Original Article Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.202183192-202

Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) in Mono and Dual-isocentric Techniques of Breast Cancer Radiation Therapy

Kaveh Shirani Tak Abi[a], Sediqeh Habibian[b], Marzieh Salimi*[c,d], Ahmad Shakeri[b], Mohammad Mahdi Mojahed[b], Hussain Gharaati[d]

[a] *Sina Radiation Oncology Department, Bu Ali hospital, Tehran, Iran*
[b] *Valiasr Radiation Oncology Center, Qom, Iran*
[c] *School of Physics and Astronomy, University of Exeter, Exeter, UK*
[d] *Department of Medical Physics and Biomedical Engineering, Tehran University of Medical Sciences, Tehran, Iran*

ARTICLE INFO

Received:
03 March 2021
Revised:
19 March 2021
Accepted:
22 March 2021

Key words:
Tumor control probability, normal tissue complication probability, external beam, radiation therapy, breast cancer.

ABSTRACT

Background: Nowadays, radiation therapy plays an important role in the treatment of breast cancer. The important point is the optimal control of the tumor along with the protection of organs at risk. This study aims to investigate and compare the radiobiological factors of the tumor and organs at risk in two different radiation therapy techniques of breast cancer.

Methods: Ten left-sided breast cancer patients with breast-conservative surgery were selected for this study. Three-dimensional treatment planning was performed using CT scan images of the patients using PCRT 3D software. Two different tangential external beam techniques were compared: first, dual-isocentric technique (DIT) with two isocentre, one on the breast tissue, and the other one on the supraclavicular lymph nodes and second, a mono-isocentric technique (MIT) with one isocentre at the intersection of the tangential and the supraclavicular field. The total prescribed dose was 5000 cGy per 25 fractions. Dose-volume histograms (DVHs), Tumor control probability (TCP), and normal tissue complication probability (NTCP) curves were used to compare the dosimetric and radiobiological parameters of the tissues in the prementioned techniques.

Results: The results showed that the maximum doses in planning target volume (PTV) with mean values of 109% and 110% in the SI and DIT were not significantly different in both techniques and that they were indeed at the optimum level based on the RTOG 1005 protocol. The dose homogeneity index in MMIT was more than that in DIT, while the conformity index and the mean TCP did not show a significant difference in the two techniques. Furthermore, minimum, mean, and maximum dose in the lung and the probability of pneumonitis decreased in MIT. On the other hand, the maximum dose, the dose of 33%, 66%, and 100% of the heart, and the probability of pericarditis in MIT were lower than the figure in DIT.

Conclusion: Due to the absence of hot spots at the intersection of tangential and supraclavicular fields and the reduction of mechanical movements of the coach and collimator in MIT, the superiority of this method was confirmed.

*** Address for correspondence:**
Marzieh Salimi, PhD
Address: School of Physics and Astronomy, University of Exeter, Exeter, UK
Tel: :+44-1392-725652
Email: m.a.salimi@exeter.ac.uk

Introduction

Breast cancer is one of the most commonly diagnosed cancers among women worldwide with 1.4 million cases per year, accounting for almost one-third of malignancies in women.[1,2] Postoperative radiation therapy has a proven role in the treatment of

early stages of breast cancer to improve local control, survival, and reducing cancer recurrence.[3-10] On the other hand, breast radiation therapy can be accompanied by several complications such as cardiovascular and pulmonary damages that are due to irradiation of non-target tissues around the breast, chest wall, and regional lymph nodes.[1, 4, 6, 11-19] Two opposite-parallel tangent fields are used for breast tissue irradiation and one anterior field is applied for the supraclavicular irradiation. It is possible to have overdose or underdose at the intersection of two adjacent radiation fields that can be due to mismatch of the borders of the fields, which will ultimately have a direct impact on the treatment complications and tumor control.

Current guidelines for the locally advanced breast cancer normally recommend that elective nodal irradiation should be applied to the regional lymphatics as well as the whole breast.[20] Also, nodal irradiation is recommended strongly by the National Comprehensive Cancer Network (NCCN) guidelines for N1 breast cancer patients.[21] Furthermore, supraclavicular-axillary irradiation decreases the locoregional recurrence and mortality in the patients with lymph-node-positive breast cancer.[22] In the study of Kim et al., regional recurrence in the supraclavicular nodes occurred in only 1% of patients. This is a very low recurrence rate showing that supraclavicular-axillary irradiation should be performed in all patients. This study has also shown that supraclavicular-axillary irradiation can significantly decrease the risk of distant metastasis, as well as regional lymph-node recurrence.[23]

A study by Whelan et al. showed that metastasis-free survival increased in the patients who received supraclavicular-axillary irradiation compared to other patients who did not have regional nodal irradiation (78% vs. 75%, P=0.02). Also, breast cancer mortality was lower among patients in the nodal-irradiation group than control patients. Besides that, the rate of heart disease or deaths from heart disease did not increase among patients who received regional nodal irradiation at a follow up of 9.5 years.[24] Tai et al. evaluated the role of supraclavicular-axillary irradiation according to the nodal ratio (NR). The results revealed that for patients with >10 nodes examined, supraclavicular-axillary irradiation significantly increased the survival in the median and high NR patients but not in the low NR patients. In their study, the patients were considered in three NR groups: low (LNR, <25%), medium (MNR, 25% to 75%), and high (HNR >75%) nodal involvement.[25]

The effects of radiation therapy on cancer and healthy cells are characterized by two probabilities: first, tumor control probability (TCP), which indicates the probability of not having any cancer cells after radiation treatment, and second, the likelihood of expected complications called normal tissue complication probability (NTCP).[26-28] One of the most critical factors that have a significant effect on the treatment complications is the radiation therapy technique. Several techniques have been proposed for external breast cancer radiotherapies such as 2D, 3D, Intensity-modulated radiation therapy (IMRT), Image-guided radiation therapy (IGRT), and field-in-field technique with advanced technologies and special software. Moreover, several methods such as mono-isocenter, multi-isocenter, half-beam, and full beam have been developed for application in the prementioned techniques.[29,30] In this study, two different techniques in 3D radiation therapy including mono-isocentric technique (MIT) and dual-isocentric technique (DIT) were selected for dosimetric and radiobiologic evaluation and comparison. The dosimetric comparisons between the two techniques have been performed in many studies[4, 17, 19, 29, 31]; so in this study, we evaluated the radiobiologic factors such as TCP and NTCP as well as the dosimetric factors and lung and cardiac exposure rate using different external breast radiation therapy techniques.

Methods

Patients' information

In this study, ten patients with early-stage invasive ductal carcinoma breast cancer and conservation surgery were selected at the Radiation

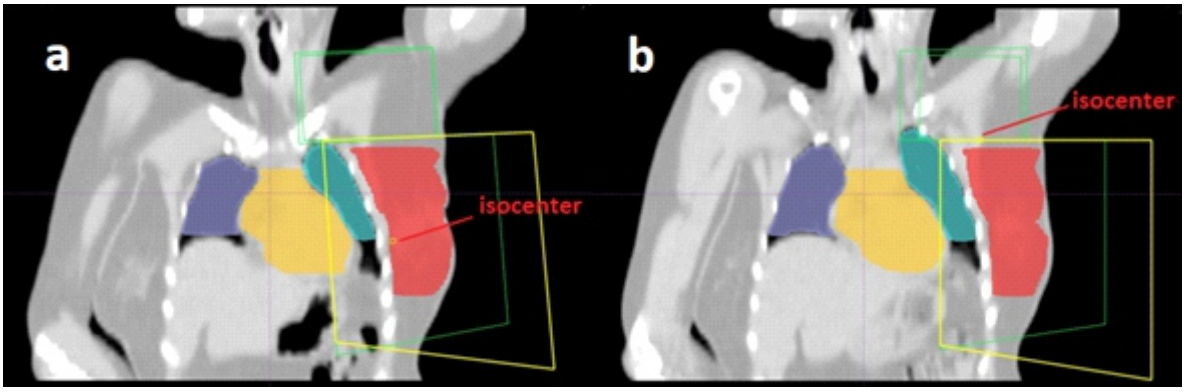

Figure 1. Isocenter positioning. a) dual-isocentric technique with isocenter applied to the breast tissue, b) mono-isocentric technique with isocenter located at the intersection of the two tangent and supraclavicular fields.

and Oncology Center of Vali-e-Asr Hospital in Qom.

Treatment Planning

In the DIT which is the most common method of whole breast radiation therapy, two isocenters are defined; one on the breast tissue and the other on the upper area of the breast tissue to irradiate the supraclavicular lymph nodes.[32] It is worth mentioning that, in this technique, there is a gap between the two adjacent fields due to the radiation beam divergence (Figure 1a).

In the MIT, only one isocenter is defined at the intersection of the tangent and supraclavicular fields, so that the upper field is blocked for the radiation of the tangent field, and then the lower field is blocked for the radiation of the supraclavicular field (Figure 1b).[33] In this case, a non-divergence beam leads to the optimal matching of adjacent fields. Unlike the DIT, there is no collimator and couch rotation in the MIT.

Patients' CT scans were transferred to PCRT 3D (6.0.2.14) software for planning radiation fields. The lung, heart, and PTV tissues were contoured in all slices of the axial CT scans by a radiation oncologist. Due to breathing, patient position, breast swelling, and setup inaccuracies, usually 1 cm margin was considered around the clinical target volume (CTV) and Planning Target Volume (PTV).

Radiation dose and fractionation

A dose of 50 Gy in 25 fractions over 5 weeks was prescribed for 100% of the isodose, so that patients received 2Gy per fraction. Treatment planning was performed to cover the entire PTV by the isodose 95% and the maximum PTV dose less than 110%.[34]

Beam characteristics

The SHINVA linear accelerator with 6 MV X-rays, 40 cm× 40 cm asymmetrical jaws, and orthogonal mechanical wedges was capable of matching the 40 cm length of the field of view (FOV). The PCRT treatment planning software was also used for this study to access the target volume and organ at risk dose rate.

Limitations of lung and heart radiation

Dosimetric goals of study for lung and heart were defined according to the recommendations of the radiotherapy and oncology group, termed RTOG, as follows:[35]

V20≤20%, V10≤40%, V5≤55% for the lung

D33% ≤60Gy, D66% ≤45Gy, D100% ≤40Gy, and V10≤35% for heart

These values were extracted from DVHs for each organ.

Dose homogeneity index and conformity index

Dose homogeneity index (HI) and conformity index (CI) are two possibilities used to evaluate breast conformal treatment plans.[34,36,37]

The following equation was used for HI calculation:

$$HI = D5 / D95 \quad (1)$$

Where D5 is a minimum dose of 5% in PTV, indicating a maximum dose (Dmax) and D95 is a minimum dose of 95% PTV, representing a minimum dose (Dmin). The lower (close to one) the factor, the better is the dose homogeneity.

CI is also defined as the ratio of the volume surrounded by the reference isodose (which according to ICRU, is 95%) to the target volume planned by the physicist and its formula is as follows:

$$CI = VRI / TV \quad (2)$$

Where VRI is the reference isodose volume and TV is the target volume.

TCP and NTCP assessment for lung and heart tissues

The TCP is the probability that no clonogenic cell can survive in the treated volume at the end of the treatment. It is described by a Poisson distribution with parameter λ which gives the final number of clonogenic cells. The model parameters are:

αm: mean linear radio sensitivity coefficient for the tumor (Gy-1)
βm: mean quadratic radio sensitivity coefficient for the tumor (Gy-2)
σα: standard deviation of α
σβ: standard deviation of β
Tdup: doubling time for the tumor (days)
Tk: onset time for accelerated proliferation (days)
T: total time (natural days) of treatment (days)
Q0: initial density of clonogenic tumor cells

Initially, since all of the radiobiological parameters for standard fractionation (2 Gy per session) have been calculated, the dose-response curve for this fractionation is plotted. In the case of breast cancer, because of the uniformity of dose per fraction with standard fractionation, there is no need for uniformity and change in the dose-response curve. The mean values of radiation sensitivity and their related standard deviations are already available in the software. Finally, using the model, the final number of clonogenic cells is calculated with each radiation sensitivity.

$$N(i,j) = \sum_{h=1}^{k} \rho_0 . v_h \, e^{\left\{-(\alpha i . Dh + \beta j . D_h . d) + \left(\frac{Ln2}{Tdup}\right).(T-Tk)\right\}} \quad (3)$$

$$TCP = \sum_{i=1}^{200} g_{\alpha i} \sum_{j=1}^{200} g_{\beta j} \, e^{-N(i,j)} \quad (4)$$

Where $\alpha = 0.51\ Gy^{-1}$, $\beta = 0.061\ Gy^{-2}$, $T_k = 12$, $T_{pot} = 12$, and Density of 1000 Cell/Cm^3 were considered for breast cancer.

NTCP calculation was performed using Lyman-Kutcher and Burman model. This model also known as a normal or empirical model which calculates the complications probability of normal tissues in a non-uniform irradiation using dose-response histograms. Moreover, this model can estimate the probability of complications for uniformly irradiated organs. In this regard, we applied the method of effective volume in which a non-uniform dose-volume histogram was mapped onto a uniform dose-volume histogram with a volume equal to the effective volume and a dose equal to the organ maximum dose. This effective volume was calculated by the following equation:

$$V_{eff} = \sum_{i=1}^{k} v_i \left(\frac{Di}{D_{max}}\right)^{\frac{1}{n}} \quad (5)$$

Where (vi , Di) are the histogram pairs, vi is normalized to 1, D_{max} is the organ maximum dose and k is the number of histogram pairs. First, the histogram must be transformed to the standard fractionation schedule (2 Gy/fraction). Subsequently, the following equation is used for NTCP:

$$NTCP = \frac{1}{(2\pi)^{\frac{1}{2}}} \int_{-\infty}^{t} e^{\frac{-x^2}{2}} dx \quad (6)$$

$$t = \frac{(D_{max} \cdot V_{eff}^{n})}{m.D_{5\ 0}} \quad (7)$$

Where n and m are obtained empirically by fitting the expression for NTCP to the tolerance doses for each organ totally and partially irradiated with a uniform dose; D50 is the dose that causes complications with 50% probability when the tissue is homogeneously irradiated. For NTCP calculation, the parameters were defined in Table 1.

Table 1. The parameters used for NTCP calculation in left lung and heart

Parameters	Left lung	Heart
α (Gy^{-1})	0.035	0.058
β (Gy^{-2})	0.008	0.029
n	0.87	0.35
m	0.18	0.1
D_{50}(Gy)	24.5	48

Results

PTV

The results of dosimetric analysis in PTV are summarized in Table 2 and Figures 2 and 3.

The minimum dose in MIT (1044 cGy) was significantly lower than that in DIT (1641cGy) (p-value = 0.03). Also, the mean dose in the MIT (4810 cGy) was lower than that in DIT (4928 cGy) (p-value = 0.00). On the other hand, the maximum dose in the MIT (5463 cGy) and DIT (5510 cGy) did not show a significant difference (p-value = 0.19). The maximum dose percentage of PTV was 109% and 110% in the MIT and DIT, respectively (Table 2). This value was lower than the ideal threshold recommended by RTOG 1005 (115%), indicating that there was no hot spot in both techniques (Figure 2).

Table 2. Comparison of calculated values in two mono-isocentric and dual-isocentric-techniques for PTV. The values include D_{min} (minimum dose), D_{mean} (mean dose), D_{max} (maximum dose), HI (Homogeneity index), and CI (Conformity index)

parameter	MIT*	DIT*	P-value	RTOG*	
				Ideal	Acceptable
D_{min}	1044.1	1641.5	0.03		
D_{mean}	4810.4	4928.6	0		
D_{max}	5463.4	5510.1	0.19		
D_{max}	109.29	110.21	0.2	<115%	<120%
HI*	1.15	1.12	0		
CI*	1.52	1.51	0.96		

*Abbreviations: DIT = Dual-isocentric Technique, MIT= Mono-Isocenteric Technique, HI= Hemogeneity Index, CI= Conformity Index, RTOG= Radiation Therapy Oncology Group

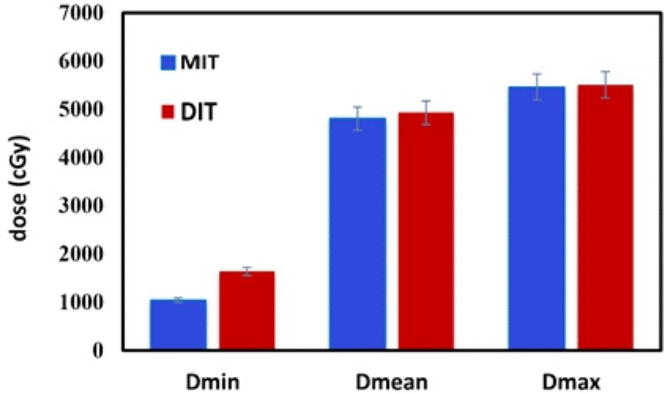

Figure 2. The mean values of the minimum, mean and maximum dose of PTV in both mono-isocenteric and dual-isocentric techniques.

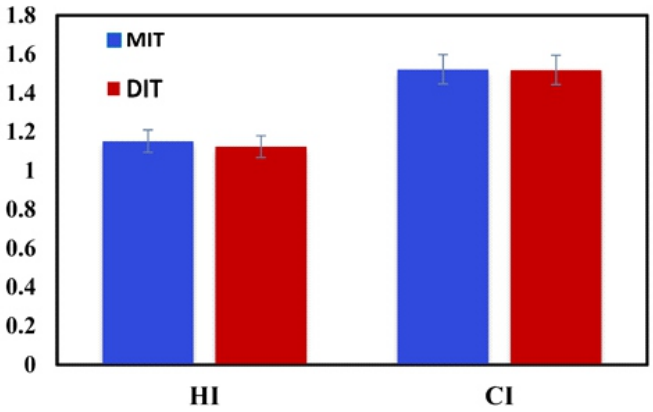

Figure 3. Homogeneity index and conformity index in the mono-isocenteric and dual-isocentric techniques

The homogeneity index of the beam in the MIT (1.15) was higher than that in the DIT (1.12). Given the fact that the amount of this factor was close to 1 in both techniques, the results showed that homogeneity was acceptable in these techniques (Figure 3). Furthermore, the conformity index with mean values of 1.52 in the MIT and 1.51 in the DIT did not show a significant difference (p-value = 0.96). As Figure 4 shows, the isodose curves in the DIT and MIT are similar and there is no significant difference between the two techniques.

Left lung

As shown in Table 3, all parameters calculated for the left lung decreased in MIT (p-value < 0.05), except V20 (Figure 5a).

V20 was not significantly different in the two techniques (p-value = 0.1); the values of this parameter in both MIT and DIT (23% and 26%, respectively) were higher than the acceptable threshold by RTOG 1005 (20%). Additionally, V5 and V10 were ideal and lower than the threshold [38] (Figure 5b).

Heart

Based on the information given in Table 4, the mean value of D_{min} was 127.9 and 173.3 for MIT and DIT, respectively. Also, the mean value of D_{max} was 4843 and 4960 in SI and DIT, respectively (Figure 6a). The P-values calculated for these parameters indicated a reduction in the MIT, while the D_{mean} with a mean value of 831 for SI and 883 for DIT did not show a significant difference between the two techniques. D33%, D66%,

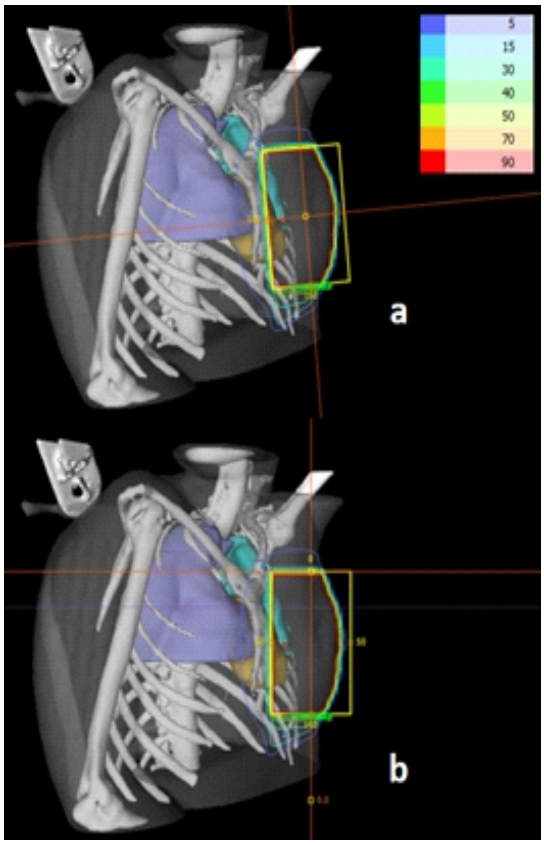

Figure 4. Isodose curves in the medial tangent beam. a) the dual-isocentric technique with collimator and couch rotation and b) the mono-isocentric technique without those rotations.

Table 3. Comparison of the calculated values in two mono-isocentric and dual-isocenteric techniques for the left lung.

parameter	MIT*	DIT*	P-value	RTOG	
				Ideal	acceptable
D_{min} (cGy)	125.6	149.8	0.01		
D_{mean} (cGy)	1219.8	1374.2	0.04		
D_{max} (cGy)	4914.3	5058	0.00		
V20* (%)	23.33	25.98	0.1	<15%	<20%
V10* (%)	25.89	30.24	0.02	<35%	<40%
V5* (%)	29.99	37.24	0.00	<50%	<55%

*Abbreviations: DIT = Dual-Isocentric Technique, MIT= Mono- Isocenteric Technique, V5, V10 and V20 = the volume of lung receiving 5,10 and 20 Gy, respectively.

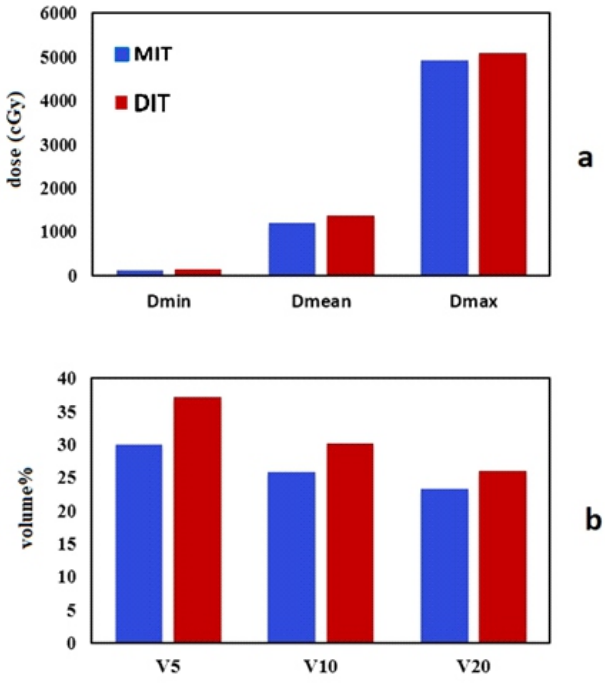

Figure 5. Parameters were calculated for the lung in two mono-isocentric and dual-isocentric techniques. a) the minimum, mean and maximum dose of the lung, b) the volume of the lung (V5, V10, and V20) receiving 5, 10, and 20 Gy, respectively.

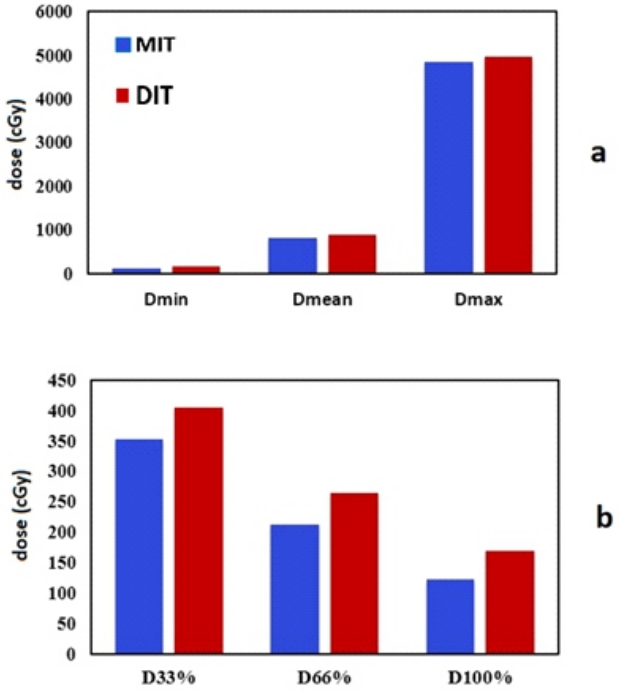

Figure 6. Parameters calculated for the heart in MIT and DIT. a) the minimum, mean, and maximum heart dose, b) the dose of 33%, 66% and 100% volume of the heart.

and D100% were lower in MIT; however, the values for both techniques were acceptable according to RTOG. V10 was lower than the RTOG threshold with no significant difference between the two techniques (Figure 6b).

TCP and NTCP

TCP and NTCP calculations were performed using the radiobiological part in the PCRT 3D software. The corresponding curves were drawn and the TCP and NTCP values were extracted for the 50Gy prescribed dose. As shown in Table 5, TCP in the MIT with a mean value of 82.8% (the range of 69-89%) and a mean value of 84.8% in the DIT (the range of 73-95%) did not reveal a significant difference (P-value = 0.08). On the other hand, the mean NTCP for the left lung in MIT was 6% (the range of 2.9-10.6%), less than that in the DIT (mean value of 7.5% and the range of 4.1-12.4%). The heart NTCP was 0.77% (the range of 0.19-1.8%) and 0.97% (the range of 0.24-1.9%) in the MIT and DIT, respectively (Figure 7).

Table 4. Comparison of calculated values in two mono-isocenteric and dual-isocentric techniques for the heart.

parameter	MIT	DIT	P-value	RTOG	
				Ideal	Acceptable
D_{min} (cGy)	127.9	173.3	0.00		
D_{mean} (cGy)	831.4	883.8	0.24		
D_{max} (cGy)	4843.1	4960.8			
$D_{33\%*}$ (cGy)	353.2	404.2	0.00	≤60Gy	
$D_{66\%*}$ (cGy)	212.9	265.1	0.00	≤45Gy	
$D_{100\%*}$ (cGy)	122.2	170.3	0.00	≤40Gy	
V_{10} (%)	16.47	17.71	0.26	<30%	<35%

*$D_{33\%}$, $D_{66\%}$, and $D_{100\%}$= dose of 33%, 66% and 100% of heart volume.

Table 5. Values of target volume TCP and NTCP of organs at risk

parameter	MIT	DIT	P-value
TCP of PTV (%)	82.8±2.2	84.8±2	0.08
NTCP of Lung (%)	6.16±0.8	7.57±1	0.02
NTCP of Heart (%)	0.77±0.2	0.97±0.17	0.04

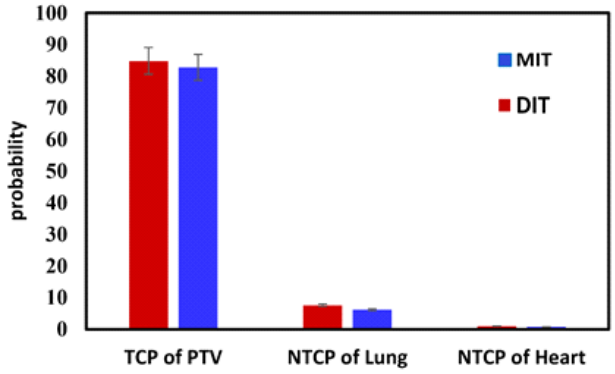

Figure 7. TCP and NTCP calculated for dual and mono-isocentric technique.

Discussion

In general, the outcomes of successful radiation treatment planning are tumor control and the incidence of complications. However, the simultaneous control of these outcomes is not only possible by dosimetric factors; the radiobiologic factors seem to be also essential to evaluate and optimize treatment planning. In this study, two external radiation therapy techniques for breast cancer including MIT and DIT were investigated using radiobiological factors such as TCP and NTCP as well as dosimetric parameters.

Despite dual or mono-isocentric (conventional) techniques, advanced radiotherapy techniques such as VMAT, IMRT-IGRT, tomotherapy and protontherapy are not widely available for breast cancer radiotherapy and are restricted to highly selected patients.[39] Although advanced techniques such as intensity-modulated radiotherapy (IMRT) and volumetric imageguided radiotherapy (V-IGRT) improve the tumor control and normal tissue complication, conventional radiotherapy in breast cancer have remained the standard treatment techniques. The interaction between tomotherapy and nodal irradiation improved the outcome, although it did not reach significance.[40]

Taylor et al. published a review article on heart dose in breast cancer, summarizing 149 articles and 398 regimens, showing that the mean heart dose was 5.4Gy (range between 1.6-8) in the 3D breast cancer radiotherapy without intramammary lymph nodes. The values obtained in our study were 8.3Gy for MIT and 8.8Gy for DIT that was at the upper limit of Taylor's article.[4] The values obtained in the study by Adam et al. for the mean and maximum heart dose in the 3D technique were 13 Gy and 51Gy, respectively[37], which were more than the values in our study for both DIT and MIT (Table 6).

According to the protocol published by the RTOG 0972[41], cardiac exposure limitations for 33%, 66%, and 100% of the heart are 60, 45, and 40Gy, respectively. The values of heart tissue tolerance in the study by Emami et al. were similar to those of RTOG 0972, although the extracted values in our study were significantly lower than those in their study. According to the RTOG 1005 protocol, the ideal volume limit for the heart tissue receiving 10Gy and more is 30% and in our study, these values were 16% and 17% for MIT and DIT, respectively.[41] In contrast, Chan reported a V10 of 3.4 ± 5.5% for heart in left breast 3D radiotherapy[17], which is lower than those in our study.

Ohashi et al. claimed that cardiac complications would be minimized if the heart receives less than 30Gy.[42] Emami et al. also stated that if the mean heart dose is less than 26Gy, the pericardial inflammation would be less than 15%.[43] Radiation-induced heart-related injuries include acute and chronic damage. Pericardial inflammation is an acute injury that is often transient but can be chronic. The probability of cardiac complications calculated in our study for pericardial inflammation with a mean of 0.77 in SI and 0.97 in DIT was consistent with the study by Astudillo et al. who reported 0-1 for heart NTCP. In the current study, the heart dosimetric parameters in MIT were lower than that in DIT, and in fact, heart exposure was reduced in MIT. Furthermore, NTCP results indicated that the inflammation risk of the pericardium decreased due to the heart dose reduction.[44]

Chan et al. reported 52.3 and 10.7 Gy for the maximum and mean doses of the lung, respectively.[17] The maximum dose of the lung in the current study with a mean value of 49 Gy in MIT and 50 Gy in DIT was lower than that in the study by Chan et al; while the mean dose calculated for MIT with 12 Gy and DIT with 13.7 Gy was higher than that in their study. In Chan et al.'s study, V5, V10, and V20 values for the lung were 35.9, 28.5, and 21.8%, respectively, and V5 and V10 in their research in MIT were more than that in our study, while these values in DIT were less than those in our study.

On the other hand, V20 in our study was higher than reported values in both techniques in the previous research and the RTOG 1005 threshold.[38] Although in the previous RTOG recommendation (version 0972[30]), the threshold for V20 was 35% which was consistent with our study. In Adam's

study, V20 for lung was 24% and higher than that in our study. The mean dose of the left lung was reported to be 12 Gy which was identical to the values of the MIT but less than the DIT values in our study. Emami et al. claimed that pulmonary inflammation due to irradiation was the most common complication among patients with breast radiation therapy and that the risk of this complication often limited the prescription dose in the treatment. They estimated the risk of pulmonary inflammation at 10% when V20 was less than 31%, arguing that the likelihood of inflammation was 5% for V5 less than 42%. These values resemble the values obtained in the current study and consequently, it was expected that the NTCP for the pulmonary inflammation would be the same as the value reported by Emami et al.[43] In our study, the NTCP was 7.57 and 6.16 for the DIT and MIT, respectively while the mean value of the left lung NTCP in the study conducted by Astudillo ranged from 6 to 53%. Hurkman also reported that pulmonary inflammation was not observed in the patients receiving 8 Gy mean lung dose.[14]

The normalization point of the tangential field was defined in the same region with a slight difference in both techniques. The maximum dose was received in the DIT and it was in the acceptable limit according to RTOG 1005; no hot point was observed. Reducing the hot spots in the isodose curves has a direct effect on the treatment outcomes and decreases the superficial breast skin burns. The average value of TCP, which represented the result of all dosimetric calculations, did not show a significant difference in the two techniques, and in fact, both techniques provided similar tumor control. Kara et al. pointed to the superiority of the MIT, with a reduction of more than 50% in hot spots, and the values of the minimum and mean dose in the MIT were close to the values of the prescription dose.[45] In our study, all values for the left lung, except V20, were significantly different in the two methods, and in the MIT, the dose and volume of the exposed lung decreased. A significant decrease in the parameters for the heart was observed in the MIT technique in the DIT in our study. Rosenow et al. also reported lung dose reduction in the MIT technique.[11]

However, the dose-volume curves of organs at risk of the lung and heart showed a significant difference in all patients with a history of breast conservative surgery and mastectomy.[11]

Kagkiouzis published a review of three-field techniques in breast cancer radiation therapy, which introduced tangent and supraclavicular fields matching as the most complex clinical problem that could be due to breast disordered morphology (Such as breast shape and chest slope) and divergence of radiotherapy fields.[46] Also, in the clinic, these parameters such as patient setup and fixing the collimators have more effect on the adjacent radiation fields matching than the type of treatment technique. Several papers pointed to the reduction of hot spots in MIT. The MIT technique reduces the overall time of the treatment and also decreases the errors caused by the patient's movements but the disadvantage is that treatment planning takes longer. It has been argued that a slight difference in breast and supraclavicular field matching leads to high dosimetry changes in the target volume, lung, and bilateral breast, and there is a need for high precision and jaw control in the treatment.[46]

The presence of one isocenter as well as the absence of collimator and couch rotation in the MIT increases the speed of patient setup and reduces the treatment time. On the other hand, the need for displacing the isocenter point for two different fields increases precision and repeatability. The main point is the absence of hot spots, cold spots, overlaps of the tangent and supraclavicular fields, which reduces the risk of treatment complications and cancer recurrence.[11,47,48] It is worth mentioning that the collimators cover a maximum length of 40 cm. Using asymmetric jaws and the MIT allows the opening of therapeutic fields up to 20 cm, which may not be enough for some patients with a large breast (length of more than 20 cm); so in these cases, the dual-isocentric technique should be used. Another issue that we encountered in the clinic is the effect of the isocenter location on the treatment accuracy. In the MIT, the isocenter is located close to the axillary region and the repeatability of the treatment is reduced in patients with obesity or those having tissue irregularities and flexure due to breast surgery. Consequently, the treatment does not have adequate accuracy and, thus, it is recommended to use a dual-isocentric technique with two separate isocenters.

To compare different conventional breast radiotherapy techniques, the mean absolute dose deviation (MADD) has been developed; this parameter measures how widely the dose delivered to an organ deviates from a reference dose prescribed for that organ and integrates the balance between tumor control and normal tissue complication. Wang et al. evaluated the dosimetric advantage of prone setup compared to supine for left-breast radiotherapy. In their study, radiation doses to heart, lungs, breasts, and tumor bed were assessed using MADD. Subsequently, as a weighted sum of the MADDs was normalized to the breast prescribed dose, a penalty score was computed for each treatment plan.[49]

Several limitations to this study need to be acknowledged. First, the sample size was small due to the inclusion/exclusion criteria in this study and the time limitation that the researchers encountered during this project. With a larger sample size, more significant results could have been extracted from the data. Second, the present study was subject to some potential methodological weaknesses; for example, a) TCP and NTCP are multi-parametric non-linear

Table 6. The results of our study and those of the other studies cited in this study.

		Current Study		Taylor	Adam	Emami	RTOG	RTOG	Chan	Astudilo
		DIT	MIT				0972	1005		
Heart	Mean dose (Gy)	8.8	8.3	5.4	13					
	Max dose (Gy)	49	48		51					
	D33% (Gy)	4	3.5			60	60			
	D66% (Gy)	2.6	2.1			45	45			
	D100% (Gy)	1.7	1.2			40	40			
	V10 (%)	17	16					30	3.4	
	NTCP (%)	1	0.8							0-1
Lung	Max dose (Gy)	50	49						52.3	
	Mean dose (Gy)	14	12		12				10.7	
	V5 (%)	37	30					55%	35.9	
	V10 (%)	30	25					40%	28.5	
	V20 (%)	25	23		24		35%	20%	21.8	
	NTCP (%)	7.6	6.2			10% for V20<31%				6-53%

models that have not received formal validation. The more parameters, the greater the likelihood of a model being wrong, b) TCP and NTCP were evaluated differently, one set of equations for targets, another set for organs, intrinsically disparate metrics, c) Using TCP and NTCP can only be hypothesis-generating.

Regarding the findings of this study and the review of other studies, in both MIT and DIT the dose coverage of PTV and tumor control probability was similar, while the dose of organs at risks such as heart and lung was reduced in the MIT. All in all, it can be stated that the MIT provided an improved treatment plan compared to the DIT.

Conflict of Interest

None.

Ethical Consideration

This study have obtained research ethics committee approval from Tehran University of Medical Sciences.

References

1. Shah C, Badiyan S, Berry S, Khan AJ, Goyal S, Schulte K, et al. Cardiac dose sparing and avoidance techniques in breast cancer radiotherapy. Radiotherapy and Oncology. 2014;112(1):9-16.
2. Sonnik D, Selvaraj RN, Faul C, Gerszten K, Heron DE, King GC. Treatment techniques for 3D conformal radiation to breast and chest wall including the internal mammary chain. Medical Dosimetry. 2007;32(1):7-12.
3. Mukesh MB, Harris E, Collette S, Coles CE, Bartelink H, Wilkinson J, et al. Normal tissue complication probability (NTCP) parameters for breast fibrosis: pooled results from two randomised trials. Radiotherapy and Oncology. 2013;108(2):293-8.
4. Taylor CW, Wang Z, Macaulay E, Jagsi R, Duane F, Darby SC. Exposure of the heart in breast cancer radiation therapy: a systematic review of heart doses published during 2003 to 2013. International Journal of Radiation Oncology* Biology* Physics. 2015;93(4):845-53.
5. Yadav BS, Sharma SC, Patel FD, Ghoshal S, Kapoor RK. Second primary in the contralateral breast after treatment of breast cancer. Radiotherapy and Oncology. 2008;86(2):171-6.
6. Lind PA, Marks LB, Hardenbergh PH, Clough R, Fan M, Hollis D, et al. Technical factors associated with radiation pneumonitis after local±regional radiation therapy for breast cancer. International Journal of Radiation Oncology Biology Physics. 2002;52(1):137-43.
7. Avanzo M, Stancanello J, Trovò M, Jena R, Roncadin M, Trovò MG, et al. Complication probability model for subcutaneous fibrosis based on published data of partial and whole breast irradiation. Physica Medica. 2012;28(4): 296-306.
8. Veldeman L, Schiettecatte K, De Sutter C, Monten C, Van Greveling A, Berkovic P, et al. The 2-year cosmetic outcome of a randomized trial comparing prone and supine whole-breast irradiation in large-breasted women. International Journal of Radiation Oncology Biology Physics. 2016;95(4):1210-7.
9. Polgár C, Major T, Fodor J, Németh G, Orosz Z, Sulyok Z, et al. High-dose-rate brachytherapy alone versus whole breast radiotherapy with or without tumor bed boost after breast-conserving surgery: seven-year results of a comparative study. International Journal of Radiation Oncology Biology Physics. 2004;60(4):1173-81.
10. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. The lancet oncology. 2013;14(11):1086-94.
11. Rosenow UF, Valentine ES, Davis LW. A technique for treating local breast cancer using a

single set-up point and asymmetric collimation. International Journal of Radiation Oncology* Biology Physics. 1990;19(1):183-8.
12. Conte G, Nascimben O, Turcato G, Polico R, Idi MB, Belleri LM, et al. Three-field isocentric technique for breast irradiation using individualized shielding blocks. International Journal of Radiation Oncology Biology Physics. 1988;14(6):1299-305.
13. Hurkmans CW, Borger JH, Bos LJ, van der Horst A, Pieters BR, Lebesque JV, et al. Cardiac and lung complication probabilities after breast cancer irradiation. Radiotherapy and oncology. 2000;55(2):145-51.
14. Hurkmans CW, Cho BJ, Damen E, Zijp L, Mijnheer BJ. Reduction of cardiac and lung complication probabilities after breast irradiation using conformal radiotherapy with or without intensity modulation. Radiotherapy and oncology. 2002;62(2):163-71.
15. Korreman SS, Pedersen AN, Josipović M, Aarup LR, Juhler-Nøttrup T, Specht L, et al. Cardiac and pulmonary complication probabilities for breast cancer patients after routine end-inspiration gated radiotherapy. Radiotherapy and oncology. 2006;80(2):257-62.
16. Rancati T, Wennberg B, Lind P, Svane G, Gagliardi G. Early clinical and radiological pulmonary complications following breast cancer radiation therapy: NTCP fit with four different models. Radiotherapy and oncology. 2007;82(3):308-16.
17. Chan TY, Tan PW, Tan CW, Tang JI. Assessing radiation exposure of the left anterior descending artery, heart and lung in patients with left breast cancer: A dosimetric comparison between multicatheter accelerated partial breast irradiation and whole breast external beam radiotherapy. Radiotherapy and Oncology. 2015;117(3):459-66.
18. Lee D, Dinniwell R, Lee G. A Retrospective Analysis of Lung Volume and Cardiac Dose in Left-Sided Whole Breast Radiotherapy. Journal of Medical Imaging and Radiation Sciences. 2016;47(3):S10-S4.
19. Wollschläger D, Karle H, Stockinger M, Bartkowiak D, Bührdel S, Merzenich H, et al. Radiation dose distribution in functional heart regions from tangential breast cancer radiotherapy. Radiotherapy and Oncology. 2016;119(1):65-70.
20. Brackstone M, Fletcher GG, Dayes IS, Madarnas Y, SenGupta SK, Verma S. Locoregional therapy of locally advanced breast cancer: a clinical practice guideline. Current Oncology. 2015;22(Suppl 1):S54.
21. Wood DE. National Comprehensive Cancer Network (NCCN) clinical practice guidelines for lung cancer screening. Thoracic surgery clinics. 2015;25(2):185-97.
22. Group EBCTC. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. The Lancet. 2005;366(9503):2087-106.
23. Kim J, Park W, Kim JH, Choi DH, Kim Y-J, Lee ES, et al. Clinical significance of lymph-node ratio in determining supraclavicular lymph-node radiation therapy in pN1 breast cancer patients who received breast-conserving treatment (KROG 14-18): A Multicenter Study. Cancers. 2019;11(5):680.
24. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al. Regional nodal irradiation in early-stage breast cancer. New England Journal of Medicine. 2015;373(4):307-16.
25. Tai P, Joseph K, Sadikov E, Mahmood S, Lien F, Yu E. Nodal ratios in node-positive breast cancer—long-term study to clarify discrepancy of role of supraclavicular and axillary regional radiotherapy. International Journal of Radiation Oncology Biology Physics. 2007;68(3):662-6.
26. Keinj R, Bastogne T, Vallois P. Multinomial model-based formulations of TCP and NTCP for radiotherapy treatment planning. Journal of theoretical biology. 2011;279(1):55-62.
27. Stocks T, Hillen T, Gong J, Burger M. A stochastic model for the normal tissue complication probability (NTCP) and applications. Mathematical medicine and biology: a journal of the IMA. 2016;34(4):469-92.
28. Hillen T, De VrIeS G, Gong J, Finlay C. From cell population models to tumor control probability: including cell cycle effects. Acta Oncologica. 2010;49(8):1315-23.
29. Petrova D, Smickovska S, Lazarevska E. Conformity Index and Homogeneity Index of the Postoperative Whole Breast Radiotherapy. Open access Macedonian journal of medical sciences. 2017;5(6):736.
30. Vanaken ML, Breneman JC, Elson HR, Foster AE, Lukes SJ, Little R. Incorporation of patient immobilization, tissue compensation and matchline junction technique for three-field breast treatment. Medical Dosimetry. 1988; 13(3):131-5.
31. Fan Ll, Luo Yk, Xu Jh, He L, Wang J, Du Xb. A dosimetry study precisely outlining the heart substructure of left breast cancer patients using intensity-modulated radiation therapy. Journal of applied clinical medical physics. 2014;15(5): 265-74.
32. Banaei A, Hashemi B, Bakhshandeh M. Comparing the monoisocentric and dual isocentric techniques in chest wall radiotherapy of mastectomy patients. Journal of applied clinical medical physics. 2015;16(1):130-8.

33. Klein EE, Taylor M, Michaletz-Lorenz M, Zoeller D, Umfleet W. A mono isocentric technique for breast and regional nodal therapy using dual asymmetric jaws. International Journal of Radiation Oncology Biology Physics. 1994;28(3):753-60.
34. Kataria T, Sharma K, Subramani V, Karrthick K, Bisht SS. Homogeneity Index: An objective tool for assessment of conformal radiation treatments. Journal of medical physics/Association of Medical Physicists of India. 2012;37(4):207.
35. Salimi M, Abi KST, Nedaie HA, Hassani H, Gharaati H, Samei M, et al. Assessment and Comparison of Homogeneity and Conformity Indexes in Step-and-Shoot and Compensator-Based Intensity Modulated Radiation Therapy (IMRT) and Three-Dimensional Conformal Radiation Therapy (3D CRT) in Prostate Cancer. Journal of medical signals and sensors. 2017;7(2):102.
36. Moshiri Sedeh N. Dosimetric and radiobiological comparison of Forward Tangent Intensity Modulated Radiation Therapy (FT-IMRT) and Volumetric Modulated Arc Therapy (VMAT) for early stage whole breast cancer. 2015:7.
37. Adam D, Suditu MD, Popa R, Ciocaltei V. Volumetric-modulated arc therapy vs. 3D-conformal radiotherapy for breast cancer. Rom Rep Phys. 2015 Jan 1;67:978-86
38. Ritter T, Quint DJ, Senan S, Gaspar LE, Komaki RU, Hurkmans CW, et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. International Journal of Radiation Oncology Biology Physics. 2011;81(5):1442-57.
39. Arsene-Henry A, Foy J-P, Robilliard M, Xu H-P, Bazire L, Peurien D, et al. The use of helical tomotherapy in the treatment of early stage breast cancer: indications, tolerance, efficacy—a single center experience. Oncotarget. 2018;9(34):23608.
40. Heymann S, Dipasquale G, Nguyen NP, San M, Gorobets O, Leduc N, et al. Two-level factorial pre-tomobreast pilot study of tomotherapy and conventional radiotherapy in breast cancer: post hoc utility of a mean absolute dose deviation penalty score. Technology in cancer research & treatment. 2020;19:1533033820947759.
41. Emami B, Lyman J, Brown A, Cola L, Goitein M, Munzenrider J, et al. Tolerance of normal tissue to therapeutic irradiation. International Journal of Radiat ion Oncology* Biology* Physics. 1991;21(1):109-22.
42. Ohashi T, Takea A, Shigematsu N, Fukada J, Sanuki N, Amemiya A, et al. Dose distribution analysis of axillary lymph nodes for three-dimensional conformal radiotherapy with a field-in-field technique for breast cancer. International Journal of Radiation Oncology Biology Physics. 2009;73(1):80-7.
43. Emami B. Tolerance of normal tissue to therapeutic radiation. Reports of radiotherapy and Oncology. 2013;1(1):35-48.
44. Astudillo V, Paredes G, Resendiz G, Posadas V, Mitsoura E, Rodriguez L, et al. Tcp and NTCP radiobiological models: conventional and hypo fractionated treatments in radiotherapy. 2015;47(7):13 .
45. Kara FG, Haydaroğlu A, Eren H, Kitapçıoğlu G. Comparison of different techniques in breast cancer radiotherapy planning. The journal of breast health. 2014;10(2):83.
46. Kagkiouzis J, Platoni K, Kantzou I, Dilvoi M, Patatoukas G, Kypraiou E, et al. Review of the three-field techniques in breast cancer radiotherapy. Journal of BU ON: official journal of the Balkan Union of Oncology. 2017;22(3):599-605.
47. Marshall MG. Three-field isocentric breast irradiation using asymmetric jaws and a tilt board. Radiotherapy and Oncology. 1993;28(3):228-32.
48. Romeo N. A new isocentric technique for exact geometric matching in the radiotherapy of the breast and ipsilateral supraclavicular fossa using dual asymmetric jaws. Physica Medica. 2012;28(4):281-7.
49. Wang X, Fargier-Bochaton O, Dipasquale G, Laouiti M, Kountouri M, Gorobets O, et al. Is prone free breathing better than supine deep inspiration breath-hold for left whole-breast radiotherapy? A dosimetric analysis. Strahlentherapie und Onkologie. 2021;197(4):317-31.