Ultra-hypofractionated radiotherapy in early left-sided breast cancer – personalization of planning and irradiation techniques

Agnieszka Krzystyniak[1], Joanna Topczewska[2], Vitali Papok[2], Ewa Rożkowska[2], Rafał Maksim[2], Jakub Łukasik[1], Agnieszka Babińska[1], Adrian Bielecki[1], Anna Kozłowska[2], Tomasz Filipowski[2]

[1] Department of Medical Physics – Białystok Oncology Centre, ul. Ogrodowa 12, 15-369 Białystok, e-mail: akrzystyniak@onkologia.bialystok.pl

[2] Department of Radiotherapy – Białystok Oncology Centre, ul. Ogrodowa 12, 15-369 Białystok

Abstract

Breast cancer is the most common cancer among women, both in Poland and worldwide. Radiotherapy in early breast cancer plays an important role in the oncological treatment process.

The aim of this study is a comparative analysis of dose distribution in the target areas and organs at risk (OAR) in the treatment of early left-sided breast cancer in an ultra-hypofractionated radiotherapy regimen (26 Gy in 5 fractions) depending on the treatment planning technique and delivery technique: on free breathing (FB) or deep inspiration breath hold (DIBH).

A comparative analysis of dose distribution, depending on delivery on deep hold inspiration and free breathing, was performed on a group of 70 patients - 62 on DIBH, 8 on FB - irradiated with the dynamic technique VMAT (Volumetric Modulated Arc Therapy) at the Białystok Oncology Centre. In order to compare the different planning techniques in terms of received doses in the OARs and target volume, homogeneity and conformality, 10 patients were randomly selected out of 62, performed on DIBH and irradiated with VMAT-A (4 arc beams: 190°-250°, collimator: 0°-5° and 85°-90°) or VMAT-B (opposite 4 arc beams: 60°-75°, collimator: 0°-5° and 85°-90°). Each of selected patients received 3 treatment plans with the techniques: 3D-CRT (3D Conformal Radiation Therapy; 2-4 tangential beams with wedges), VMAT-A and VMAT-B. A comparison of dose distribution shows dose reductions in all organs at risk when implementing radiotherapy with respiratory gating, while achieving the recommended parameters in the target volume. Statistically significant differences are shown in the heart and left anterior descending coronary artery (LAD). In the LAD, maximum and mean doses were obtained for DIBH and FB, respectively: (5.11±3.35) Gy vs (9.83±4.26) Gy and (2.04±0.57) Gy vs (3.01±0.95) Gy. In the heart, on the other hand, the greatest differences were observed at D_{max} of (7.24±4.38) Gy for DIBH and (12.90±4.58) Gy for FB, and at V1.5Gy volumes of (15.45±7.65) % for DIBH and (25.62±3.57) % for FB.

A comparative analysis of different radiotherapy planning techniques showed that the use of dynamic techniques allows higher conformality and homogeneity of dose distribution in the target volume than in static beam plans (p<0.05). In VMAT-A and VMAT- B plans, lower maximum doses were obtained in the heart and LAD compared to 3D-CRT plans. In contrast, statistically significant reductions in low-dose volumes were observed in the heart (V1.5Gy), left lung (V4Gy) and right lung (V2.5Gy) in the 3D-CRT plans.

The implementation of irradiation on the DIBH and the use of dynamic techniques allows optimal dose distribution to be achieved in the target volume while sparing critical organs. Ultra-hypofractionated radiotherapy in early left-sided breast cancer using dynamic techniques and DIBH is a good therapeutic option in overloaded oncology centres.

Keywords: radiotherapy, breast cancer, 3D-CRT, VMAT, FAST- Forward, ultra-hypofractionation, radiotherapy on deep inspiration breath hold (DIBH), radiotherapy on free breathing (FB)

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Introduction

Breast cancer is a serious public health problem affecting women worldwide. It is the most frequently diagnosed neoplasm and the second most common cause of cancer-related deaths among women globally [1].

Radiotherapy plays a fundamental role in the treatment of breast cancer patients, ranging from early-stage disease and locally advanced cases to the treatment of metastases in generalised disease [2]. Radiotherapy treatment in the second half of the 20th century was not as advanced as it is today. Target areas were delineated based on two-dimensional X-ray images, and organs at risk of radiation were protected using universal, lead shielding. Consequently, the delivery of radiotherapy was only minimally adapted to the individual. Therefore, some literature data concerning long-term follow-up (15-20 years) demonstrated that breast radiotherapy, particularly for the left breast, is associated with the risk of late radiation reactions in the form of cardiotoxicity, including dysfunction of the coronary vessels, myocardium, heart valves, and the cardiac conduction system [3].

Modern radiotherapy, based on three-dimensional image reconstruction obtained from a CT simulator and the use of a *Multi-Leaf Collimator* (MLC), makes it possible to plan treatment tailored to the patient's individual anatomy. The application of dynamic techniques, such as *Intensity Modulated Radiation Therapy* (IMRT) and *Volumetric Modulated Arc Therapy* (VMAT), enables precise dose distribution adjustments within the target volumes while sparing healthy tissues [4]. Furthermore, to minimise doses to the OARs, particularly the heart and the *left anterior descending coronary artery* (LAD), *Deep Inspiration Breath Hold* (DIBH) irradiation is used in patients with left-sided breast cancer. It has been shown that the use of DIBH increases the distance between the anterior surface of the heart and the LAD and the posterior surface of the chest wall, which enables dose reduction in these structures [5, 6]. Compared to *Free Breathing* (FB), DIBH in conventional dose fractionation leads to a significant reduction in heart V30Gy (7.1% vs 2.4%; $p<0.0001$), mean heart dose (6.9 Gy vs 3.9 Gy; $p<0.0001$), maximum dose in the *Planning Risk Volume* (PRV) for the LAD with a 5 mm margin (51.6 Gy vs 45.6 Gy; $p=0.0032$) and mean dose in the LAD PRV (31.7 Gy vs 21.9 Gy; $p<0.001$) [6].

For many years, the standard regimen for adjuvant radiotherapy in the treatment of breast cancer following *Breast Conserving Therapy* (BCT) was 50 Gy in 25 fractions [7]. However, over the past two decades, studies have demonstrated that moderate hypo-fractionation regimens (40-42.5 Gy in 15-16 fractions) have a similar safety profile and are equally effective as the previously used standard treatment regimens [8, 9, 10, 11]. The study by Whelan et al. showed that the local recurrence rate over a 10-year follow-up period was 6.7% in the conventional fractionation group, compared to 6.2% in the hypo-fractionation group (95% *Confidence Interval* (CI), -2.5 to 3.5) [9].

Currently, hypo-fractionated radiotherapy for breast cancer is the standard, both after BCT and after mastectomy [12]. In patients with early breast cancer and good prognostic factors, where the target volume is the breast itself or the chest wall, ultra-hypofractionation of the dose is possible. The rationale for this approach stems from the results of the FAST-Forward trial [10], which demonstrated that adjuvant radiotherapy to the breast at a dose of 26 Gy in 5 fractions is non-inferior to the standard 3-week treatment regimen of 40.05 Gy/15 fr. The estimated cumulative risk of local recurrence over 5 years was 2.1% for the 40.05 Gy dose and 1.4% for 26 Gy. Changes in breast appearance (reduction, swelling, breast distortion) occurred with similar frequency in both groups (40.05 Gy vs 26 Gy was 9.9% vs 11.9%, respectively; $p=0.17$). No differences were observed in the risk of locoregional recurrence, distant metastases, disease-free survival, or overall survival. Regarding late radiation reactions in the lungs (pulmonary fibrosis: 40.05 Gy vs 26 Gy – 0.4% vs 0.5%, respectively) and the heart (ischaemic heart disease: 40.05 Gy vs 26 Gy – 0.9% vs 0.7%, respectively), no significant differences were recorded between the two study groups either.

For several months, ultra-hypofractionated radiotherapy has been used in patients with early breast cancer at the Department of Radiotherapy in the Białystok Oncology Centre. Treatment plans are prepared using the dynamic VMAT technique and are delivered under both DIBH and FB. This study aims to analyse and compare the dose distribution in the target volumes and OARs in the ultra-hypofractionated radiotherapy regimen for patients with left-sided breast cancer irradiated with the VMAT technique delivered under DIBH and FB. Additionally, to determine the effectiveness of different irradiation techniques, comparative plans were prepared using the *3D Conformal Radiation Therapy* (3D-CRT) technique and two VMAT techniques (VMAT-A, VMAT-B).

Materials and methods

An analysis was conducted on plans prepared for 70 patients with early left-sided breast cancer (pT1-T2 pN0), who underwent surgical treatment in the form of a breast-conserving procedure along with sentinel lymph node biopsy. Radiotherapy was delivered in a regimen consistent with the FAST- Forward trial protocol – 5.2 Gy in 5 fractions, up to a total dose of 26 Gy, administered over 5 consecutive days [10, 13]. The target volume included the whole breast. In cases of clinical indications for a dose boost to the tumour bed or additional irradiation of the lymph node area, the radiotherapy regimen deviated from the above scheme.

All patients underwent two-day training regarding the possibility of undergoing Deep Inspiration Breath Hold radiotherapy, using the Active Breathing Coordinator system (Elekta, Sweden) or AlignRT (VisionRT, England). Radiotherapy was delivered under DIBH for 62 patients, while for the remainder (8), it was delivered under Free Breathing, due to their insufficient ability to achieve a reproducible and repeatable breath hold.

Each patient underwent a Computed Tomography (CT) scan using the SOMATOM Definition AS CT scanner (Siemens Medical Solutions, Germany). For patients irradiated under DIBH, two CT scans were performed: the first under Free Breathing, and the second under DIBH. The patients were positioned supine with their arms raised. The *All-in-One* (AIO) immobilisation system (Orfit Industries, Belgium) was used for patient set-up. On the acquired tomographic images, the *Clinical Target Volume* (CTV), which was the left breast, and the critical organs: heart, LAD, left lung, right lung, right breast, and spinal cord, were delineated. Depending on the radiotherapy delivery technique, a margin of 6 mm (DIBH) or 8 mm (FB) was added to the CTV, creating the *Planning Target Volume* (PTV).

Patient treatment plans were prepared using an individually customised, dynamic, multi-arc radiotherapy technique with intensity modulation, generated beforehand in the Monaco v.6.1 treatment planning system (Elekta, Sweden), employing the Monte Carlo algorithm. To compare the different planning techniques in terms of received doses in the OARs and target volume, homogeneity, and conformality, 10 patients were randomly selected from the 62 treated under DIBH. Each patient had plans prepared using the 3D-CRT technique and two VMAT techniques: VMAT-A and VMAT-B, described in detail later in the „Materials and Methods" section. The 3D-CRT plans were prepared in the Oncentra External Beam v.4.5 system (Elekta, Sweden), using the Collapsed Cone algorithm. All plans were executed in accordance with the dosimetric specification protocol currently in force at the Białystok Oncology Centre (BOC) for radiotherapy delivered under the 26 Gy in 5 fractions regimen, with a fractional dose of 5.2 Gy (Table 1), based on the FAST-Forward trial protocol [10] and guidelines from ICRU Report No. 83 [14].

The *Homogeneity Index* (HI), used to analyse the uniformity of dose distribution within the target volume, was calculated according to the ICRU-83 recommendations [14]:

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}} \quad (1)$$

where: $D_{2\%}$ – the dose received by 2% of the PTV volume, $D_{98\%}$ – the dose received by 98% of the PTV volume, $D_{50\%}$ – the average dose.

A Homogeneity Index equal to 0 corresponds to an ideally uniform dose distribution in the target volume.

To assess the degree of matching the prescribed dose volume to the size and shape of the therapeutic area, the *Paddick Conformity Index* (PCI), developed by Paddick and recommended in the ICRU-83 report [14, 15], was used:

$$PCI = \frac{TV_{Rx}^2}{TV \cdot V_{Rx}} \quad (2)$$

where: TV_{Rx} – the PTV volume covered by the prescribed dose, TV – the PTV volume, V_{Rx} – the total volume covered by the prescribed dose.

Table 1 *Dosimetric specification in breast radiotherapy according to the FAST-Forward protocol for a dose of 26 Gy in 5 fractions. Radiotherapy delivered under FB or DIBH*

	Parameter	Recommended	Acceptable
PTV	V95%	≥ 95%	≥ 90%
	V105%	≤ 5%	≤ 7%
	V107%	-	≤ 2%
	$D_{0,5cm^3}$	-	≤ 28,6 Gy
Lung on irradiated side	V8Gy	≤ 15%	≤ 17%
Heart	V7Gy	-	≤ 5%
	V1.5Gy	-	≤ 30%
LAD	D_{max}	≤ 6 Gy	≤ 10 Gy
	D_{mean}	≤ 3 Gy	≤ 5 Gy

Source: [10].

A Conformity Index equal to 1 corresponds to ideal coverage and matching of the target area by the prescribed dose.

3D-CRT

The 3D-CRT treatment plan utilised 2-4 tangential photon beams (Fig. 1) with a nominal accelerating potential of 6 MV and 15 MV, employing wedges. The isocentre was placed inside the PTV, halfway along its long (Y) axis. The Multi-Leaf Collimator (MLC) leaves were automatically adjusted to the PTV, including a 2 cm margin from the patient's external surface.

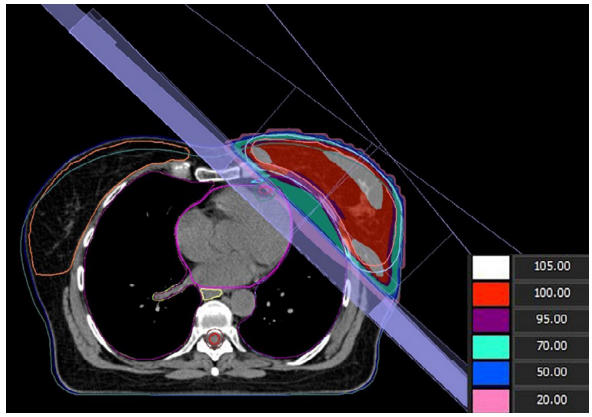

Fig. 1 *Dose distribution along with beam geometry – 3D-CRT technique. Isodose values are shown in percentages.*
Source: Own elaboration.

VMAT-A

VMAT-A plans utilised four photon arc beams with a nominal accelerating potential of 6 MV. The arc rotation angle ranged from 190° to 250°. The collimator rotation angle was 0°-5° and 85°-90° (Fig. 2). The beam isocentre was placed near the PTV, halfway along its length along the Y-axis. In all plans, the *„auto flash margin"* function with a 2 cm margin was additionally applied, which forces the position of the collimator leaves to be 2 cm beyond the patient's body contour.

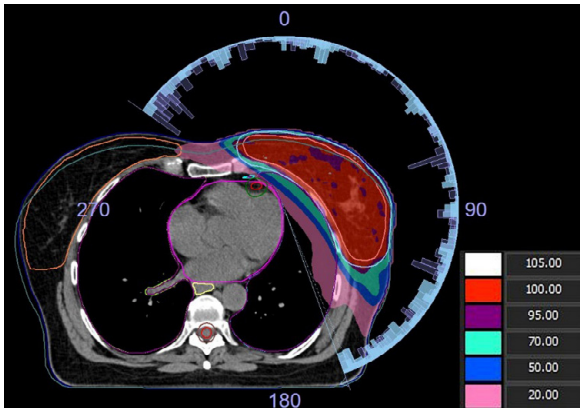

Fig. 2 *Dose distribution along with beam geometry – VMAT-A technique. Isodose values are shown in percentages.*
Source: Own elaboration.

VMAT-B

VMAT-B treatment plans utilised four tangential arc beams with an angle range of 60°-75°, with a collimator angle of 0°-5° and 85°-90° (Fig. 3). Photon beams with a nominal accelerating potential of 6 MV were used for planning. The isocentre was placed near the target volume, halfway along its long axis. Similar to VMAT-A, the *„auto flash margin"* function was applied, forcing the position of the collimator leaves to be 2 cm beyond the patient's body contour.

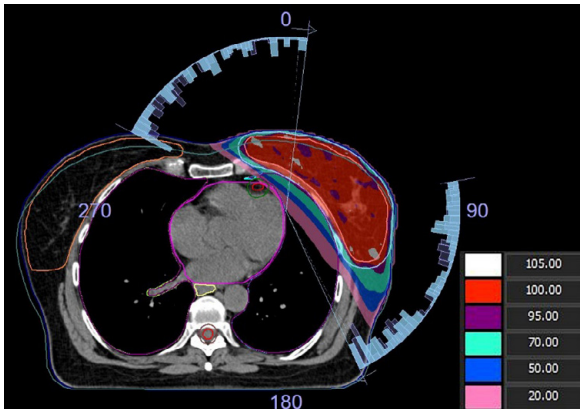

Fig. 3 *Dose distribution along with beam geometry – VMAT-B technique. Isodose values are shown in percentages.*
Source: Own elaboration.

Radiotherapy was delivered on VersaHD linear accelerators (Elekta, Sweden), equipped with an Agility Multi-Leaf Collimator, consisting of 160 leaves with a width of 0.5 cm at the accelerator's isocentre.

In addition to the parameters included in Table 1, an analysis of supplementary parameters, including low-dose volumes (<V20%), was performed for the following structures: left lung (D_{max}, D_{mean}, V4Gy), right lung (D_{max}, D_{mean}, V2.5Gy), and right breast (D_{max}, D_{mean}). The values for the low doses (V2.5Gy and V4Gy) were adopted based on the work of Sigaudi et al. [16]. When comparing different planning techniques, the V100% parameter in the CTV was additionally analysed.

The results were statistically analysed. The mean value and Standard Deviation (SD) were calculated for each parameter. Statistical tests were used to compare the 3D-CRT, VMAT-A, and VMAT-B techniques. If the Shapiro-Wilk test was satisfied, the Student's t-test was used for comparative analysis; otherwise, the Mann-Whitney U test was applied. A significance level of α=0.05 was adopted for all tests, where $p<\alpha$ indicated statistically significant differences.

Results

a) Assessment of dosimetric parameters of VMAT Plans Depending on Radiotherapy Delivery: DIBH vs FB

The analysis of the absorbed dose distribution in the target volume (left breast) and in the organs at risk was performed for both Free Breathing and Deep Inspiration Breath Hold radiotherapy. The mean values of the dosimetric parameters in the PTV and OAR, along with the standard deviation, are presented in Table 2 and Table 3.

i) Target volume – left breast

Table 2 *Averaged dose distribution parameters including standard deviation in healthy organs for DIBH and FB techniques*

Target volume	Parameter	Mean ± SD	
		DIBH	FB
PTV	Volume [cm³]	1,169.20 ± 433.75	1,753.45 ± 964.60
	V95% [%]	95.80 ± 1.65	96.31 ± 1.04
	V105% [%]	1.34 ± 1.20	0.83 ± 0.41
	V107% [%]	0.04 ± 0.06	0.11 ± 0.24
	$D_{0,5\,cm^3}$ [Gy]	27.69 ± 0.16	27.72 ± 0.17

Source: Own elaboration.

Table 3 *Averaged dose distribution parameters including standard deviation in OAR for DIBH and FB techniques*

Target volume	Parameter	Mean ± SD	
		DIBH	FB
Left lung	D_{max} [Gy]	26.28 ± 0.99	26.18 ± 0.89
	D_{mean} [Gy]	3.85 ± 0.63	4.24 ± 0.50
	V8Gy [%]	11.59 ± 2.91	12.79 ± 2.25
	V4Gy [%]	27.57 ± 7.74	32.48 ± 4.45
Right lung	D_{max} [Gy]	6.68 ± 3.43	7.15 ± 2.92
	D_{mean} [Gy]	1.18 ± 0.48	1.31 ± 0.39
	V2,5Gy [%]	11.59 ± 11.42	13.58 ± 9.22
Heart	D_{max} [Gy]	7.24 ± 4.38	12.90 ± 4.58
	D_{mean} [Gy]	1.00 ± 0.23	1.31 ± 0.11
	V7Gy [%]	0.07 ± 0.17	0.66 ± 0.72
	V1,5Gy [%]	15.45 ± 7.65	25.62 ± 3.57
LAD	D_{max} [Gy]	5.11 ± 3.35	9.83 ± 4.26
	D_{mean} [Gy]	2.04 ± 0.57	3.01 ± 0.95
Right breast	D_{max} [Gy]	4.43 ± 1.79	4.94 ± 1.70
	D_{mean} [Gy]	1.13 ± 0.48	1.28 ± 0.55

Source: Own elaboration.

Analysing the results presented in Table 2, it was observed that the dose distributions within the target volume do not differ in terms of standard deviations for both breathing techniques. All the above dose distributions comply with the recommended criteria for treatment plan acceptance, as currently applied at the BOC (Table 1).

ii) Healthy organs

Analysing the mean values of individual parameters for healthy tissues (Table 3), it can be concluded that the use of the DIBH technique leads to a reduction in the mean dose in all OARs. In the heart, differences were observed in both maximum and low doses, depending on the use of respiratory gating. The maximum heart dose with DIBH was (7.24±4.38) Gy, while in plans delivered under FB it was (12.90±4.58) Gy. Similarly, for the LAD, the maximum and mean doses with DIBH were (5.11±3.35) Gy and (2.04±0.57) Gy, whereas in plans delivered under Free Breathing they were (9.83±4.26) Gy and (3.01±0.95) Gy. In the case of the left lung, smaller volumes were obtained for both V8Gy and V4Gy. Organs located on the opposite side of the chest wall – the right breast and right lung – also receive lower mean doses. The use of smaller PTV margins in techniques delivered under Deep Inspiration Breath Hold reduces the exposure of healthy organs to radiation.

b) Assessment of dosimetric parameters of plans prepared with 3D-CRT, VMAT-A, VMAT-B techniques for DIBH delivery

Ten patients, randomly selected from the 62 treated under DIBH, had comparative treatment plans prepared using the 3D-CRT, VMAT-A, and VMAT-B techniques. The obtained dosimetric parameters in the target volumes and critical organs were subjected to statistical analysis and compared against each other depending on the planning technique: 3D-CRT vs VMAT-A, 3D-CRT vs VMAT-B, VMAT-A vs VMAT-B (Table 4).

Analysing the results presented in Table 4, it was observed that most plans created with the 3D-CRT technique do not meet the treatment plan acceptance criteria adopted at the BOC (Table 1) concerning high doses in the target volume and the maximum dose in the LAD (3 cases). In the 3D-CRT technique plans, parameters outside the range of „acceptable" values were obtained for the following dose-volume dependencies in the PTV: V105%<7% – (17.1±8.5)%, V107%<2% – (7.01±4.77)%, $D_{0.5cm^3}$< 28.6 Gy – (29.2±0.3) Gy.

All plans executed using dynamic techniques met the required parameters within the „recommended" tolerance limits and demonstrated greater homogeneity and conformality compared to the 3D-CRT plans.

Table 4 *Averaged values of dosimetric parameters including standard deviation in critical organs and target volume in plans created using 3D-CRT, VMAT-A, VMAT-B techniques*

Target volume	Parameter	Mean ± SD			*p-value*		
		3D-CRT	VMAT-A	VMAT-B	3D-CRT vs VMAT-A	3D-CRT vs VMAT-B	VMAT-A vs VMAT-B
CTV	V100% [%]	85.66 ± 5.12	91.42 ± 7.31	93.66 ± 2.19	< 0.05	< 0.05	0.76
PTV	V95% [%]	91.91 ± 1.62	96.76 ± 1.11	95.50 ± 0.73	< 0.05	< 0.05	< 0.05
	V105% [%]	17.08 ± 8.51	1.14 ± 1.20	4.47 ± 0.81	< 0.05	< 0.05	< 0.05
	V107% [%]	7.01 ± 4.77	0.02 ± 0.03	0.14 ± 0.05	< 0.05	< 0.05	< 0.05
	$D_{0.5cm^3}$ [Gy]	28.84 ± 0.29	27.63 ± 0.12	27.88 ± 0.14	< 0.05	< 0.05	< 0.05
Left lung	D_{max} [Gy]	26.47 ± 0.55	26.12 ± 0.85	26.45 ± 0.75	0.45	0.82	0.41
	D_{mean} [Gy]	3.30 ± 0.50	3.79 ± 0.40	3.23 ± 0.42	< 0.05	0.41	< 0.05
	V8Gy [%]	12.69 ± 2.36	10.73 ± 1.48	11.00 ± 1.62	0.07	0.15	0.94
	V4Gy [%]	19.50 ± 3.10	27.94 ± 4.65	22.26 ± 2.96	< 0.05	< 0.05	< 0.05
Right lung	D_{max} [Gy]	2.00 ± 0.86	6.24 ± 2.39	1.99 ± 0.38	< 0.05	0.94	< 0.05
	D_{mean} [Gy]	0.19 ± 0.04	1.25 ± 0.31	0.45 ± 0.06	< 0.05	< 0.05	< 0.05
	V2,5Gy [%]	0.02 ± 0.03	11.03 ± 7.79	0.00 ± 0.00	< 0.05	0.15	< 0.05
Heart	D_{max} [Gy]	12.12 ± 6.57	5.55 ± 3.48	5.26 ± 2.66	< 0.05	< 0.05	0.84
	D_{mean} [Gy]	0.71 ± 0.17	0.98 ± 0.21	0.89 ± 0.17	< 0.05	< 0.05	0.39
	V7Gy [%]	0.30 ± 0.46	0.06 ± 0.18	0.02 ± 0.05	0.16	0.08	0.51
	V1,5Gy [%]	7.17 ± 4.13	13.25 ± 8.14	10.35 ± 6.73	0.10	0.33	0.50
LAD	D_{max} [Gy]	8.14 ± 5.45	4.09 ± 2.19	2.99 ± 1.02	0.08	< 0.05	0.22
	D_{mean} [Gy]	2.22 ± 0.83	1.76 ± 0.44	1.61 ± 0.41	0.15	0.07	0.41
Right breast	D_{max} [Gy]	1.93 ± 2.22	4.26 ± 1.46	2.08 ± 0.74	< 0.05	0.05	< 0.05
	D_{mean} [Gy]	0.25 ± 0.07	1.13 ± 0.31	0.54 ± 0.13	< 0.05	< 0.05	< 0.05
HI		0.26 ± 0.06	0.11 ± 0.02	0.14 ± 0.03	< 0.05	< 0.05	< 0.05
PCI		0.71 ± 0.03	0.82 ± 0.07	0.82 ± 0.05	< 0.05	< 0.05	0.94

Source: Own elaboration

To illustrate the differences in dose distribution within the target volumes and healthy organs depending on the technique used, averaged Dose- To illustrate the differences in dose distribution within the target volumes and healthy organs depending on the technique used, averaged *Dose-Volume Histograms* (DVH) were created for individual structures (Figs. 4-10).

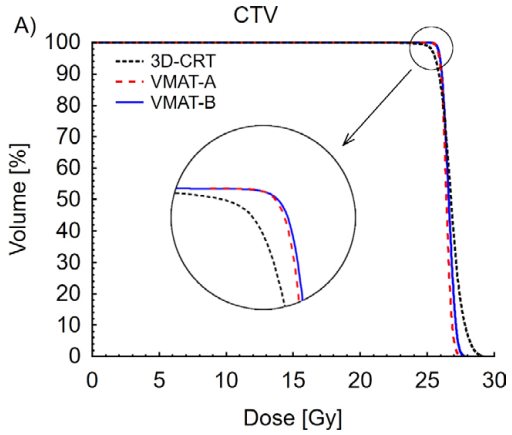

Fig. 4 *Averaged Dose-Volume Histograms for plans prepared with 3D-CRT, VMAT-A, VMAT-B techniques for DIBH delivery – CTV*
Source: Own elaboration.

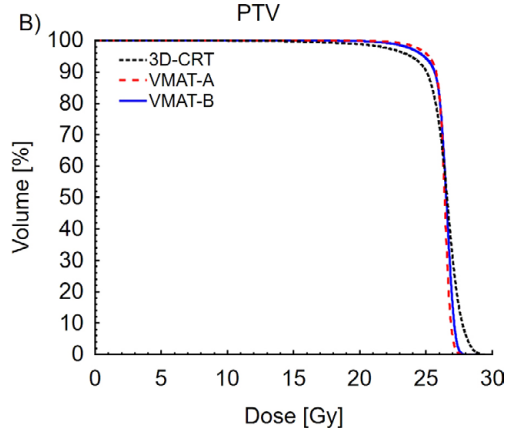

Fig. 5 *Averaged Dose-Volume Histograms for plans prepared with 3D-CRT, VMAT-A, VMAT-B techniques for DIBH delivery – PTV*
Source: Own elaboration.

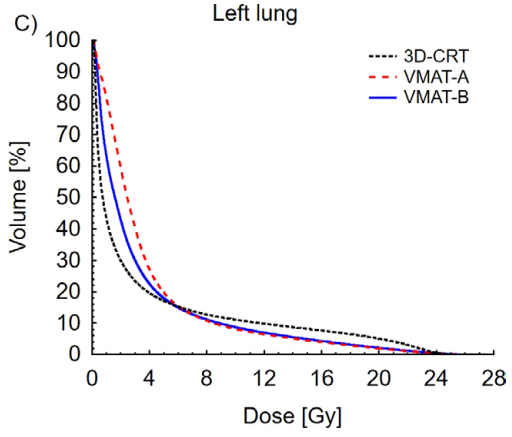

Fig. 6 *Averaged Dose-Volume Histograms for plans prepared with 3D-CRT, VMAT-A, VMAT-B techniques for DIBH delivery – left lung*
Source: Own elaboration.

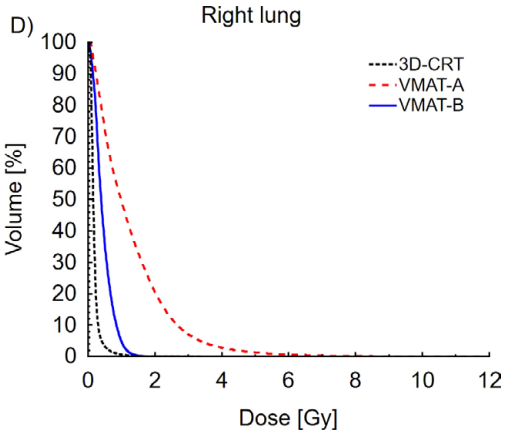

Fig. 7 *Averaged Dose-Volume Histograms for plans prepared with 3D-CRT, VMAT-A, VMAT-B techniques for DIBH delivery – right lung*
Source: Own elaboration.

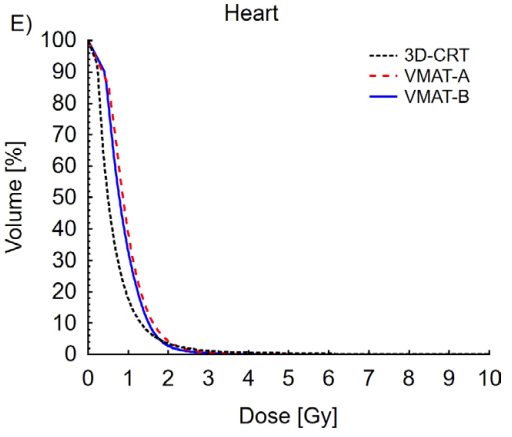

Fig. 8 *Averaged Dose-Volume Histograms for plans prepared with 3D-CRT, VMAT-A, VMAT-B techniques for DIBH delivery – heart*
Source: Own elaboration.

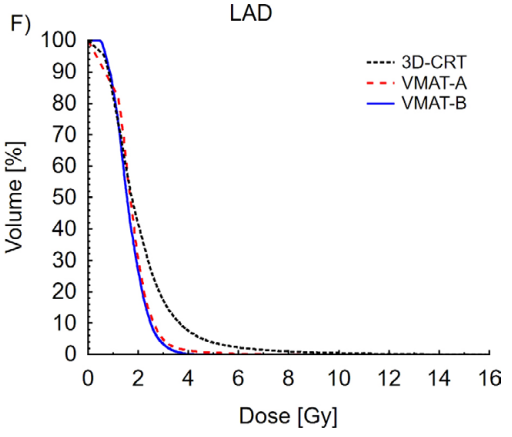

Fig. 9 *Averaged Dose-Volume Histograms for plans prepared with 3D-CRT, VMAT-A, VMAT-B techniques for DIBH delivery – LAD*
Source: Own elaboration.

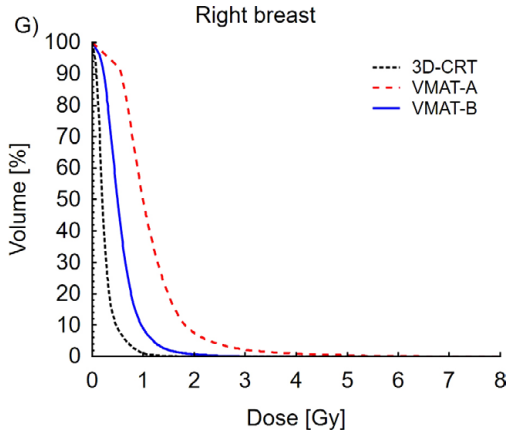

Fig. 10 *Averaged Dose-Volume Histograms for plans prepared with 3D-CRT, VMAT-A, VMAT-B techniques for DIBH delivery – right breast*
Source: Own elaboration.

i) 3D-CRT vs VMAT-A

Compared to the plans prepared with the 3D-CRT technique, VMAT-A plans are characterised by better target volume coverage (V100% in CTV – (91.42±7.31)% and V95% in PTV – (96.76±1.11)%; $p<0.05$), as well as greater homogeneity ($p<0.05$) and conformality of the plans ($p<0.05$). The use of the VMAT-A technique allowed for the maximum dose to be reduced by half in both the heart – 12.12 Gy±6.57 Gy vs 5.55 Gy±3.48 Gy; $p<0.05$ – and the LAD – 8.14 Gy±5.45 Gy vs 4.09 Gy±2.19 Gy; $p=0.08$. Conversely, the use of the 3D-CRT technique significantly reduced the mean dose in the right lung (0.19 Gy±0.04 Gy and 1.25 Gy±0.31 Gy; $p<0.05$) and in the right breast (0.25 Gy±0.07 Gy and 1.13 Gy ±0.31 Gy; $p<0.05$), as well as limiting low doses spreading to both lungs and the heart (Table 5).

Table 5 *Averaged parameters referring to the low-dose range in the left lung, right lung, and heart – 3D-CRT and VMAT-A*

Target volume	Parameter	Technique		*p*-value
		3D-CRT	VMAT-A	
Left lung	V4Gy [%]	19.50 ± 3.10	27.94 ± 4.65	< 0.05
Right lung	V2.5Gy [%]	0.02 ± 0.03	11.03 ± 7.79	< 0.05
Heart	V1.5Gy [%]	7.17 ± 4.13	13.25 ± 8.14	0.10

Source: Own elaboration.

ii) 3D-CRT vs VMAT-B

VMAT-B plans, compared to 3D-CRT plans, were characterised by better target volume coverage, as well as greater homogeneity and conformality ($p<0.05$). In the LAD, a smaller maximum dose (8.14 Gy±5.45 Gy vs 2.99 Gy±1.02 Gy; $p<0.05$), as well as a smaller mean dose (2.22 Gy±0.83 Gy vs 1.76 Gy±0.44 Gy; $p<0.05$), was achieved with the VMAT-B technique. In the left lung, the obtained values for D_{max}, V8Gy, and D_{mean} did not show statistical significance, while statistically significant differences were shown for V4Gy in favour of the 3D-CRT technique: (19.50±3.10)% and (22.26±2.96)%. There were no statistically significant differences in the values obtained in the right lung, except for the mean dose, which was statistically significantly lower for the 3D-CRT technique: (0.19±0.04) Gy vs (0.45±0.06) Gy. In the right breast, the maximum doses were similar (1.93 Gy±2.22 Gy and 2.08 Gy±0.74 Gy; $p=0.05$), while the mean dose was higher in VMAT-B (0.25 Gy±0.07 Gy vs 0.54 Gy±0.13 Gy; $p<0.05$).

iii) VMAT-A vs VMAT-B

In both techniques, similar mean V100% values in the CTV were achieved. The mean V95% values in the PTV differed significantly in favour of the VMAT-A technique: 96.76%±1.11% vs 95.50%±0.73%; $p<0.05$. The use of the VMAT-B technique contributed significantly to an increase in the volume of high doses in the PTV (V105%, V107%, D0.5cm³). Limiting the arm rotation range in VMAT-B resulted in the reduction of low doses in all OARs (Table 6), particularly a reduction in the mean dose in the right lung (1.25 Gy±0.31 Gy vs 0.45 Gy±0.06 Gy; $p<0.05$) and the right breast (1.13 Gy±0.31 Gy vs 0.54 Gy±0.13 Gy; $p<0.05$). Differences in all parameters concerning the heart and LAD were not statistically significant. Plans prepared with the VMAT-A technique showed greater homogeneity of dose distribution in the target volume (HI:0.11±0.02 vs 0.14±0.03; $p<0.05$). No statistically significant differences were found between the PCI coefficients ($p=0.94$).

Table 6 *Averaged parameters referring to the low-dose range in the left lung, right lung, and heart – VMAT-A and VMAT-B*

Target volume	Parameter	Technique		*p*-value
		VMAT-A	VMAT-B	
Left lung	V4Gy [%]	27.94 ± 4.65	22.26 ± 2.96	< 0.05
Right lung	V2.5Gy [%]	11.03 ± 7.79	0.00 ± 0.00	< 0.05
Heart	V1.5Gy [%]	13.25 ± 8.14	10.35 ± 6.73	0.50

Source: Own elaboration.

Discussion

Breast cancer is a neoplasm increasingly detected at early stages and affects increasingly younger women. Precise radiological, histopathological, and molecular diagnostics of neoplasms mean that oncological treatment for breast cancer patients is highly individualised based on clinical and pathological factors. Progress in surgical treatment (Breast Conserving Therapy, sentinel lymph node procedure), a wide range of systemic drugs (chemotherapy, hormone therapy, immunotherapy using monoclonal antibodies, CDK4 inhibitors, PARP inhibitors), along with the dynamically developing technological capabilities in radiotherapy, result in increasingly better treatment outcomes for breast cancer, reducing the risk of local recurrence and prolonging the overall survival of patients.

Radiotherapy has played a significant role in breast cancer treatment for many decades. The results of the EBCTCG meta-analysis showed that radiotherapy after Breast Conserving Therapy or mastectomy significantly reduces the risk of recurrence and mortality from breast cancer [17, 18]. A retrospective analysis of the fate of approximately 300,000 patients showed that patients who underwent irradiation of the left breast have a significantly higher risk of cardiovascular death than

patients who underwent right breast radiotherapy (RR: 1.12; 95% CI: 1.07-1.18; p<0.001). This risk increases with the length of time since exposure to radiation and is significantly higher after 15 years (RR: 1.23; 95% CI: 1.08-1.41; p < 0.001) [19]. Considering the risk-benefit balance and the predicted long lifespan of breast cancer patients, progress in radiotherapy has long been directed towards protecting healthy organs – the heart and its structures, lungs, and the healthy breast – while ensuring the delivery of a high dose to the treated breast.

Numerous scientific studies confirm the benefits associated with the use of respiratory gating during left breast radiotherapy. Moving the heart and LAD away from the posterior surface of the chest wall (ribs, sternum) and increasing lung volume reduces the exposure of these organs to radiation [20, 21, 22, 23, 24, 25]. Particular differences have been noted in the heart and LAD, where the reduction in absorbed dose helps to minimise the risk of late cardiac complications. The study by Sakyanun et al. showed that the use of DIBH during conventional radiotherapy (50 Gy/25 fr) reduces doses to the heart, LAD, and lungs [21]. Also, a paper on partial irradiation of breasts treated in a hypofractionation scheme (42.5 Gy/16 fr) using DIBH showed a reduction in organ doses [25].

In current literature, there are only single reports comparing plans delivered under FB and DIBH in left-sided breast cancer patients treated according to the 26 Gy/5 fr regimen. The study by Piras et al. showed that the heart V5% dosimetric parameters were lower with DIBH than with FB (22.39% vs 29.47%) [24]. Our own data analysis showed that the Deep Inspiration Breath Hold irradiation technique enables dose reduction in OARs while maintaining the desired coverage of the target volume with the therapeutic dose. To conduct a full comparative analysis of the absorbed dose distribution in the OAR and the target volume, a larger number of plans performed without respiratory gating would need to be included. It should be emphasised, however, that our work concerned the analysis of plans that were delivered, and the uneven distribution of patients depending on the radiotherapy delivery technique (DIBH – 62 patients, FB – 8 patients) results from the fact that we endeavour to qualify for this treatment regimen (26 Gy/5 fr) patients who are able to cooperate in terms of breath control. Despite the uneven distribution of patients in the study groups, an analysis of the mean values of individual parameters in healthy tissues (Table 3) shows that the use of the DIBH technique reduces the mean dose in all organs, which is consistent with the observations of other authors [20, 21, 22, 23, 24, 25]. Notably, the FAST-Forward trial protocol did not include any recommendations regarding the method of radiotherapy delivery with respect to respiratory gating (DIBH, FB) [10]. Our own multi-year experience with the use of DIBH in breast cancer hypo-fractionated radiotherapy regimens and available literature data prompted us to use DIBH in the largest possible number of patients.

Another possibility for achieving simultaneous OAR protection along with optimal target volume coverage with the therapeutic dose are dynamic irradiation techniques – VMAT. Literature data show that the VMAT technique enables organ protection within specified dose-volume parameters, but at the same time is characterised by a large volume of healthy tissues receiving low doses [24, 29, 30, 31]. Available literature data do not provide an unambiguous answer as to which irradiation technique should be used in left breast radiotherapy [26, 27].

In our plans prepared with the VMAT-A and VMAT-B techniques, higher homogeneity and conformality were achieved compared to 3D-CRT plans, while meeting the „recommended" tolerance doses in healthy organs according to the protocol in force at the Białystok Oncology Centre (Table 1). Our results are consistent with those of other authors [24, 25, 28, 29, 30, 31]. The study by Mo et al. showed that the PCI coefficient in the VMAT technique (0.77±0.03) was higher than in the 3D-CRT technique (0.55±0.04) (p<0.05). Compared to the 3D-CRT technique, the dynamic VMAT-A and VMAT-B techniques reduced the volume of high doses in the PTV and in the organs on the irradiated side but also increased the volume of low doses in OARs. Similar data were obtained by Piras et al., where the 3D-CRT technique reduced the V5% volume in the heart (8.16% vs 22.39%), while V30% in the left lung was increased (12.13% vs 8.33%). In the VMAT-B plans analysed, the low-dose volume in the OARs was partially reduced by using tangential arc beams. Particular differences, compared to VMAT-A, were obtained in the right breast (D_{mean}: 1.13 Gy±0.31 Gy vs 0.54 Gy±0.13 Gy) and the right lung (D_{mean}:1.25 Gy±0.31 Gy vs 0.45 Gy±0.06 Gy), which is consistent with the observations of other authors [29, 31, 32]. The study by Virén et al. compared plans with a prescribed dose of 50 Gy/25 fr, which showed a lower mean dose for the right lung (0.9 Gy±0.1 Gy vs 1.6 Gy±0.7 Gy) and the right breast (0.9 Gy±0.1 Gy vs 1.6 Gy±0.7 Gy) when using tangential arc beams [29]. Similarly, the study by Zhao et al. observed a reduction in mean doses in the right lung (0.3 Gy±0.1 Gy vs 0.8 Gy±0.4 Gy) and the right breast (0.9 Gy±0.3 Gy vs 1.8 Gy±0.3 Gy) with the use of a technique similar to VMAT-B [32].

The reduction in dose to the right breast is particularly worth emphasising, as exposure to ionising radiation is associated with a greater risk of secondary cancer [33, 34]. As shown by studies conducted on approximately 2,400 Danish patients irradiated between 1982 and 2007, the estimated risk of radiotherapy-induced neoplasm translates into the occurrence of one secondary cancer for every 200 women treated with ionising radiation [35]. This risk increases with the time elapsed since treatment and amounts to 1.55 (95% CI: 1.11-1.61) in the 10-14 year period and 1.79 (95% CI: 1.14-2.81) after 15 years of follow-up. The above report concerns older radiotherapy delivery techniques. Data regarding the impact of dynamic techniques on the risk of secondary neoplasms are not unambiguous [36, 37], and the large volume of tissues receiving low doses has long raised concerns about the possibility of inducing secondary cancers [38, 39]. The study by Fogliata indicates that the risk of secondary neoplasms in breast cancer patients is comparable when using 3D-CRT and VMAT [40]. However, reports by Karpf et al. suggest

that the use of both IMRT and VMAT in left breast radiotherapy is associated with a greater risk of secondary cancer, although the absolute risk associated with excessive radiation exposure is greater with the VMAT technique and concerns the healthy breast and right lung (2-5/10,000 people annually) [41].

It is worth noting that the use of the FAST-Forward regimen in radiotherapy requires a short treatment time (5 days), which means it can be successfully applied in overloaded oncology centres. This may be significant in the future, as projections from the World Health Organization suggest that by 2045, the total number of malignant neoplasms worldwide, regardless of type, gender, and age of patients, will increase to approximately 31 million, representing a rise of about 55% compared to 2022 (approximately 20 million) [42]. These demographic and epidemiological trends underscore the need to search for and implement into daily clinical practice irradiation regimens with the shortest possible fractionation, such as FAST-Forward.

Our results demonstrate that delivery of irradiation using respiratory gating combined with the VMAT technique enables an optimal dose distribution in the target volume while sparing healthy organs, which consequently may favourably affect the patient's quality of life after completion of radiotherapeutic treatment.

Due to differences in patient anatomical structure, including the size of the target volume, chest wall type, positioning of healthy organs relative to the target volume, and the coexistence of diseases such as heart or lung disease, the choice of planning technique was individualised. Knowledge of the advantages and disadvantages of each VMAT technique (VMAT-A and VMAT-B) can be useful when selecting the safest option for the patient, considering their individual clinical situation.

Using the VMAT-B technique, the second breast can be effectively protected in younger patients and the heart and LAD in patients with cardiovascular diseases, achieving a satisfactory dose distribution in the left breast and healthy organs. Conversely, in some patients, such as those with a large breast volume and without comorbidities, the VMAT-A technique may provide an optimal balance in dose distribution between the target volume and the OAR.

The values obtained for OARs, target volumes, and the conformality and homogeneity indices are often comparable in both techniques, and the differences between them, even when reaching a statistically significant level, may not be clinically relevant. Therefore, further prospective studies are necessary to compare various irradiation techniques, considering the risk of late radiation toxicity and cosmetic outcomes. Personalisation of radiotherapy is particularly important in patients with early left-sided breast cancer, who are generally characterised by a good prognosis and favourable survival outcomes.

Perhaps the time has come for the establishment of a Polish Breast Cancer Radiotherapy Group to exchange experiences between radiotherapy centres and develop the best therapeutic strategies, enabling the personalisation of planning and irradiation techniques for breast cancer patients? Maybe we, as radiation oncologists and medical physicists, should consider creating a multi-centre Polish database where data from delivered treatment plans and clinical information, such as the stage of the neoplasm, histopathological report, location of the site of neoplastic recurrence, and late radiation reactions in long-term follow-up, will be collected. The collected data could be useful when using artificial intelligence algorithms to optimise dose distribution for patients in the future.

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