treatment Technique in Radiotherapy Planning for Early Stage Left Breast Cancer

Erken Evre Sol Meme Kanseri Radyoterapi Planlamasında Hibrit Tedavi Tekniğinin Rolü

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Abstract

Objective: The application of effective techniques has an important place in the control of the disease in the breast, which is an anatomically complex region. The aim of this study is an early stage left breast irradiation, in addition to Intensity-Modulated Radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT) plans, it is to compare the data obtained by the HYBRID planning technique obtained with 5 different loadings and also to determine the appropriate weight ratios in HYBRID plans in terms of critical organ doses.

Materials and Methods: IMRT and VMAT plans were prepared for all patients included in the study. HYBRID plans with different beam weight rates were prepared to determine the optimal dose distribution hybrid beam weight ratio. Dose distributions, heterogeneity, and conformity indices of all plans were compared among themselves. In addition, dosimetric comparison was made in terms of critical organ doses.

Results: In the study, it was seen that the HYBRID3 plan was statistically significant in terms of the heart dose. This result shows that in terms of cardiac dose, the HİBRİT 3 plan provides the desired low dose in terms of cardiac diseases. Considering the D_{mean} (≤ 1 Gy) value of the contralateral breast (CB) for the plans created in this study, it was found that all HYBRID loading plans were statistically significant compared to the IMRT plans. HYBRID plans have the lowest CB D_{max} .

Conclusion: If one is unable to obtain appropriate results with VMAT techniques, then HYBRID plans formed by the combination of IMRT and VMAT plans reduce organs at risk doses, in the mean time ensuring that the dose wraps around the planned target volume in a targeted manner.

Keywords: Breast cancer, Intensity-Modulated Radiotherapy, volumetric arc therapy, HYBRID plans, critical organ doses

Öz

Amaç: Meme, anatomik olarak kompleks bir bölgede olduğundan etkili tekniklerin uygulanması hastalığın kontrolünde önemli bir yer tutar. Bu çalışmanın amacı; erken evre sol meme ışınlaması için Yoğunluk Ayarlı Radyoterapi (IMRT), hacimsel yoğunluk ayarlı ark tedavisi (VMAT) planlarına ilave olarak 5 farklı yüklemeye elde edilen HİBRİT planlama tekniği ile elde edilen verileri kıyaslamak ve ayrıca kritik organ dozları açısından HİBRİT planlarda uygun ağırlık oranlarını tespit etmektir.

Gereç ve Yöntemler: Çalışmaya dahil edilen tüm hastalar için IMRT ve VMAT planları hazırlandı. Optimal doz dağılımlı hibrit yükleme oranının tayini için farklı yükleme oranları ile HİBRİT planları hazırlandı. Tüm planların doz dağılımları, heterojenite ve konformite endeksleri kendi aralarında karşılaştırıldı. Ayrıca kritik organ dozları açısından dozimetrik karşılaştırma yapıldı.

Bulgular: Çalışmada HİBRİT 3 planlarının kalp dozu açısından istatistiksel olarak anlamlı olduğu görüldü. Bu sonuç kardiyak dozda HİBRİT 3 planın kalp hastalıkları açısından istenilen düşük dozu sağladığını göstermektedir. Bu çalışmada oluşturulan planlar için karşı memenin D_{mean} (≤ 1 Gy) değeri dikkate alındığında, tüm HİBRİT yükleme planlarının IMRT planlarına göre istatistiksel olarak anlamlı olduğu görülmüştür. HİBRİT planlar en düşük kontra lateral meme D_{maks} değerine sahiptir.

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Sonuç: VMAT teknikleri ile uygun sonuçlar elde edilemiyorsa, IMRT ve VMAT planlarının birleşiminden oluşan HİBRİT planlar, kritik organ dozlarını azaltırken, dozun PTV'yi istenen şekilde sarmasını sağlar.

Anahtar Kelimeler: Meme kanseri, Yoğunluk Ayarlı Radyoterapi, volümetrik ayarlı ark terapi, HİBRİT planları, kritik organ dozları

Introduction

Adjuvant radiotherapy following breast-conserving surgery is effective in reducing the risk of loco-regional recurrence and distant metastasis in patients with early-stage breast cancer (1). With advances in radiation therapy (RT) techniques, 5-year survival of breast cancer patients has increased to 89%, 10-year survival to 83%, and 15-year overall survival to 78% (2). This improvement in survival suggests the need to reduce complications associated with RT.

Since the breast is in an anatomically complex region, the application of effective techniques has an important place in the control of the disease. To prevent complications in the late period, several clinical studies have recommended preservation of organs at risk (OAR) such as ipsilateral lung (IL), contralateral lung (CL), heart and contralateral breast (CB) at different dose volume levels (3). They also mentions that the literal dose homogeneity and the reduction of skin dose help to minimize radiation-induced toxicities such as fibrosis, erythema and wet-desquamation (4).

Since each patient is different, the right choice of the individual treatment technique becomes important. With the right treatment technique, it provides the desired adequate dose coverage to the planned target volume (PTV), while providing low critical organ doses. Compared to Intensity-Modulated Radiotherapy (IMRT)/volumetric-modulated arc therapy (VMAT) plans, Three dimensional (3D) conformal radiotherapy (CRT) plans tend to result in lower target coverage, more heterogeneous dose coverage, and greater volumes of doses up to 20 Gy (5).

It has been proven that IMRT and VMAT techniques provide more appropriate and homogeneous dose distribution when it is desired to be treated by defining it as the only PTV that includes the chest wall and regional nodes after modified radical mastectomy (6).

In studies on the subject, although the IMRT technique provides the desired dose homogeneity throughout the breast volume, it has been determined as a disadvantage that it is more sensitive to set-up and movement uncertainties. In addition, studies report that IMRT increases dose homogeneity and reduces acute skin toxicity and CB dose. The IMRT technique causes the doses of critical organs and normal tissues close to the target volume to decrease compared to conventional treatment, resulting in a decrease in acute and late toxicity rates (7).

VMAT, another technique that has started to be used outside of IMRT, is an approach applied using single or multiple arc irradiation. In this technique, depending on the device structure, the multi leaf collimator (MLC) position, gantry

rotation speed and dose rate are modulated to treat the field to be irradiated (8). Advanced treatment techniques such as IMRT and VMAT improve PTV coverage, quality index and homogeneity, while reducing the dose received by critical organs, especially the heart. Despite this, studies say that while high doses of critical organs decrease, these organs that receive low doses cause an increase in irradiated volumes, and accordingly, the risks of secondary cancer cases may increase (9).

The primary aim of this study is to dosimetrically compare IMRT, VMAT and HYBRID (IMRT/VMAT) planning techniques for whole breast irradiation in terms of PTV coverage, Heterogeneity index (HI-), Conformity index (CI) and OAR. In addition, it is to investigate the clinical usability in practice compared to IMRT and VMAT plans by determining which loading is more appropriate in the hybrid plans obtained by trying different loadings.

Materials and Methods

Patient Selection

Images of 20 randomly selected Caucasian origine, female patients were included in this study with left breast carcinoma (Ca) aged 40-69 years (median mean: 48) who had previously received primary breast radiotherapy for ductal Ca. In the patient images used in the study, patient personal information is hidden for privacy.

During the simulation, the breast board and arms were positioned up, with the chest wall parallel to the gantry, with an under-head support pillow suitable for the neck structure. After the immobilization of the patients in the supine position with suitable angled wedge supports under the legs for patient comfort, the patient is given fixed breathing training in advance, adhering to the clinical protocol with the Toshiba Aquillion 64 CT (computed tomography) simulator (by adding at least 5 cm to the upper and lower limits of the irradiation volume). While breathing steadily, 3 mm thick sections were taken.

The patient's information was submitted to the ethics committee. The study was approved by Aydın Adnan Menderes University Faculty of Medicine, Non-interventional Clinical Research Ethics Committee (approval number: 10, protocol no: 2022/07) and was carried out in accordance with the Declaration of Helsinki.

Volume definition: "Breast Atlas for Radiation Therapy Oncology Group Radiotherapy" is considered as a reference for contouring in all patient plans. After the PTV and critical organs adjacent to the PTV are determined, a 3 mm automatic margin is applied over the PTV in accordance

with our clinical protocol. For organs risk evaluation, the treatment dose (total: 50 Gy) was defined as the isodose covering 95% of the PTV, using the criteria in Table 1.

IMRT plans: Treatment planning system (TPS) (Elekta, Business Area-Software-Systems, UK) are in the Monaco (version 5.10), using 6 MV Elekta Agility Linear Accelerator (Elekta LIMITED, UK) device (leaf-thickness 0.5 cm), 6 MV photon energy parameters, IMRT plans have 7 areas with an angle of approximately 310°, 330°, 342°, 30°, 80°, 105°, 132° (± 5) dynamic IMRT treatment technique and using Monte-Carlo Algorithm. The collimator angle is defined as 2° to prevent leaf leakage.

VMAT plans: It was calculated using the Monte Carlo Algorithm with the double-arc treatment technique [approximately angles CW 286° starting-angle, 232° arc-angle as reference (± 5) 15° intervals], starting from the CW direction, using the same concentricity in VMAT plans, on the same IMRT contours, with the same central axes. The collimator angle was defined as 2° to prevent leaf leakage.

HYBRID plans: HYBRID plans; of previously calculated IMRT and VMAT plans (HYBRID 1: 20% IMRT - 80% VMAT, HYBRID 2: 80% IMRT - 20% VMAT, HYBRID 3: 40% IMRT - 60% VMAT, HYBRID 4: 60% IMRT-40% VMAT and considering planning algorithm structure, in terms of set up practicality, HYBRID 5: 52% IMRT - 48% VMAT) is the combination of loadings at different rates, in accordance with the device parameters in the TPS, MLC in the IMRT treatment technique modulates irradiation at fixed gantry angles, while according to the doses defined in the VMAT treatment technique (PTV, OAR) MLCs irradiate modulated depending on the gantry speed and dose rate during irradiation.

The CI defines the degree to which the predicted isodose volume matches the shape and size of the target volume. The ideal value of a correct plan in CI was expected to be close to "1". As OAR, lung dose, mean CL dose, maximum and minimum CB doses and mean heart dose ratio were

considered Table 1 values were used as evaluation criteria for OARs (10). For the HI-, the value in the algorithm of the Monaco Planning System was applied.

Statistical Analysis

The obtained data were analyzed using the Statistical Package for the Social Sciences (SPSS Statistics 25.0; SPSS Inc. Chicago, IL, USA) program. The distribution of the data was evaluated with the Kolmogorov-Smirnov test. While evaluating the study data, paired sample t-test was used to evaluate the descriptive statistical methods [mean, standard deviation (SD), frequency] as well as pairwise comparisons of normally (Gaussian) distributed parameters. Values at the significance level were accepted at $p < 0.05$ levels. As a result of the analysis, $p < 0.05$ and below values were accepted as significant. According to the parameters examined, the data in this study are the values obtained by taking the averages of all patients (20 patients), and the SD were obtained by using these averages, and the results were evaluated accordingly.

Results

Considering the statistical results, then the following points gain importance.

HYBRID plans were obtained with different loading rates of IMRT and VMAT plans, while PTV reference isodose (95%) was given 50 Gy. Statistical differences of HYBRID plans compared to IMRT and VMAT plans, HI-, conformity index (CI) values and the statistical results of critical organ doses (OAR: lung dose, CL dose, CB and heart dose) are shown in Table 2 collectively.

When a total dose of 50 Gy to PTV is given, we look at the differences between the IMRT and VMAT plans according to the reference 95% isodose volume (V_{95}) and the HYBRID plans according to IMRT and VMAT appears to be statistically significant. When the HI-, HYBRID 1 ($p < 0.010$), HYBRID 2 ($p < 0.037$) and HYBRID 5 ($p < 0.028$) loading plans were examined, it is found statistically significant compared to IMRT when VMAT plans and HYBRID 5 ($p < 0.012$) plans were compared. This shows that the HI is high in IMRT plans and low in VMAT plans.

In terms of CI, it is seen that all HYBRID plans compared to VMAT plans ($p < 0.003$, $p < 0.013$, $p < 0.002$, $p < 0.004$, $p < 0.005$) and VMAT plans are statistically compared to IMRT plans ($p < 0.018$).

There was no statistical significance in any of the loadings in terms of counter-lung dose. However, when the IMRT plan with 20% loading (HYBRID 1) is compared with the VMAT plans, it shows a value close to statistical significance ($p < 0.095$) when other results are taken into account.

In the comparison made in terms of lung dose in the irradiated field, all other loadings were found to be statistically significant except for the HYBRID 4 loading

Table 1. Dose constraints for planning target volumes and organs at risk used for treatment plans

PTV (total dose 50 Gy)	95% REF Iso dose $D_{95} \% \geq 47.5$ Gy
Lung dose	Nodal irradiation (-) $V_{20} < \%10-20$ Nodal irradiation (+) $V_{20} < \%25$
Contralateral lung dose	$V_{5Gy} \leq 10\%$
Contralateral breast dose	$D_{mean} \leq 1$ Gy
Heart dose	$V_{5Gy} \leq 40\%$ $V_{25Gy} \leq 10\%$
Mean heart dose (LAD)	$D_{mean} 3-5$ Gy
Normal tissue	Minimum dose

Table 2. Statistical summary of CI, HI-, OAR and PTV (V_{95}) values obtained from IMRT, VMAT and HYBRID differents loading plans using Elekta Agility Linear Accelerator Device and Monaco (version 5.10) Planning System

		n	PTV (V_{95})	Heterogeneity Index (-)	Conformity Index	Lung dose	Contralateral lung dose	Contralateral breast dose	Mean heart dose (LAD)
Pair 1	Correlation		0.355	0.449	0.251	0.635	0.597	0.836	0.450
	Significant	20	0.315	0.193	0.484	0.049	0.068	0.003	0.192
	p		0.317	0.054	0.079	0.020	0.237	0.027	0.219
Pair 2	Correlation		-0.559	0.456	0.969	0.981	0.988	0.990	0.792
	Significant	20	0.093	0.185	0.000	0.000	0.000	0.000	0.006
	p		0.322	0.087	0.498	0.027	0.236	0.007	0.958
Pair 3	Correlation		-0.011	0.000	0.467	0.580	0.814	0.894	0.707
	Significant	20	0.977	1.000	0.173	0.079	0.004	0.000	0.022
	p		0.311	0.344	0.525	0.022	0.239	0.009	0.594
Pair 4	Correlation		-0.371	0.000	0.832	0.656	0.937	0.919	0.778
	Significant	20	0.291	0.999	0.003	0.040	0.000	0.000	0.008
	p		0.314	0.344	0.362	0.398	0.237	0.009	0.676
Pair 5	Correlation		-0.241	0.445	0.704	0.889	0.893	0.935	0.777
	Significant	20	0.503	0.198	0.023	0.001	0.000	0.000	0.008
	p		0.316	0.012	0.990	0.022	0.209	0.007	0.601
Pair 6	Correlation		0.941	0.659	0.957	0.968	0.936	0.698	0.861
	Significant	20	0.000	0.038	0.000	0.000	0.000	0.025	0.001
	p		0.002	0.010	0.003	0.033	0.095	0.813	0.385
Pair 7	Correlation		-0.034	0.559	0.256	0.574	0.518	0.754	0.400
	Significant	20	0.926	0.093	0.475	0.083	0.125	0.012	0.252
	p		0.216	0.037	0.013	0.023	0.150	0.130	0.111
Pair 8	Correlation		0.671	0.305	0.878	0.394	0.826	0.856	0.515
	Significant	20	0.034	0.392	0.001	0.260	0.003	0.002	0.128
	p		0.014	0.344	0.002	0.741	0.107	0.697	0.038
Pair 9	Correlation		0.266	0.304	0.614	0.561	0.671	0.622	0.434
	Significant	20	0.458	0.392	0.059	0.092	0.034	0.055	0.210
	p		0.066	0.344	0.004	0.020	0.132	0.795	0.054
Pair 10	Correlation		0.270	0.054	0.703	0.790	0.729	0.833	0.494
	Significant	20	0.450	0.881	0.023	0.007	0.017	0.003	0.147
	p		0.107	0.028	0.005	0.023	0.146	0.720	0.051
Pair 11	Correlation		0.554	0.272	0.168	0.421	0.389	0.681	0.122
	Significant	20	0.097	0.447	0.643	0.226	0.266	0.030	0.738
	p		0.332	1.000	0.018	0.023	0.168	0.070	0.206

1: HYBRID 1: 20% IMRT - 80% VMAT, HYBRID 2: 80% IMRT - 20% VMAT, HYBRID 3: 40% IMRT - 60% VMAT, HYBRID 4: 60% IMRT - 40% VMAT, HYBRID 5: 52% IMRT - 48% VMAT. 2: HI-, CI: Critical organ dose (OAR) values obtained by giving 50 Gy to the 95% reference dose covered PTV. HI-: Heterogeneity Index, CI: Conformity Index, N: Number of samples, IMRT: Intensity-modulated radiotherapy, VMAT: Volumetric-modulated arc therapy. Vn: The percentage volume (V) of an organ receiving (n) dose. Data distributions were calculated by Kolmogorov-Smirnov test, statistical methods paired sample t-test. P<0.05 and less were considered significant

plans IMRT ($p<0.398$) and 40% IMRT - 60% VMAT loading plan was according to VMAT ($p<0.741$).

Considering the contralateral-breast dose, it was seen that all HYBRID loading plans statistically significant compared to IMRT plans.

Considering the heart dose, the 40% IMRT - 60% VMAT loading plans were statistically significant compared to the VMAT plan ($p<0.038$). In addition, HYBRID 4 ($p<0.054$) and HYBRID 5 ($p<0.051$) loading plans showed a value close to significance, even though they were outside the significance acceptance limits compared to the VMAT plan.

Discussion

The two main goals in breast radiotherapy are to deliver the desired homogeneous dose to the PTV, while preserving as much normal tissue as possible and reducing patient toxicity. It is aimed to provide disease control with these criteria. While using radiotherapy techniques, targeted PTV coverage leads to low dose exposure of adjacent OARs such as the IL, contralateral chest, and lung. It is known that this low dose effect leads to an increase in the rate of radiation-induced secondary malignancies. Studies also show that free breathing and chest/chest wall motion are in the range of 3 mm or less (11). Also, Jeulink et al. (12) concluded in their dosimetric study that the free breathing mode was sufficient for left breast irradiation.

IMRT and VMAT techniques are not always sufficient depending on the patient's structure, and HYBRID treatment techniques are needed for both homogeneous irradiation of PTV and lowering of OAR doses. Studies reporting planning comparisons have shown that in post-mastectomy breast cases, VMAT is preferred over IMRT and 3 DCRT to OARs to achieve lower dose and better PTV coverage with CI and HI.

In addition, in the study of Chen et al. (13), it is mentioned that the HYBRID - VMAT technique is advantageous in terms of appropriate PTV dose, heart dose and MU. On the other hand, Pignol et al. (14) reported about the decrease in target dose homogeneity during treatment leading to significantly increase in acute skin toxicity dose homogeneity in the irradiated PTV volume provides superiority in tumor control and reduces the possibility of radiation-induced toxicity.

This study showed the comparison of PTV in terms of target coverage and homogeneity, and thus the desired target coverage can be achieved by considering HYBRID 1 and HYBRID 3 values provided that the mean HYBRID loading rate is ± 10 (30% IMRT - 70% VMAT). In the study, the HI-shows that it index is high in IMRT plans and low in VMAT plans.

In terms of statistical significance the CI shows that all HYBRID plans are more suitable than VMAT plans.

The risk of radiation-induced pneumonia is an important complication of radiotherapy in breast cancer patients after radiotherapy. Willner et al. (15) reported that the incidence of radiation-induced pneumonitis increased by 10% for every 10% increase in V_{10Gy} . Yorke et al. (16) suggested the

use of V_{5Gy} and V_{10Gy} in the affected lung may be the cause of radiation-induced lung injury.

The study of Lai et al. (5) shows that the use of VMAT covers smaller volumes in the lung at higher doses (V_{20Gy}) smaller volumes, while low doses (V_{5Gy}) cover larger lung volumes.

In the study, however, there was no statistical significance in any plan in terms of CL dose. Considering the values, it is seen that the HYBRID 1 loading plan gives a better result than the others, although it is not statistically significant ($p<0.095$) compared to the VMAT plan.

From the lung dose adjacent to the treatment area point of view, all plans except HYBRIT 3-HYBRID 4 provide the desired low lung dose.

Doses vary for different patient anatomies, although common dose limits are used. According to the study of Taylor et al. (17), right breast doses are lower than left breast in terms of changes in cardiac doses. Darby et al. (18) reported a linear relationship between ischemic heart disease and D_{mean} for the heart. However, Hu et al. (19) used different techniques and observed that the heart dose was significantly reduced in the so called target segmented plans of IMRT that received 9 fields of the heart dose was used as the critical organ. In addition, in the same study, it was stated that VMAT plans significantly reduced the irradiated dose volume in the IL and the D_{max} dose was lower in the CB.

In the study, in terms of heart dose, HYBRID loading plan with 40% IMRT - 60% VMAT rates ($p<0.038$) is found statistically significant.

Breast cancer radiotherapy also has an effect on the CB. Popescu et al. (20) used the Rapid Arc® technique and reported that the D_{mean} of the CB was below 3.2 Gy, which could significantly reduce the risk of secondary carcinogenesis induced by RT, especially for the young female patient. In this study, consideration of the D_{mean} (≤ 1 Gy) value in the CB, it is determined that the HYBRID planes had the lowest CB D_{max} .

Conclusion

There is no standard radiotherapy treatment planning technique for breast cancer after radical mastectomy yet, and there are several options using different technologies. It is seen both in our study and in the literature that patient-based HYBRID methods provide more protection especially in terms of critical organ doses.

The literature indicates that the VMAT technique provides dose appropriateness and homogeneity while providing an adequate prescription dose for the target of RT. It also significantly reduces the risk of complications of the IL and CB with lower dose radiation exposure for breast cancer patients. In cases where we cannot obtain appropriate results with VMAT techniques, HYBRID plans reduce the OAR doses, while the dose envelops the PTV in a targeted manner. In the study, it was observed that HYBRID plans,

especially HYBRID 2, HYBRID 3 and HYBRID 4 loading plans had lower OAR values than IMRT and VMAT. In addition, HYBRID 3 and HYBRID 4 loading plans were statistically significant for PTV.

The results show that it is possible to obtain the desired dose including the desired critical organ doses and PTV, with patient-specific HYBRID plans obtained with different loadings in line with clinical needs.

Ethics

Ethics Committee Approval: The study was approved by Aydın Adnan Menderes University Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee (approval number: 10, protocol no: 2022/07) and was carried out in accordance with the Declaration of Helsinki.

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.Ö., N.Özb., Concept: N.Ö., N.Özb., Design: N.Ö., N.Özb., Data Collection or Processing: N.Ö., N.Özb., Analysis or Interpretation: N.Ö., N.Özb., Literature Search: N.Ö., N.Özb., Writing: N.Ö., N.Özb.

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References

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, Cutter D, 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: 1707-16.
2. Byers T, Wender RC, Jemal A, Baskies AM, Ward EE, Brawley OW. The American Cancer Society challenge goal to reduce US cancer mortality by 50% between 1990 and 2015: Results and reflections. *CA Cancer J Clin* 2016; 66: 359-69.
3. Chung E, Corbett JR, Moran JM, Griffith KA, Marsh RB, Feng M, et al. Is there a dose-response relationship for heart disease with low-dose radiation therapy? *Int J Radiat Oncol Biol Phys*. 2013; 85: 959-64.
4. Tortorelli G, Di Murro L, Barbarino R, Cicchetti S, di Cristino D, Falco MD, et al. Standard or hypofractionated radiotherapy in the postoperative treatment of breast cancer: a retrospective analysis of acute skin toxicity and dose inhomogeneities. *BMC Cancer* 2013; 13: 230.
5. Lai Y, Chen Y, Wu S, Shi L, Fu L, Ha H, Lin Q. Modified Volumetric Modulated Arc Therapy in Left Sided Breast Cancer After Radical Mastectomy With Flattening Filter Free Versus Flattened Beams. *Medicine (Baltimore)*. 2016; 95: e3295.
6. Ma C, Zhang W, Lu J, Wu L, Wu F, Huang B, et al. Dosimetric Comparison and Evaluation of Three Radiotherapy Techniques for Use after Modified Radical Mastectomy for Locally Advanced Left-sided Breast Cancer. *Sci Rep* 2015; 5: 1-9.
7. Harsolia A, Kestin L, Grills I, Wallace M, Jolly S, Jones C, et al. Intensity-modulated radiotherapy results in significant decrease in clinical toxicities compared with conventional wedge-based breast radiotherapy. *Int J Radiat Oncol Biol Phys* 2007; 68: 1375-80.
8. Liu YC, Chang HM, Lin HH, Lu CC, Lai LH. 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* 2020; 9: 1-14.
9. Balaji K, Yadav P, BalajiSubramanian S, Anu Radha C, Ramasubramanian V. Hybrid volumetric modulated arc therapy for chest wall irradiation: For a good plan, get the right mixture. *Phys Medica*. 2018; 52: 86-92.
10. ICRU Report 83. 3 Special Considerations Regarding Absorbed-Dose and Dose-Volume Prescribing and Reporting in IMRT. *J ICRU* 2010; 10: 27-40.
11. Michalski A, Atyeo J, Cox J, Rinks M. Inter- and intra-fraction motion during radiation therapy to the whole breast in the supine position: a systematic review. *J Med Imaging Radiat Oncol* 2012; 56: 499-509.
12. Jeulink M, Dahele M, Meijnen P, Slotman BJ, Verbakel WF. Is there a preferred IMRT technique for left-breast irradiation? *J Appl Clin Med Phys* 2015; 16: 5266.
13. Chen YG, Li AC, Li WY, Huang MY, Li XB, Chen MQ, et al. The feasibility study of a hybrid coplanar arc technique versus hybrid intensity-modulated radiotherapy in treatment of early-stage left-sided breast cancer with simultaneous-integrated boost. *J Med Phys* 2017; 42: 1-8.
14. Pignol JP, Olivetto I, Rakovitch E, Gardner S, Sixel K, Beckham W, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. *J Clin Oncol* 2008; 26: 2085-92.
15. Willner J, Jost A, Baier K, Flentje M. A little to a lot or a lot to a little? An analysis of pneumonitis risk from dose-volume histogram parameters of the lung in patients with lung cancer treated with 3-D conformal radiotherapy. *Strahlenther Onkol* 2003; 179: 548-56.
16. Yorke ED, Jackson A, Rosenzweig KE, Braban L, Leibel SA, Ling CC. Correlation of dosimetric factors and radiation pneumonitis for non-small-cell lung cancer patients in a recently completed dose escalation study. *Int J Radiat Oncol Biol Phys* 2005; 63: 672-82.
17. Taylor CW, Povall JM, McGale P, Nisbet A, Dodwell D, Smith JT, et al. Cardiac Dose From Tangential Breast Cancer Radiotherapy in the Year 2006. *Int J Radiat Oncol Biol Phys* 2008; 72: 501-7.
18. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, et al. Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer. *N Engl J Med* 2013; 368: 987-98.
19. Hu J, Han G, Lei Y, Xu X, Ge W, Ruan C, et al. Dosimetric Comparison of Three Radiotherapy Techniques in Irradiation of Left-Sided Breast Cancer Patients after Radical Mastectomy. *Biomed Res Int* 2020; 2020: 7131590.
20. Popescu CC, Olivetto IA, Beckham WA, Ansbacher W, Zavgorodni S, Shaffer R, et al. Volumetric Modulated Arc Therapy Improves Dosimetry and Reduces Treatment Time Compared to Conventional Intensity-Modulated Radiotherapy for Locoregional Radiotherapy of Left-Sided Breast Cancer and Internal Mammary Nodes. *Int J Radiat Oncol Biol Phys* 2010; 76: 287-95.