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A comparative dosimetric study between free-breathing and forced inspiration used radiotherapy 3D techniques in the left breast cancer

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ABSTRACT: Introduction – Radiotherapy (RT) is a therapeutic approach for the treatment of left breast cancer. However, different breathing techniques free breathing (FB) and deep inspiration breath-hold (DIBH) can be used. **Objectives** – To identify which of the breathing techniques, DIBH or FB, has obtained better irradiation of the planning target volume (PTV) and a lower dose at the organs at risk (OAR). Check if the DIBH technique allows a dose reduction in the left ventricle. **Method** – Twenty female patients with pathology in the left breast were selected. In computed tomography, the contours of PTV and OAR were made. We obtained dosimetric data for each patient, with each of the two types of breathing techniques. Dosimetric data for all patients were compared and for both respiratory techniques. **Results** – The DIBH technique reduced the mean dose (D_{mean}) and $V_{20\%}$ in the left lung, only being higher in four patients. In the left ventricle, there was a decrease in D_{mean} and $V_{30\%}$ in all patients. The spinal cord in either DIBH or FB did not reach the reference limit, however, there was an improvement when using DIBH. **Conclusions** – The DIBH technique presents lower doses in the organs at risk, improvements in PTV dose coverage, as well as conformity, homogeneity, and quality indexes when compared to the FB technique.

Keywords: Left breast cancer; Radiotherapy; Free-breathing; Deep inspiration breath-hold; Left ventricle.

Estudo dosimétrico comparativo entre a respiração livre e inspiração forçada com radioterapia conformacional a 3D no tratamento do cancro da mama esquerda

RESUMO: Introdução – A radioterapia (RT) é uma abordagem terapêutica para tratamento do cancro da mama esquerda. Contudo, diferentes técnicas respiratórias Respiração Livre (FB) e Inspiração Forçada (DIBH) podem ser usadas. **Objetivos –** Identificar em qual das técnicas de respiração, DIBH ou FB, se consegue obter uma melhor irradiação do Planning Target Volume (PTV) e uma menor dose nos órgãos de risco (OR). Perceber se a técnica de DIBH permite uma diminuição de dose no ventrículo esquerdo. **Método –** Foram selecionadas 20 doentes, do sexo feminino, com patologia na mama esquerda. Na tomografia computorizada foram feitos os contornos do PTV e dos OAR. Obtiveram-se os dados dosimétricos de cada uma das doentes, com cada um dos dois tipos de técnica respiratória, que foram comparados. **Resultados –** Em média, a técnica DIBH reduziu a dose média (D_{med}) e $V_{20\%}$ no pulmão esquerdo, apenas sendo superior em quatro doentes. No ventrículo esquerdo observou-se uma diminuição de D_{med} e $V_{30\%}$ em todos os doentes. A medula quer em DIBH quer em FB não atingiu o limite de referência; contudo, verificou-se uma melhoria quando usado o DIBH. **Conclusões –** A técnica respiratória DIBH apresenta menor dose nos órgãos de risco, melhoria na cobertura de dose no PTV, bem como nos índices de conformidade homogeneidade e qualidade comparativamente à técnica de FB.

Palavras-chave: Cancro mama esquerda; Radioterapia; Respiração livre; Inspiração forçada; Ventrículo esquerdo.

Introduction

Worldwide, breast cancer is one of the most frequent types of carcinoma in women. In the treatment of breast cancer, radiotherapy (RT) can play an important role. However, and specifically in left breast cancer, there is a possibility of medium and/or long-term cardiac toxicity resulting from the dose received by the heart[1].

Radiotherapy, in this type of cancer, reduces the rate of locoregional recurrence and improves overall survival[1]. In addition to these benefits, adjuvant irradiation of the breast after conservative surgery provides equivalent results to mastectomy, while presenting better cosmetic results[2].

Otherwise, with better survival rates, more patients are at risk of developing several late side effects as a result of irradiation. The scientific community has a great concern about the heart doses in young patients[1,3-4]. However, dose-related side effects in organs at risk (OAR) during postoperative radiotherapy for breast cancer should be considered. This situation is characterized by partial exposure of the heart volume to high doses of radiation[1]. These changes may decrease with treatment or appear late, leading to an increased risk of mobility and cardiac death[4]. Sardaro *et al* reported that the increase of 1Gy in the Dmean of the heart comprises a 4% increase in the risk of late heart disease[3,5].

Over the years, important concepts of radiobiology and radioprotection have been introduced. To reduce the risk of short or long-term side effects, and to decrease heart exposure, treatment techniques with intensity-modulated radiotherapy (IMRT), different patient positioning techniques or respiratory control techniques are available. Since then, RT has become more precise and so it has become possible to irradiate a lower percentage of cardiac volume[3].

This dosimetric study is based on a retrospective study comparing dosimetric planning in patients whose treatment was performed in FB and DIBH, with 2Gy and 2.25Gy doses per fraction using the 3DCRT treatment technique. DIBH is expected to significantly reduce the cardiac dose during total left breast irradiation[4] due to increased distance from the cardiac wall to target volume and treatment[2].

The main purpose of this study is to assess which breathing technique, namely, DIBH or FB, presents a better PTV coverage of the prescribed dose with a minimum dose in the OAR. We also evaluate if the DIBH technique shows a dose decrease in the left ventricle.

Materials and Methods

Demographic, clinical, and dosimetric data were used from 20 cancer patients aged between 29 and 69 years, all females with left breast cancer, treated at the Greater Poland Cancer Center in Poznań, Poland. From the patient sample, 15 patients performed a mastectomy, four of these performed lymph node resection, and five performed conservative surgery without lymph nodes resection. All patients were treated between 9 October 2019 and 16 January 2020.

The patient selection included women that performed surgery and radiotherapy to the left breast with 45 Gy to 50 Gy.

All patients were planned using 4DCT (Siemens Definition AS). For each patient, a CT was performed in FB and another in DIBH, where they were in a supine position with the breast support and arms in abduction above the head, and the head rotated to the right side. The Varian RPM™ (Varian Medical System, Palo Alto, California) system was used to monitor respiratory movement. The anatomical region acquired for CT had as upper limit the mandible and as a lower limit 1-2cm below the diaphragmatic, with a CT slice spacing of 3mm.

Dosimetric planning was performed in FB and DIBH and Varian Eclipse v. 15 software was used. In each patient, dosimetric and clinical data were collected and a database was created in Statistical Package for the Social Sciences (SPSS) version 26.0 for Windows[7]. PTV breast, left lung, the left ventricle of the heart and spinal cord were delineated structures for treatment planning.

The results were considered significant at a significance level of 5%. To test the normality of the data, the Shapiro-Wilk test was used. For the comparison of FB and DIBH techniques, the Wilcoxon test was used, since the assumption of normality was not verified[8].

Results and Discussion

a) Conformity, Homogeneity and Quality Indexes: relation with PTV coverage

Conformity Indexes (CI), Homogeneity Indexes (HI), and Quality Indexes (QI) were calculated for all patients[9-11], using both breathing techniques as can be seen in Table 1.

Regarding the HI statistically, significant differences were found (p=0.002). For HI, Table 1 presents significantly lower values with the DIBH technique when compared to FB.

b) Breast PTV dose coverage

Regarding PTV, between the two techniques, statistically significant differences were detected in relation to:

i) Maximum percentage dose (D_{max}) (p=0.000), verifying that the DIBH technique presents the highest percentages; ii) D_{mean} (p=0.000), where the DIBH technique presented significantly higher percentages; iii) Minimum percentage dose (D_{min}) (p=0.000) with the DIBH technique showing significantly higher percentages; iv) $V_{95\%}$ (p=0.008), with the DIBH technique showing significantly lower Gy values;

Table 1. CI, HI e QI for FB and DIBH

	CI		HI		QI	
Patient	FB	DIBH	FB	DIBH	FB	DIBH
1	0,73	0,87	0,91	0,92	0,81	0,79
2	1,14	1,11	0,91	0,88	0,80	0,79
3	1,48	1,27	0,91	0,90	0,78	0,75
4	1,89	2,05	0,89	0,88	0,75	0,75
5	1,05	1,02	0,90	0,90	0,80	0,80
6	1,31	1,35	0,92	0,92	0,84	0,84
7	2,67	2,81	0,85	0,85	0,76	0,68
8	1,12	1,04	0,89	0,89	0,80	0,82
9	1,16	1,03	0,89	0,89	0,62	0,61
10	1,01	1,26	0,89	0,87	0,79	0,78
11	1,22	1,29	0,91	0,90	0,69	0,81
12	0,94	0,94	0,91	0,89	0,81	0,78
13	1,52	1,34	0,92	0,89	0,80	0,80
14	0,80	0,99	0,91	0,90	0,83	0,78
15	1,78	1,83	0,90	0,90	0,76	0,77
16	1,03	1,35	0,89	0,89	0,81	0,82
17	0,94	1,05	0,92	0,91	0,83	0,81
18	0,94	1,03	0,86	0,86	0,63	0,57
19	1,13	1,21	0,88	0,87	0,76	0,75
20	0,97	0,94	0,91	0,89	0,79	0,78

v) $V_{95\%}$ (*p*=0.000), with the DIBH technique showing significantly higher percentages; vi) $V_{5\%}$ (*p*=0.017), with the DIBH technique showing significantly higher Gy values; vii) $V_{5\%}$ (*p*=0.000), with the DIBH technique showing significantly higher percentages.

c) Left lung dose

Concerning the left lung statistically, significant differences were detected in relation to:

i) D_{max} (*p*=0.000), with the DIBH technique showing significantly higher percentages; ii) D_{mean} (*p*=0.000), with the DIBH technique showing significantly higher percentages; iii) D_{min} (*p*=0.001), with the DIBH technique showing significantly higher percentages; iv) $V_{5\%}$ percentage (*p*=0.019), with the DIBH technique also presenting significantly lower values.

d) Left ventricle dose

As for the left ventricle, statistically significant differences were detected in relation to:

i) D_{mean} (*p*=0.000), with the DIBH technique showing significantly higher; ii) $V_{30\%}$ percentage (*p*=0.000), with the DIBH technique having significantly lower percentages; iii) $V_{25\%}$ (*p*=0.000), with the DIBH technique having significantly lower percentages.

The CI allows assessing the conformation of the reference isodose to PTV. Feuvret *et al* defined as CI=TV_{ri} / TV. TV_{ri} is the total volume covered by the 95% isodose and TV is the target volume[9].

The ideal value would be equal to one (1) because this value indicates the ideal dose conformation to the target volume and according to the ICRU is the 95% isodose[9-11]. In the CI analysis, significant differences between patients and techniques were observed.

Figure 1 shows that CI in patient 7, values are greater than 2.5, which may indicate excessive irradiation of healthy tissues. However, in the D_{mean} analysis, it is observed that CI values are similar for each technique (1.2 FB and 1.3 DIBH) and close to one, as can be seen in Table 2.

Most of the obtained CI values are between 1 and 2, so the treatment is then considered in accordance with the treatment plan, however, there are two patients whose CI value is greater than 2 (patient 4 and 7, 7 being greater than 2.5).

Additionally, there are also values below 1 (patient 1 in FB and DIBH), which may mean that the target volume is not being treated in its entirety.

IH was defined as the ratio between 5% and 95% ($D_{5\%}$ / $D_{95\%}$) dose of PTV according to RTOG 93[12]. The reference value is one (1) and increases as the plan become less homogeneous[11].

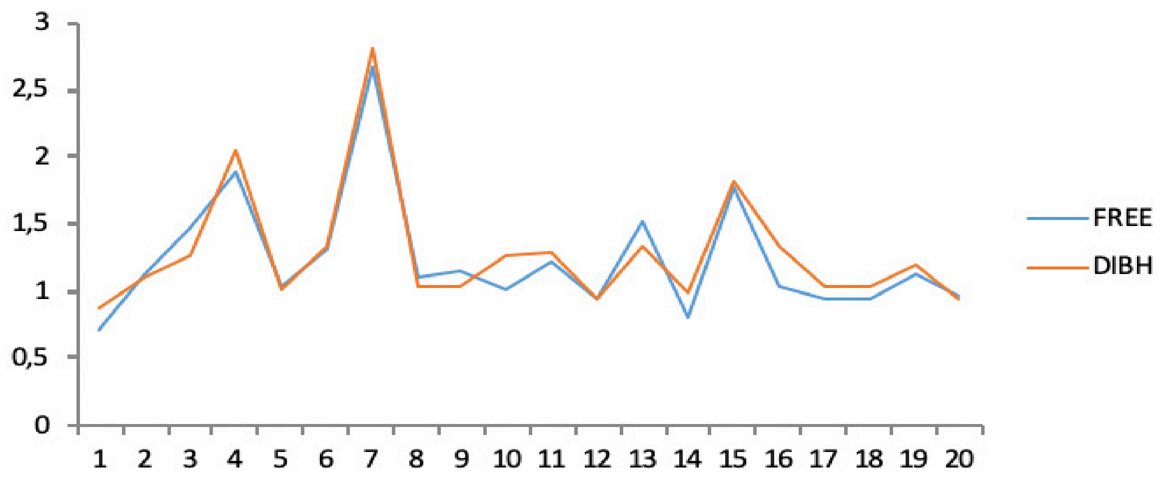

Figure 1. Conformity Index for FB and DIBH.

Table 2. Analysis of variables values for all patients

		FB		DIBH	
		Average	Standard Deviation	Average	Standard Deviation
Dosimetric Indexes	CI	1,24	0,45	1,29	0,46
	HI	0,90	0,02	0,89	0,02
	QI	0,77	0,06	0,77	0,07
Breast PTV	D_{max}	50,16	3,10	50,09	2,37
	D_{mean}	46,70	2,15	46,75	2,15
	D_{min}	7,40	7,31	34,60	7,07
	Dose V95%	43,84	1,98	43,59	2,01
	Dose V5%	48,82	2,41	48,98	2,25
Left Lung	D_{max}	46,20	4,10	46,26	2,70
	D_{mean}	14,52	6,00	11,70	3,33
	D_{min}	0,31	0,16	0,13	0,13
	V20%	29,51	15,19	26,63	13,47
	V5%	38,91	13,19	41,28	4,80
Left Ventricle	Average	4,33	2,06	2,02	1,39
	V30%	2,24	0,81	1,45	0,60
	V25%	2,70	1,08	1,68	0,71
Spinal Cord	D_{max}	8,43	9,22	6,67	8,94

As can be seen in Table 1 and Figure 2, the dose distribution plans using the DIBH breathing technique are the most homogeneous, although none of these values reach one. However, the average of the IH for both techniques is very similar (0.90 vs 0.89).

The D_{min} in PTV is important for tumour control, and the reference isodose 95% should cover the entire PTV. This corresponds to $V_{95\%}$ and therefore presents minimum values of 47.5 Gy and 42.75 Gy for prescribed doses of 50 Gy and 45 Gy, respectively[13]. The results obtained from D_{min} are all below the predicted value, however, in the majority of patients, 95% of the volume of PTV is covered with the estimated doses, as shown in Figure 3.

The D_{mean}, according to the ICRU, should be between 100% and 102%[14]. This parameter is within the expected values, however, patient 8 has a D_{mean} of 113.1% in both FB as in DIBH.

The $D_{máx}$ points within the PTV should not exceed 110%[13] of the total prescribed dose, as it will modify the treatment homogeneity, that is, 49.5 Gy and 55 Gy, for a prescribed dose of 45 Gy and 50 Gy, respectively. All patients have $D_{máx}$ values within the limits, except patients 7 and 8 who have $D_{máx}$ exceeding 110%, as can be seen in Figure 4.

Figure 2. Homogeneity Index for FB and DIBH.

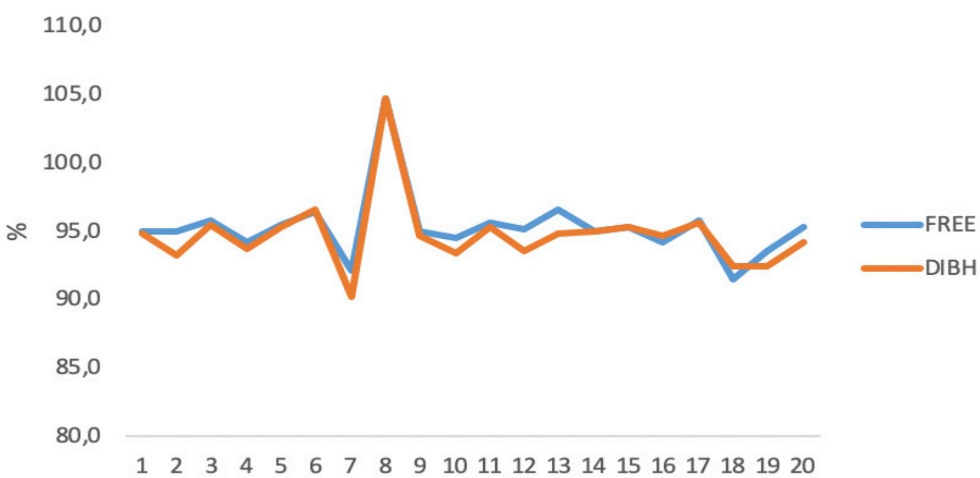

Figure 3. V95% Breast PTV for FB and DIBH.

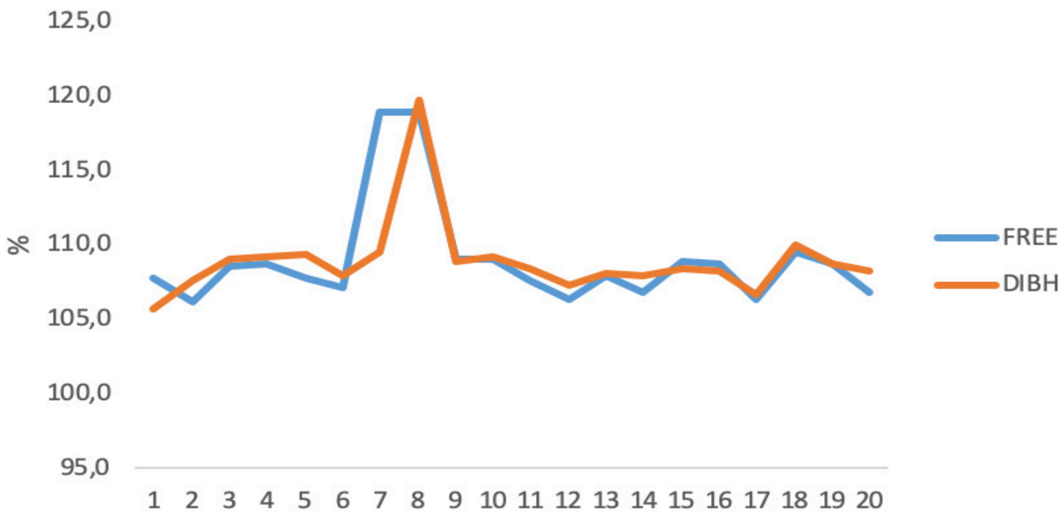

Figure 4. Maximum dose of breast PTV for FB and DIBH.

The dose in the organs at risk should be as low as possible, without compromising the irradiation of the PTV considering the criteria defined by QUANTEC[15-16]. The $D_{máx}$ in normal tissues is important to limit and evaluate the side effects of the treatment. The $D_{máx}$, with the area/volume restriction described above, should be considered to assess the homogeneity of the dose distribution[17].

Symptomatic pneumonitis radiation (SPR) is one of the most common toxicities in patients treated with radiation for lung, breast, and mediastinal lymph nodes. Therefore, it is necessary a parameter that allows predicting the risk of SPR. This usually corresponds to V_{20}<30% of the lung. Some results of this study show that these parameters are not always achieved, since most patients have hotspots, as observed in Figure 5. Some studies also observe that maintaining V_5<60-65% plays a crucial role as a predictor of the incidence of SPR[18]. All patients present this value within the desired dose rate tolerance <20%[15-16].

Clinical pericarditis and long-term cardiac mortality are the two most relevant cardiac toxicities[18]. The two values assessed in the left ventricle were $V_{25\%}$ and $V_{30\%}$ since a V_{25}<10% of the heart will be associated with a probability <1% of cardiac mortality at 15 years after radiotherapy and, V_{30}<46% is significant in multivariate analysis[18], as shown in Figure 6.

All values of the patients analysed are within the acceptability standards, and there is a significant improvement in these values when using the DIBH technique. According to the available literature for the 3DCRT method[19-21], the ipsilateral heart and lung receive a lower dose in the dose distributions with DIBH[22].

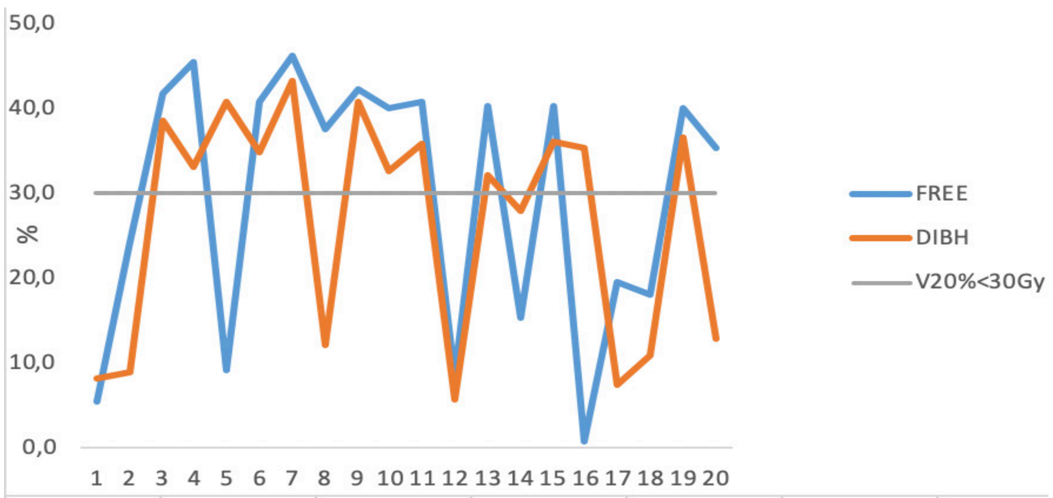

Figure 5. V20% left lung for FB and DIBH.

In this study, in general, the left lung and left ventricle receive a lower dose with DIBH. Contrarily to the results of this study Russo *et al*, suggest a significant dose reduction in the heart, better coverage of PTV, but there are no differences in

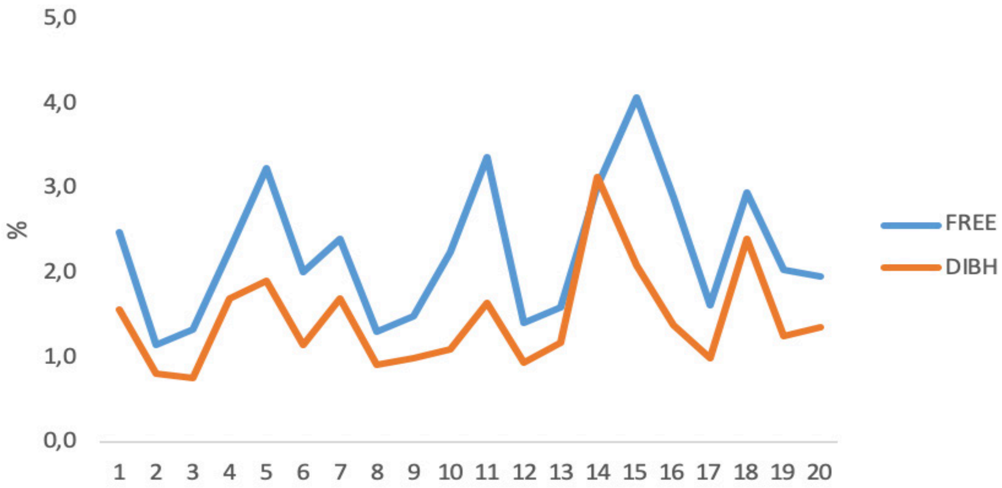

Figure 6. V30% left ventricle for FB and DIBH.

doses in the lung[23] between the two respiratory techniques. In this study, improvement in the target volume dose distribution in the left lung was observed in DIBH.

Conclusion

The DIBH breathing technique significantly reduces the cardiac dose during the total irradiation of the left breast, due to the increase in the distance from the cardiac wall to the target treatment volume, as well as it was possible to obtain better irradiation of the PTV with a lower dose administration in the OAR. This study shows that DIBH has D_{mean} of the left ventricle of 2.02 Gy vs 4.33 Gy for FB. Even so, it would have been important to have dose-related data in the descending coronary artery in this study, since it is predictive of the risk of long-term cardiac events, but it was not possible since there was no delimitation of this OAR in all patients.

In this study, it was possible to observe a 2.3 Gy decrease in the D_{mean} of the left ventricle, when comparing the FB technique with DIBH. As mentioned above, Sardaro *et al* reported that the increase in 1 Gy in the average dose of the heart corresponds to a 4% increase in the risk of late heart disease[3,5], which leads us to conclude that there was a decrease of 9.2% in the risk of late heart disease in our study. The DIBH breathing technique presents better results than the FB technique, however, more studies must be carried out to evaluate this variable.

However, respiratory training is a fundamental and complex process, which must always be applied to improve and deepen DIBH. This training can also optimize the cardiac dose and the patient's treatment[24-25].

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Conflito de interesses

Os autores declaram não possuir conflitos de interesse.

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