

Effects of modulation factors in breast cancer treatment with helical tomotherapy

S.B. Zincircioglu* and M.H. Dogan

Department of Radiation Oncology, Dicle University Faculty of Medicine, Diyarbakir, Turkey

ABSTRACT

Background: The aim of this study was to compare the dosimetric values of TomoHelical (TH) plans using modulation factors 3 and 5 in patients with breast cancer. **Materials and Methods:** Two different radiotherapy treatment plans, including modulation factors 3 and 5, were generated retrospectively for 12 consecutive intact breast cancer patients. Twelve different plans in terms of the modulation factor were generated. Other optimization parameters (i.e., pitch and field width) were the same for all plans. **Results:** No differences were found between the conformity index (CI) and homogeneity index (HI) values of both plans ($p>0.05$). The values of D mean, V5, and V20 of the ipsilateral lung in the TomoHelical plan with modulation factor 5 (TH5) were significantly lower than with modulation factor 3 (TH3) for all 12 patients (4.9 Gy, 20.14%, 3.23%. Vs, 10.95 Gy, 58.9%, 18.7%; $p=0.01$, $p=0.00$, $p=0.002$, respectively). Also, the values of Dmean and V5 of the heart in TH5 were significantly lower than in TH3 (6.45 Gy, 34.33%, vs. 7.12 Gy, 64.22%; $p=0.004$, $p=0.00$, respectively). **Conclusion:** Both the TH5 and TH3 plans provided adequate coverage of the intact breast. TH5 delivered a decreased dose to the ipsilateral organs at risk (OARs), especially in the lung and heart volume, which is the main cause of long-term toxicity. The novelty of this work is the obvious reduction in same-sided lung volume irradiation by increasing the modulation factor.

Keywords: Breast cancer, modulation factor, irradiation.

► Original article

***Corresponding authors:**
Seyit B. Zincircioglu, M.D.,
E-mail: sbzoglu@yahoo.com

Revised: February 2020

Accepted: June 2020

Int. J. Radiat. Res., April 2021;
19(2): 251-257

DOI: 10.29252/ijrr.19.2.251

INTRODUCTION

Breast cancer is the most common type of cancer in women, representing about 25% of all cancers in this population ⁽¹⁾. Surgery, radiotherapy (RT), and chemotherapy with a multimodal approach are the proven effective standard approach for breast cancer treatment. Adjuvant breast RT only increases local control rates on breast-conserving surgery ⁽²⁾. Postoperative RT has also been shown to be related to increased survival rates ⁽²⁾. As an alternative to mastectomy, breast-conserving surgery followed by irradiation of the intact breast has become the standard of care for patients with early-stage breast cancer ⁽³⁾.

Newer conformal methods of breast irradiation have been shown to sufficiently

cover the breast target volume. High-dose spots in the target volume and adjacent structures can be reduced by the TomoHelical plan with modulation factor 3 (TH3), tomotherapy (proton beam therapy), and inverse-intensity modulated radiotherapy (IMRT), although low dose spots in the volume of the normal structure are increased in TH. 3D-CRT is worse than IMRT in terms of target homogeneity, but the inverse-planned methods are a little better than forward IMRT ⁽⁴⁾. The availability of irradiation technologies, such as IMRT, were increased, and differences in plan quality should be evaluated to determine how one plan compares to others, which will determine the standard of care in most clinics. Several studies of breast irradiation with TH have been conducted ⁽⁵⁾.

The modulation factor (MF) is determined as

MF = longest open time / average open time. The inverse planning system decreases MF by reducing the max open time and increasing the average time of leaves opening. Raising the average time is obtained by eliminating the use of leafs with the minimum times of opening, thereby decreasing the dose in organs at risk (OARs) that are outside of planned target volume (PTV) ⁽⁶⁾. In our study, both the TH3 and TH5 plans are generated by using IMRT in the TomoHelical machine. The field width and pitch of the optimization parameters are kept constant while creating the plans, but the MF parameter is changed, and plans are created. TH3 plans are generated by using an MF value of 3, and TH5 plans are generated using an MF value of 5. When we increased the MF value, there was a dose reduction in OARs in TH3 plans when compared to TH5 plans. However, when we increased the MF value, we observed that treatment times increased, but the increase was not statistically significant. Also, significant differences were not observed in the PTV dose coverage between TH3 and TH5.

The aim of this study was to compare TH5 and TH3 plans dosimetrically in terms of OAR doses in helical IMRT. The importance of the study was to show how to reduce OARs doses while providing the same PTV dose coverage, especially at the ipsilateral lung volumes.

MATERIALS AND METHODS

Patients

Twelve consecutive early-stage breast cancer patients referred for adjuvant whole-breast irradiation after undergoing breast-conserving surgery were selected for this study. All patients received RT with TH plans between February 2016 and January 2017 in the Department of Radiation Oncology at the university hospital. TH plans were retrospectively created for these patients after obtaining informed consent. All of the patients had biopsy-proven early stage I-II disease according to the AJCC cancer staging system. We created two modes of tomotherapy breast-conserving therapy irradiation plans: TH3 (modulation factor 3) and TH5 (modulation

factor 5).

Simulation, contouring, planning, and plan assessment

Patients were simulated using computed tomography (CT) and positioned on a breast board (CIVCO) with their head turned to the cross side and the sided-arm raised above their head. CT images with a 3 mm thickness were obtained for TH planning. The CT images and volume contours of PTV and OARs were sent to the tomotherapy H system (Accuray Inc., Sunny Vale, CA, USA) to create treatment plans. Contours of the patients' left and right breasts were marked by placing wires throughout the CT scan. In all of the patients, the back boundary of the breast within the target volume was defined as the interface of the rib-cage pleura, whereas the upper boundary was considered to be 3 mm below the surface of the skin. The cranial boundary of the target volume was designated as the bottom of the clavicular head. The PTV volume extended from the first intercostal space in the craniocaudal direction until the xiphoid bone.

TH plans were generated rotationally to cover PTV and minimize doses to OARs, the side lung, and the contralateral breast. The intact breast was included in the irradiation volume. For TH plans, the pitch, field width, and modulation factor were 0.287, 5.048 cm, and 3 or 5, respectively.

A total dose of 50 Gy was prescribed in daily 2 Gy fractions to the PTV as the standard approach. TH3 and TH5 plans were defined according to the isodose line that best covered the PTV. TH plans were optimized such that 95% of the PTV gained the prescription dose, and the following optimization aims were used during inverse planning. For PTV, the percentage of the PTV receiving a minimum of 107% of the prescribed dose, which was defined as V107 (V53.5 Gy), was used to compare TH plans.

The homogeneity index (HI) was used to analyze the uniformity of the dose distribution in the target volume. HI is the ratio of the dose difference between D2 (the dose to 2% of the target volume) and D98 (the dose to 98% of the target volume) to D50 (the target median dose).

Int. J. Radiat. Res., Vol. 19 No. 2, April 2021

A higher HI value, which extends from 0 to 1, shows worse homogeneity, while a lower value indicates greater conformity. The effects on the target volume, OAR doses, and treatment times were assessed for each planning technique by one radiation oncologist.

Statistical analysis

Data were evaluated using SPSS version 16.00 statistical software (SPSS, Chicago, IL, USA). All data were expressed as mean $\pm$ standard deviation (SD). Statistically significant differences in dosimetric end-points between TH plans were determined using the Wilcoxon 2 related simple test. Differences were considered significant when $p < 0.05$.

RESULTS

Six patients had right-sided cancers, and six patients had left-sided breast cancers. Their median age was 44 ± 7 . The median volume of PTV of the intact breast was 1060.27 ± 454.25 cc. Table 1 summarizes the dose parameters of PTV in the TH plans, and the dose distributions of PTV for TH5 and TH3 plans are shown in figure 1.

In our study, the conformity index (CI) values of TH5 and TH3 were 0.92 and 0.94, respectively ($p > 0.05$). Similarly, the HI values in TH5 were

not significantly better than those in the TH3 plan (0.22, and 0.21, $p > 0.05$). Both the TH5 and TH3 plans demonstrated clinically acceptable target dose coverage for intact breast RT in our study. However, the Dmax values were significantly different. We found significant differences in the mean values of V107 (the volume receiving 53.5 Gy) between the TH5 and TH3 plans (3.81%, 0.70%, $p = 0.03$).

In our study, the values of D2 and Dmin for PTV, V5, and V20 for the same-sided lung, Dmean and V5 for the heart, and V5 for the contralateral breast were significantly lower in TH5 ($p < 0.005$). However, the Dmax value for PTV was significantly lower in TH3 ($p < 0.005$). Table 2 shows the dosimetric parameters for the same-sided lung, heart, contralateral breast, esophagus, and spinal cord.

The average treatment times were 6.5 minutes for the TH3 plan and 8 minutes for the TH5 plan. The increased treatment time for the TH5 plan was considered and thought to be acceptable for the treated patients. We compared the dosimetric parameters of the TH5 and TH3 plans for the patients' right and left intact breasts. Table 3 shows dosimetric comparisons of TH5 and TH3 plans of the six right-sided and six left-sided intact breasts. The most important differences were found in the dosimetric parameters of the heart and same-sided lung.

Table 1. Comparison of dosimetric parameters for PTV between TH5 and TH3 plans.

Parameter	Tomomodulation	TomoHelical	
	Mean $\pm$ SD	Mean $\pm$ SD	p value
Dmean	50.53 $\pm$ 0.50	50.61 $\pm$ 0.26	0.505
Dmin	25.79 $\pm$ 6.50	33.88 $\pm$ 5.31	0.003
Dmax	57.18 $\pm$ 1.36	55.47 $\pm$ 1.17	0.020
V95	95.81 $\pm$ 2.06	96.00 $\pm$ 1.84	0.583
V107	3.81 $\pm$ 3.25	0.70 $\pm$ 0.61	0.030
D2	59.92 $\pm$ 0.54	52.75 $\pm$ 0.62	0.003
D50	43.69 $\pm$ 17.9	50.79 $\pm$ 0.22	0.875
D95	47.96 $\pm$ 0.98	48.14 $\pm$ 0.92	0.518
D98	45.94 $\pm$ 1.17	45.97 $\pm$ 1.04	0.714
CI	0.92 $\pm$ 0.03	0.94 $\pm$ 0.03	0.210
HI	0.22 $\pm$ 0.09	0.21 $\pm$ 0.06	0.170

Dmax, maximum dose; Dmean, mean dose; Dmin, minimum dose received by 99% of target volume; D2, the dose to 2% of the target volume; D50, the dose to 50% of the target volume; D95, the dose to 95% of the target volume; D98, the dose to 98% of the target volume; Vx, volume (x) receiving x dose (Gy) or higher; CI, Conformity index; HI, Homogeneity index.

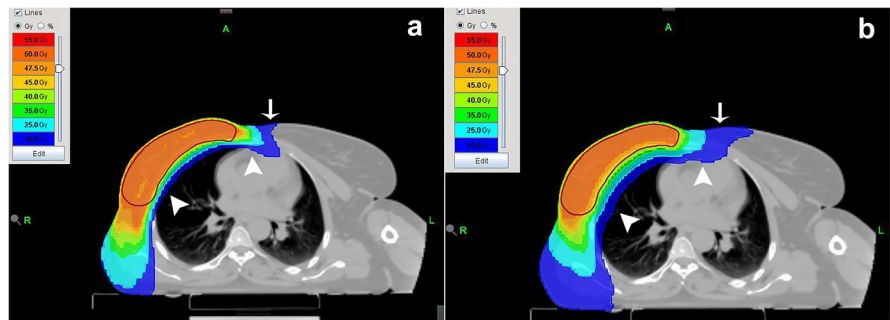


Figure 1. Dose distributions of PTV at sided-lung (arrow head), heart (arrow head) and contralateral breast (arrow) for TH5 (a) and TH3 (b) plans in representative case. Different color regions in plans demonstrating exposed radiation doses.

Table 2. Comparison of dosimetric parameters for the OARs for the TH5 and TH3 plans for 12 patients.

Parameter	Tomomodulation	TomoHelical	
	Mean $\pm$ SD	Mean $\pm$ SD	p value
Ipsilateral lung			
Dmean	4.59 $\pm$ 1.50	11.08 $\pm$ 5.33	0.001
V5	20.31 $\pm$ 9.46	57.30 $\pm$ 19.55	0.000
V20	3.31 $\pm$ 2.90	16.77 $\pm$ 7.74	0.002
Heart			
Dmean	5.51 $\pm$ 1.51	6.97 $\pm$ 1.81	0.004
V5	36.16 $\pm$ 15.12	59.10 $\pm$ 17.94	0.000
V25	1.03 $\pm$ 1.73	1.62 $\pm$ 1.42	0.064
V30	0.53 $\pm$ 1.06	0.48 $\pm$ 0.74	0.262
Spinal cord			
Dmean	0.52 $\pm$ 0.68	0.56 $\pm$ 0.65	0.088
Dmax	7.84 $\pm$ 5.10	7.70 $\pm$ 4.12	0.959
D2	5.72 $\pm$ 3.60	6.20 $\pm$ 3.01	0.156
Contralateral breast			
Dmean	3.97 $\pm$ 1.45	4.98 $\pm$ 1.60	0.136
V5	16.60 $\pm$ 8.61	39.08 $\pm$ 15.72	0.001
Esophagus			
Dmean	4.75 $\pm$ 2.42	4.98 $\pm$ 1.60	0.831

Vx, volume (%) receiving x dose (Gy) or higher; Dmax, maximum dose; Dmean, mean dose; D2, the dose to 2% of the spinal cord.

Table 3. Comparison of dosimetric parameters of TH5 and TH3 plans of the right and left-sided intact breast.

Right-sided (n=6)				Left-sided (n=6)			
	TH5	TH3		TH5	TH3		
Parameter	Mean $\pm$ SD	Mean $\pm$ SD	P value	Mean $\pm$ SD	Mean $\pm$ SD	P value	
PTV							
Dmean	50.44 $\pm$ 0.71	50.51 $\pm$ 0.36	0.893	50.63 $\pm$ 0.15	50.71 $\pm$ 0.04	0.173	
Dmin	27.43 $\pm$ 6.67	36.28 $\pm$ 3.55	0.028	24.14 $\pm$ 6.48	31.48 $\pm$ 5.97	0.046	
Dmax	57.10 $\pm$ 1.46	54.89 $\pm$ 0.85	0.028	57.26 $\pm$ 1.38	56.06 $\pm$ 1.21	0.028	
V95	95.57 $\pm$ 2.37	95.60 $\pm$ 2.40	0.917	96.05 $\pm$ 1.90	96.41 $\pm$ 1.13	0.463	
V107	4.18 $\pm$ 4.46	0.43 $\pm$ 0.54	0.046	3.44 $\pm$ 1.77	0.98 $\pm$ 0.59	0.028	
D2	53.82 $\pm$ 0.63	52.65 $\pm$ 0.68	0.046	54.03 $\pm$ 0.45	52.85 $\pm$ 0.59	0.028	
D50	44.14 $\pm$ 18.86	50.77 $\pm$ 0.26	0.600	43.24 $\pm$ 18.70	50.81 $\pm$ 0.18	0.917	
D95	47.84 $\pm$ 1.08	47.80 $\pm$ 1.13	0.917	48.08 $\pm$ 0.94	48.49 $\pm$ 0.56	0.600	
D98	45.96 $\pm$ 1.20	45.88 $\pm$ 1.37	0.917	45.93 $\pm$ 1.26	46.06 $\pm$ 0.71	0.600	
HI	.22 $\pm$ 0.11	0.20 $\pm$ 0.07	0.580	0.23 $\pm$ 0.09	0.22 $\pm$ 0.05	0.212	
CI	0.92 $\pm$ 0.04	0.93 $\pm$ 0.03	0.751	0.92 $\pm$ 0.03	0.95 $\pm$ 0.02	0.075	
Sided lung							
Dmean	4.47 $\pm$ 1.12	13.08 $\pm$ 6.98	0.028	4.70 $\pm$ 2.03	9.07 $\pm$ 3.15	0.028	
V5	17.36 $\pm$ 3.16	67.18 $\pm$ 20.54	0.028	23.27 $\pm$ 13.56	47.41 $\pm$ 16.14	0.028	
V20	4.27 $\pm$ 2.74	18.68 $\pm$ 8.98	0.028	2.36 $\pm$ 3.25	14.85 $\pm$ 7.38	0.028	
Heart							
Dmean	5.79 $\pm$ 1.44	7.06 $\pm$ 1.48	0.028	5.23 $\pm$ 1.66	6.88 $\pm$ 2.23	0.028	
V5	4.74 $\pm$ 14.16	58.59 $\pm$ 16.66	0.028	31.58 $\pm$ 15.87	59.62 $\pm$ 20.72	0.028	
V25	1.43 $\pm$ 2.03	1.08 $\pm$ 1.26	0.893	0.63 $\pm$ 1.45	2.16 $\pm$ 1.46	0.043	
V30	0.71 $\pm$ 1.30	0.21 $\pm$ 0.51	0.593	0.35 $\pm$ 0.86	0.75 $\pm$ 0.88	0.068	
Spinal cord							
Dmin	0.19 $\pm$ 0.07	0.23 $\pm$ 0.07	0.043	0.85 $\pm$ 0.87	0.88 $\pm$ 0.82	0.400	
Dmax	8.20 $\pm$ 5.24	8.13 $\pm$ 3.98	0.753	7.49 $\pm$ 5.42	7.26 $\pm$ 4.58	0.917	
D2	6.22 $\pm$ 4.04	6.61 $\pm$ 3.16	0.463	5.23 $\pm$ 3.40	5.79 $\pm$ 3.09	0.249	
Contralateral breast							
Dmean	3.42 $\pm$ 0.99	4.61 $\pm$ 2.25	0.173	4.53 $\pm$ 1.71	5.36 $\pm$ 0.49	0.345	
V5	3.19 $\pm$ 8.07	38.02 $\pm$ 21.67	0.046	20.02 $\pm$ 8.37	40.14 $\pm$ 8.45	0.028	
Esophagus							
Dmean	4.57 $\pm$ 2.02	4.60 $\pm$ 2.25	0.753	4.94 $\pm$ 2.96	5.36 $\pm$ 0.49	0.753	

PTV, Planning target volume; Dmin, minimal dose; Dmean, mean dose; D2, the dose to 2% of the volume; D50, the dose to 50% of the target volume; Dmax, maximum dose; Vx, volume % receiving x dose (Gy) or higher.

DISCUSSION

In this dosimetric comparison, we compared two modalities of tomotherapy planning with modulation factors of 3 and 5. In accordance with the published literature, our analysis has shown that both plans provide adequate coverage of the PTV ^(7,8). In the latest

publications, the potential benefits of IMRT and TH in breast RT, such as reducing the dose delivered to the same-sided lung and heart, could reduce breast complications and fibrosis through recovered dose homogeneity ⁽⁹⁾. Our aim was to perform a comprehensive analysis of TH5 and TH3 plans, which contained a limited number of patients from the standpoint of a

planned study, by comparing both techniques on the basis of several dosimetric criteria: coverage, homogeneity, and conformity, as well as the ability to avoid causing complications in normal structures (e.g., heart disease and pneumonitis).

All proton beam therapy (PBT) and IMRT plans achieved superior PTV coverage in comparison to conventional 3D-CRT and TH plans (prescription of V47.5Gy of PTVs>95%). V95 values in 3D-CRT, IMRT, TH, and PBT were 95%, 97%, 95%, and 96%, respectively. Furthermore, IMRT and PBT resulted in higher target dose homogeneity than TH and 3D-CRT (10). Tomo direct (TD), E-VMAT, and Rapid arc (RA) plans performed in this study achieved a higher dose target coverage (V95%) than the field in field (FinF) plan (11). We found that the mean value of V95 was higher for TH3 than TH5, but this difference is not statistically significant (95.99% vs. 96.36%). CI and HI are two analysis parameters of a treatment plan. The technique with segmental fields provided a more homogeneous dose distribution than using the standard of two tangential fields. The conformity index values were 1.38 and 1.43, respectively (12). Another study found that the HI values in 3D-CRT, TH, and CK were 0.13, 0.09, and 0.12, respectively (13). We found no differences between the TH5 and TH3 plans in HI and CI values. The mean value of PTV V107 was $0.2\% \pm 0.1$ in TH3, and the TH5 plan had the most conformed and homogeneous dose distribution (14). Volumetric-arc therapy (VMAT) plans were more inhomogeneous than the TH and TD plans (15). Our study showed that the value of V107 in TH3 was 0.71%, and in TH5, it was 2.67%.

The clinical advantage of RT in the treatment of breast cancer should be balanced against the increased risk of early and late toxicities (16). Toxicity can affect the breast and other OARs, and in the long-term, it can lead to secondary malignancies, premature cardiac death, lung fibrosis, and pneumonitis (17). The role and benefit of up-to-date RT for localized breast cancer are the ability to provide homogeneous and effective irradiation with a lower potential for complications (18). Some techniques can help achieve this goal; for example, 3D-CRT, TH, and

IMRT protect the heart and lungs (19-21). Compared to other techniques, TH reduces the risk of same-sided critical structures receiving higher doses but with an increase in the target volumes receiving low doses (22). In our study, the values of Dmean, V5 (i.e., the volume of lung tissue receiving at least 5 Gy), and V20 (i.e., the volume of lung tissue receiving at least 20 Gy) of the same-sided lung in TH5 were significantly lower than in the TH3 plan for all 12 patients ($p=0.01$, $p=0.00$, $p=0.02$, respectively). These results can be explained by increasing the modulation factor from 3 to 5 and the rotational delivery of TH.

Irradiation of the heart is another important issue in radiation therapy of the breast. The increased risk of cardiac events is related to the dose received by the heart and the irradiated cardiac volume. Reducing cardiac irradiation as much as possible should be a priority in the planning of thoracic irradiations. Radiotherapy practices have to be modified using modern techniques with an approach that determines the primary objective as optimizing the dose to the target volume, sparing healthy tissues, including the heart (23). The most obvious difference in treatment techniques is the level of exposure of normal structures to lower or higher radiation doses. Previous research has found that multi-beam therapy techniques can reduce the risk of delivering high doses to critical structures, such as the heart and lungs, while correcting target homogeneity so that healthy structures receive lower doses (24). There is a dose-response relationship between late complications and cardiac dose, and it has been shown that the risk arises when 20% of the heart volume receives a dose greater than 30 Gy (25). In our study, the irradiated heart volume (V5) was found to be significantly higher with the TH3 plan than the TH5 plan. Based on these rates, it can be concluded that the techniques used do not carry significant risk in terms of late cardiac complications.

In a previous study, it was reported that for TH5, 14% of the heart and 38% of the sided lung received 25 Gy and 20 Gy ($V_{25} = 14\%$ and $V_{20} = 38\%$) irradiation, respectively, in patients receiving 50 Gy breast irradiation treatment (26).

This study also reported a PTV value of 0.10 HI. Our results indicate that heart and sided-lung irradiated volumes in TH5 were significantly lower than in TH3, and our results are consistent with those of previous studies. In addition, volumes for the heart ($V_{25} < 10\%$) and sided-lung ($V_{20} < 50\%$) for Quentec⁽²⁷⁾ are consistent with our findings.

In the case of chest and breast irradiation, the dose received by the contralateral breast is also important. Raising the contralateral breast dose may increase the risk of causing additional malignancy in patients⁽²⁸⁾. Other reports showed that the relative risk of inducing secondary breast cancer via RT was only 1.19, and the calculated radiation dose to the contralateral breast was 2.82 Gy⁽²⁹⁾. Therefore, the risk of developing another breast cancer from an average contralateral breast dose in the TH5 plan with 4.21 Gy and 5.12 Gy in the TH3 plan might not be significant.

CONCLUSION

Based on the dosimetric factors, the TH5 plan could be promoted as more useful and more effective than the TH3 plan. Using a modulation factor value of 5 in the planning system can ensure the delivery of lower doses to the same-sided lung and heart volume.

Conflicts of interest: Declared none.

REFERENCES

1. Ferlay J, Shin H, Bray F, Forman D, Mathers C, Parkin D (2010) GLOBOCAN 2008, cancer incidence and mortality worldwide. *IARC CancerBase*, **10**.
2. Poortmans PM, Venselaar JL, Struikmans H, Hurkmans CW, Davis JB, Huyskens D, van Tienhoven G, Vlaun V, Lagendijk JJ and Mijnheer BJ (2001) The potential impact of treatment variations on the results of radiotherapy of the internal mammary lymph node chain: a quality-assurance report on the dummy run of EORTC Phase III randomized trial 22922/10925 in Stage I–III breast cancer. *Int J Radiat Oncol Biol Phys*, **49(5)**: 1399-408.
3. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, Aguilar M, Marubini E (2002) Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *New England Journal of Medicine*, **347(16)**: 1227-32.
4. Schubert LK, Gondi V, Sengbusch E, Westerly DC, Soisson ET, Paliwal BR, Mackie TR, Mehta MP, Patel RR, Tomé WA (2011) Dosimetric comparison of left-sided whole breast irradiation with 3DCRT, forward-planned IMRT, inverse-planned IMRT, helical tomotherapy, and tomotherapy. *Radiotherapy and Oncology*, **100(2)**: 241-6.
5. Caudell JJ, Jennifer F, Keene KS, Fiveash JB, Wang W, Carlisle JD, Popple R (2007) A dosimetric comparison of electronic compensation, conventional intensity modulated radiotherapy, and tomotherapy in patients with early-stage carcinoma of the left breast. *Int J Radiat Oncol Biol Phys*, **68(5)**: 1505-11.
6. Ryczkowski A and Piotrowski T (2013) Influence of the modulation factor on the treatment plan quality and execution time in Tomotherapy in head and neck cancer: In-phantom study. *Journal of Cancer Research and Therapeutics*, **9(4)**: 618.
7. Fogliata A, Bolsi A, Cozzi L (2002) Critical appraisal of treatment techniques based on conventional photon beams, intensity modulated photon beams and proton beams for therapy of intact breast. *Radiotherapy and Oncology*, **62(2)**: 137-45.
8. Gonzalez VJ, Buchholz DJ, Langen KM, Olivera GH, Chauhan B, Meeks SL, Ruchala KJ, Haimeri J, Lu W, Kupelian PA (2006) Evaluation of two tomotherapy-based techniques for the delivery of whole-breast intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys*, **65(1)**: 284-90.
9. Oliver M, Chen J, Wong E, Van Dyk J, Perera F (2007) A treatment planning study comparing whole breast radiation therapy against conformal, IMRT and tomotherapy for accelerated partial breast irradiation. *Radiotherapy and Oncology*, **82(3)**: 317-23.
10. Moon SH, Shin KH, Kim TH, Yoon M, Park S, Lee D-H, Kim JW, Kim DW, Park SY, Cho KH (2009) Dosimetric comparison of four different external beam partial breast irradiation techniques: three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, helical tomotherapy, and proton beam therapy. *Radiotherapy and Oncology*, **90(1)**: 66-73.
11. Koivumäki T, Fogliata A, Zeverino M, Boman E, Sierpowska J, Moeckli R, Vallet V, Cozzi L, Heikkilä J, Väänänen A (2018) Dosimetric evaluation of modern radiation therapy techniques for left breast in deep-inspiration breath-hold. *Physica Medica*, **45** 82-7.
12. Jones R, Yang W, Read P, Sheng K (2011) Radiation therapy of post-mastectomy patients with positive nodes using fixed beam tomotherapy. *Radiotherapy and Oncology*, **100(2)**: 247-52.
13. Rault E, Lacornerie T, Dang H-P, Crop F, Lartigau E, Reynaert N, Pasquier D (2016) Accelerated partial breast irradiation using robotic radiotherapy: a dosimetric comparison with tomotherapy and three-dimensional conformal radiotherapy. *Radiation Oncology*, **11(1)**: 29.
14. Orecchia R, Rojas DP, Cattani F, Ricotti R, Santoro L, Morra A, Cambria R, Luraschi R, Dicuonzo S, Ronchi S (2018)

- Hypofractionated postmastectomy radiotherapy with helical tomotherapy in patients with immediate breast reconstruction: dosimetric results and acute/intermediate toxicity evaluation. *Medical Oncology*, **35(3)**: 39.
15. Qi XS, Liu TX, Liu AK, Newman F, Rabinovitch R, Kavanagh B, Hu YA (2014) Left-sided breast cancer irradiation using rotational and fixed-field radiotherapy. *Medical Dosimetry*, **39(3)**: 227-34.
 16. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, Kamby C, Kjaer M, Gadeberg CC, Rasmussen BB (1999) Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *The Lancet*, **353(9165)**: 1641-8.
 17. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, Correa C, Cutter D, Gagliardi G, Gigante B (2013) Risk of ischemic heart disease in women after radiotherapy for breast cancer. *New England Journal of Medicine*, **368(11)**: 987-98.
 18. Grantzau T and Overgaard J (2015) Risk of second non-breast cancer after radiotherapy for breast cancer: a systematic review and meta-analysis of 762,468 patients. *Radiotherapy and Oncology*, **114(1)**: 56-65.
 19. Goddu SM, Chaudhari S, Mamalui-Hunter M, Pechenaya OL, Pratt D, Mutic S, Zoberi I, Jeswani S, Powell SN, Low DA (2009) Helical tomotherapy planning for left-sided breast cancer patients with positive lymph nodes: comparison to conventional multiport breast technique. *Int J Radiat Oncol Biol Phys*, **73(4)**: 1243-51.
 20. Lauche O, Kirova YM, Fenoglietto P, Costa E, Lemanski C, Bourgier C, Riou O, Tiberi D, Campana F, Fourquet A (2016) Helical tomotherapy and volumetric modulated arc therapy: new therapeutic arms in the breast cancer radiotherapy. *World Journal of Radiology*, **8(8)**: 735.
 21. Pignol JP, Olivetto I, Rakovitch E, Gardner S, Sixel K, Beckham W, Vu TTT, Truong P, Ackerman I, Paszat L (2008) A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. *Journal of Clinical Oncology*, **26(13)**: 2085-92.
 22. Hacıislamoglu E, Colak F, Canyilmaz E, Dirican B, Gurdalli S, Yilmaz AH, Yoney A, Bahat Z (2015) Dosimetric comparison of left-sided whole-breast irradiation with 3DCRT, forward-planned IMRT, inverse-planned IMRT, helical tomotherapy, and volumetric arc therapy. *Physica Medica*, **31(4)**: 360-7.
 23. Vandendorpe B, Servagi SV, Ramiandrisoa F, Bazire L, Kirova Y (2017) Doses to organs at risk in conformational radiotherapy and stereotaxic irradiation: The heart. *Cancer Radiotherapie*, **21(6-7)**: 626-35.
 24. Coon AB, Dickler A, Kirk MC, Liao Y, Shah AP, Strauss JB, Chen S, Turian J, Griem KL (2010) 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*, **78(1)**: 104-10.
 25. Gagliardi G, Lax I, Ottolenghi A, Rutqvist L (1996) Long-term cardiac mortality after radiotherapy of breast cancer—application of the relative seriality model. *The British journal of radiology*, **69(825)**: 839-46.
 26. Binny D, Lancaster CM, Harris S, Sylvander SR (2015) Effects of changing modulation and pitch parameters on tomotherapy delivery quality assurance plans. *Journal of Applied Clinical Medical Physics*, **16(5)**: 87-105.
 27. Murthy K, Shukeili K, Kumar S, Davis C, Chandran R, Namrata S (2010) Evaluation of dose coverage to target volume and normal tissue sparing in the adjuvant radiotherapy of gastric cancers: 3D-CRT compared with dynamic IMRT. *Biomedical Imaging and Intervention Journal*, **6(3)**: e29.
 28. Stovall M, Smith SA, Langholz BM, Boice Jr JD, Shore RE, Andersson M, Buchholz TA, Capanu M, Bernstein L, Lynch CF (2008) Dose to the contralateral breast from radiotherapy and risk of second primary breast cancer in the WECARE study. *Int J Radiat Oncol Biol Phys*, **72(4)**: 1021-30.
 29. Boice Jr JD, Harvey EB, Blettner M, Stovall M, Flannery JT (1992) Cancer in the contralateral breast after radiotherapy for breast cancer. *New England Journal of Medicine*, **326(12)**: 781-5.

