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Effects of modulation factors in breast cancer treatment with helical tomotherapy

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► ***Original article***

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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.*

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), topotherapy (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

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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).

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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 ± 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 ±SD	Mean ±SD	p value
Dmean	50.53±0.50	50.61±0.26	*0.505*
Dmin	25.79±6.50	33.88±5.31	*0.003*
Dmax	57.18±1.36	55.47±1.17	*0.020*
V95	95.81±2.06	96.00±1.84	*0.583*
V107	3.81±3.25	0.70±0.61	*0.030*
D2	59.92±0.54	52.75±0.62	*0.003*
D50	43.69±17.9	50.79±0.22	*0.875*
D95	47.96±0.98	48.14±0.92	*0.518*
D98	45.94±1.17	45.97±1.04	*0.714*
CI	0.92±0.03	0.94±0.03	*0.210*
HI	0.22±0.09	0.21±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, volüme (5) receiving x dose (Gy) or higher; CI, Conformity index; HI, Homogenity index.

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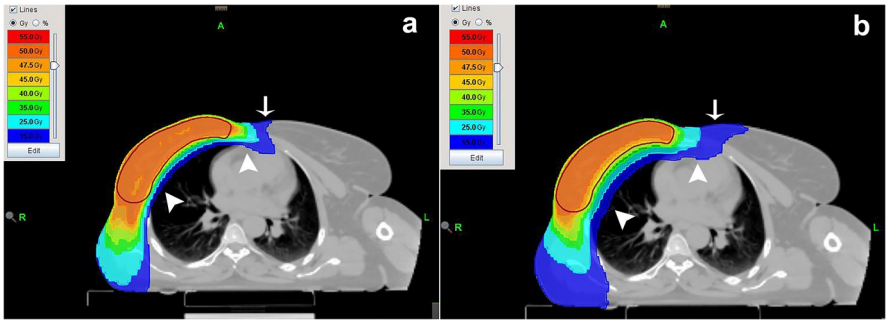


Figure 1. Dose distributions of PTV at sided-lung (arrow head), heart (arrow head) and contralateral breast (arrow) for TH5 **(a)** and TH3 **(b)** plans in representative case. Different color regions in plans demonstrating exposed radiation doses.

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

Parameter	Tomomodulation	TomoHelical	
	Mean ±SD	Mean ±SD	p value
Ipsilateral lung			
Dmean	4.59±1.50	11.08±5.33	*0.001*
V5	20.31±9.46	57.30±19.55	*0.000*
V20	3.31±2.90	16.77±7.74	*0.002*
Heart			
Dmean	5.51±1.51	6.97±1.81	*0.004*
V5	36.16±15.12	59.10±17.94	*0.000*
V25	1.03±1.73	1.62±1.42	*0.064*
V30	0.53±1.06	0.48±0.74	*0.262*
Spinal cord			
Dmean	0.52±0.68	0.56±0.65	*0.088*
Dmax	7.84±5.10	7.70±4.12	*0.959*
D2	5.72±3.60	6.20±3.01	*0.156*
Contralateral breast			
Dmean	3.97±1.45	4.98±1.60	*0.136*
V5	16.60±8.61	39.08±15.72	*0.001*
Esophagus			
Dmean	4.75±2.42	4.98±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 ±SD	Mean ±SD	P value	Mean ±SD	Mean ±SD	p value
PTV						
Dmean	50.44±0.71	50.51±0.36	*0.893*	50.63±0.15	50.71±0.04	*0.173*
Dmin	27.43±6.67	36.28±3.55	*0.028*	24.14±6.48	31.48±5.97	*0.046*
Dmax	57.10±1.46	54.89±0.85	*0.028*	57.26±1.38	56.06±1.21	*0.028*
V95	95.57±2.37	95.60±2.40	*0.917*	96.05±1.90	96.41±1.13	*0.463*
V107	4.18±4.46	0.43±0.54	*0.046*	3.44±1.77	0.98±0.59	*0.028*
D2	53.82±0.63	52.65±0.68	*0.046*	54.03±0.45	52.85±0.59	*0.028*
D50	44.14±18.86	50.77±0.26	*0.600*	43.24±18.70	50.81±0.18	*0.917*
D95	47.84±1.08	47.80±1.13	*0.917*	48.08±0.94	48.49±0.56	*0.600*
D98	45.96±1.20	45.88±1.37	*0.917*	45.93±1.26	46.06±0.71	*0.600*
HI	.22±0.11	0.20±0.07	*0.580*	0.23±0.09	0.22±0.05	*0.212*
CI	0.92±0.04	0.93±0.03	*0.751*	0.92±0.03	0.95±0.02	*0.075*
Sided lung						
Dmean	4.47±1.12	13.08±6.98	*0.028*	4.70±2.03	9.07±3.15	*0.028*
V5	17.36±3.16	67.18±20.54	*0.028*	23.27±13.56	47.41±16.14	*0.028*
V20	4.27±2.74	18.68±8.98	*0.028*	2.36±3.25	14.85±7.38	*0.028*
Heart						
Dmean	5.79±1.44	7.06±1.48	*0.028*	5.23±1.66	6.88±2.23	*0.028*
V5	4.74±14.16	58.59±16.66	*0.028*	31.58±15.87	59.62±20.72	*0.028*
V25	1.43±2.03	1.08±1.26	*0.893*	0.63±1.45	2.16±1.46	*0.043*
V30	0.71±1.30	0.21±0.51	*0.593*	0.35±0.86	0.75±0.88	*0.068*
Spinal cord						
Dmin	0.19±0.07	0.23±0.07	*0.043*	0.85±0.87	0.88±0.82	*0.400*
Dmax	8.20±5.24	8.13±3.98	*0.753*	7.49±5.42	7.26±4.58	*0.917*
D2	6.22±4.04	6.61±3.16	*0.463*	5.23±3.40	5.79±3.09	*0.249*
Contralateral breast						
Dmean	3.42±0.99	4.61±2.25	*0.173*	4.53±1.71	5.36±0.49	*0.345*
V5	3.19±8.07	38.02±21.67	*0.046*	20.02±8.37	40.14±8.45	*0.028*
Esophagus						
Dmean	4.57±2.02	4.60±2.25	*0.753*	4.94±2.96	5.36±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

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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% ±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 (V25 = 14% and V20 = 38%) irradiation, respectively, in patients receiving 50 Gy breast irradiation treatment [26].

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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 (V25 < 10%) and sided-lung (V20 < 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.

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