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Dosimetric comparison of normal breathing and deep inspiration breath hold technique for synchronous bilateral breast cancer using 6MV flattened beam and flattening filter free beam

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ABSTRACT

Background: The present study was to investigate the usefulness of deep inspiration breath hold (DIBH) in bilateral breast patients using 6MV flattened beam (FB) and flattening filter free beam (FFFB).

Materials and methods: Twenty bilateral breast cancer patients were simulated, using left breast patients treated with DIBH technique. CT scans were performed in the normal breathing (NB) and DIBH method. Three-dimensional conformal radiotherapy (3DCRT) and volumetric arc therapy (VMAT) plans were generated.

Results: In our study the best organ at risk (OAR) sparing is achieved in the 3DCRT DIBH plan with adequate PTV coverage (V_{95} ≥ 47.5 Gy) as compared to 6MV FB and FFFB VMAT DIBH plans. The DIBH scan plan reduces the heart mean dose significantly at the rate of 49% in 3DCRT (p = 0.00) and 22% in VMAT (p = 0.010). Similarly, the DIBH scan plan produces lesser common lung mean dose of 18% in 3DCRT (p = 0.011) and 8% in VMAT (0.007) as compared to the NB scan. The conformity index is much better in VMAT FB (1.04 ± 0.04 *vs.* 1.04 ± 0.05), p =1.00 and VMAT FFFB (1.04 ± 0.05 *vs.* 1 ± 0.24, p = 0.345) plans as compared to 3DCRT (1.63 ± 0.2 *vs.* 1.47 ± 0.28, p = 0.002). The homogeneity index of all the plans is less than 0.15. The global dmax is more in VMAT FFFB DIBH plan (113.7%). The maximum MU noted in the NB scan plan (478 *vs.* 477MU, 1366 *vs.* 1299 MU and 1853 *vs.* 1788 MU for 3DCRT, VMAT FB and VMAT FFFB technique as compared to DIBH scan.

Conclusion: We recommend that the use of DIBH techniques for bilateral breast cancer patients significantly reduces the radiation doses to OARs in both 3DCRT and VMAT plans.

Key words: deep inspiration breath hold; free breething

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Introduction

The incidence of synchronous bilateral breast cancer (SBBC) is about 2.1% of all breast cancer patients [1]. Surgery, chemotherapy and radiotherapy are the choice to treat the breast cancer. Radiotherapy planning of synchronous bilateral breast cancer is complex due to concavity of planning target volume (PTV), time consuming in planning and difficult to reduce the dose to the common lung, heart and higher scatter in the wider treatment volume [2]. The treatment goal

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of radiotherapy planning is to protect normal tissue and to deliver prescription dose uniformly throughout the target. Practically, in breast planning the entrance and exit beams pass through the lung, heart and liver, which is totally unavoidable in all the treatment techniques like three-dimensional conformal radiotherapy (3DCRT), intensity modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT). The use of traditional tangential beam arrangement (3DCRT) has some drawbacks, such as inhomogeneous dose distribution, hot spot, inadequate PTV coverage, difficulty in OAR sparing and high dose volume near the heart and lungs [3]. The use of the VMAT technique is increased nowadays in all treatment sites due to the clinically acceptable target coverage and OAR sparing [4]. VMAT plan will generate the highly conformal, homogenous dose distribution inside the PTV and spare the adjacent OARs by simultaneous modulation of dose rate, gantry and multi-leaf collimator speed [5].

To reduce cardiac and lung toxicity [6, 7], the breath hold technique is needed. The application of the DIBH technique in left breast patients [8, 9] will displace the heart from the inner chest wall and total lung volume increased due to air filling the lungs. Parkes et al. [10, 11] reported that the organ movement during breathing affects image quality in diagnostic procedure and also radiation delivery. To reduce the organ movement, the breath hold technique is implemented with the help of a mechanical ventilator. This technique will increase the oxygen level in the lungs and remove carbon dioxide and will enable a safe prolonged breath-holds in a single session in the DIBH technique at duration of 5 minutes.

The development in technology will help to manufacture the advanced treatment devices and treatment technique. Recently the Varian True beam linear accelerator capable to deliver the flattened beam and flattening filter-free beam. The FFF beam has several advantages like increased dose rate, reduced the head scatter, lesser beam ON time and reduced out of field dose as compared to flattened beam [12].

DIBH technique is used mostly in left breast cancer patients and rarely in right breast cancer patients. The planning study of the DIBH techniques in bilateral breast patients is not available to the best of our knowledge. The aim of the study was to analyse the advantage of the DIBH technique in comparison to normal breathing in bilateral breast cancer patients using the 6MV FB and FFFB.

Materials and methods

In this study twenty early stage left breast BCS (breast conservation surgery) patients in the age group of 35–45 were selected randomly, for simulating the patients for synchronous bilateral breast cancer analysis. Patients were immobilized on the breast board in a supine position with the arms over the head. The CT scan was performed in NB and DIBH. To maintain the breathing pattern, adequate breath hold training was given to the patients. The DIBH scan is acquired with breathing instruction given from console and the breathing pattern is recorded using Varian real time position management system. The gating window for all the patients depends upon the inspiration capacity.

The CT slice thickness was acquired at 3mm intervals. The PTV and OARs, such as the common lungs, heart, liver and spinal cord were contoured in respective CT slices based on the Radiation Therapy Oncology Group atlas. Clinical target volume (CTV) consists of bilateral breasts and expanded 5mm in all directions (except towards the body) to form the planning target volume (PTV).

The prescribed dose was 50 Gy in 25 fractions. The planning goal is to cover ≥ 95% of PTV to ≥ 95% of the prescription dose (≥ 47.5 Gy). The OAR dose constraints were the heart $V_{25\,Gy} \leq 10\%$, common lung $V_{20\,Gy} \leq 30\%$, and the dose to the other volumes ($V_{5\,Gy}$ to $V_{40\,Gy}$) are as low as reasonable to achieve.

The whole patient treatment planning was performed in the Varian eclipse treatment planning system (Ver.11.0) using a true beam linear accelerator equiped with a millennium multileaf collimator (MLC). The selected beam energy is 6 MV FB (dose rate: 600 MU/min) and 6MV FFF beam (dose rate: 1400 MU/min). Totally, 6 plans were generated for each patient. Three plans — 6MV FB 3DCRT (NB), 6MV FB VMAT (NB) and 6MV FFFB VMAT (NB) — in free breathing CT scan and three plans — 6MV FB 3DCRT (DIBH), 6MV FB VMAT (DIBH) and 6MV FFFB VMAT (DIBH) were generated on DIBH scans.

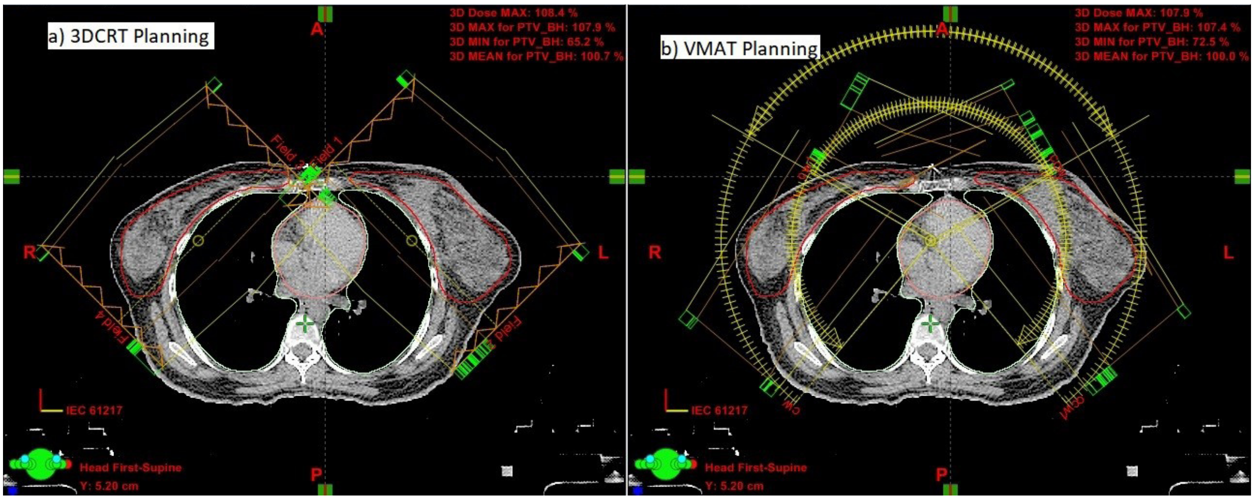

Figure 1. Beam placement of three-dimensional conformal radiation therapy (3DCRT) (left) and volumetric modulated arc therapy (VMAT) planning (right).

Single isocenter is used in VMAT and two isocenters for 3DCRT planning. Field in filed 3DCRT plans consist of two tangential beams placed on the left breast [52° ± 5° for medial tangent (MT) and 120° ± 5° for lateral tangent (LT)] and, similarly, for the right breast (300° ± 5° for MT and 220° ± 5° for LT). In our study the field in field technique is used in 3DCRT planning to get optimized desired dose distribution and will help to minimize the breath hold time in comparison to wedge planning. In VMAT planning, four partial arcs were placed: two arcs for the left breast (300°–120°) and two arcs for the right breast (60°–220°). Beam placement of 3DCRT (left) and VMAT planning (right) is shown in Figure 1.

Dose calculation was performed on an anisotropic analytical algorithm (AAA) and the calculation gird size was 2.5 × 2.5 mm^2. The statistical analyses between the groups were carried out. Paired sample-t test was performed using the Statistical Package for the Social Sciences (SPSS) version 20 (SPSS Inc., USA). The p value of ≤ 0.05 was considered as statistically significant.

Conformity index (CI), homogeneity index (HI) [13], low gradient index (LGI) and high-gradient index (HGI) of all plans were calculated using the below formula 1 to 4. To evaluate dose homogeneity in the planning target volume (PTV), homogeneity index is used.

$$CI = \frac{V95\%}{PTV\ Volume} \quad (1)$$

Conformity index is the ratio of volume of 95% isodose line divided by PTV volume, which is used to evaluate the coverage criteria of the prescribed dose for the plans. The CI = 1 indicate good conformity.

$$HI = \frac{D2\% - D98\%}{D50\%} \quad (2)$$

where $D_{98\%}$, $D_{50\%}$, and $D_{2\%}$ were dose received by 98%, 50%, and 2% PTV, respectively [9]. HI = 0 represents the homogeneous dose distribution in the PTV.

Low and high gradient indices were calculated using the following formula [14].

$$Low\ Gradient\ Index\ (LGI) = \frac{V25\%PID}{V50\%PID} \quad (3)$$

$$High\ Gradient\ Index\ (HGI) = \frac{V50\%PID}{V90\%PID} \quad (4)$$

Where $V_{25\%}$, $V_{50\%}$, &$V_{90\%}$ were volumes receiving 25%, 50%, and 90% of the prescription isodose dose (PID), respectively.

To evaluate the dose received by the OAR's, the following parameters were noted: for the common lung, $V_{5\,Gy}$, $V_{10\,Gy}$, $V_{15\,Gy}$, $V_{20\,Gy}$, $V_{30\,Gy}$, V_{40Gy} and mean dose; for the heart $V_{5\,Gy}$, $V_{10\,Gy}$, $V_{15\,Gy}$, $V_{20\,Gy}$, $V_{25\,Gy}$,$V_{30\,Gy}$, $V_{40\,Gy}$ and mean dose. The mean dose of the liver and spinal cord Dmax were also noted as were the body–PTV mean dose, low dose volume of $V_{1\,Gy,}$ $V_{2\,Gy,}$ $V_{3\,Gy,}$ $V_{4\,Gy,}$ $V_{5\,Gy,}$ $V_{10\,Gy,}$ $V_{20\,Gy,}$ $V_{30\,Gy,}$ $V_{40\,Gy,}$ $V_{50\,Gy}$ and monitor units (MU).

Results

The mean volume of PTV, common lung, heart and liver of all 20 patients were 1329 ± 396 cm^3, 1930 ± 349cm^3, 490 ± 69 cm^3 and 1342 ± 272 cm^3 [mean ± standard deviation (SD)] in the NB scan and 1281 ± 427 cm^3, 3168 ± 931 cm^3, 442 ± 73 cm^3 and 1207 ± 226 cm^3 in the DIBH scan, respectively. Table 1 and Table 2 summarizes planning target volume and OAR dose comparison between free breathing and deep inspiration breath hold scans for the 3DCRT and VMAT plans. Table 3 represents the common lung physical properties for NB and DIBH scans. Figure 2 represents the transverse plane isodose distribution for one patient in all six plans. The DVH comparison between NB and DIBH scan for 6MV 3DCRT, 6MV FB VMAT and 6MV FFFB VMAT plan is shown in Figures 3–5. Figure 6 represents the bar plot for the heart (V_{25Gy} and Dmean) and common lung (V_{20Gy} and Dmean) for NB versus DIBH scan. Figures 7–9 represents the dose fall off (1 Gy to 40 Gy) in the BODY — PTV region for NB and DIBH scan for the 3DCRT, FB VMAT and FFFB VMAT techniques.

PTV coverage, indexes, OAR sparing and MU for NB versus DIBH scans for 3DCRT and 6MV FB/FFFB VMAT plans

In our study, in all the treatment plans, the PTV $D_{95\%}$ was 47.5 Gy, as plans were normalized such that 95% of PTV covered 95% of the prescription dose; however, the higher global Dmax was observed in the 6MV FFFB VMAT DIBH plan (113.7%, p = 0.556) as compared to the NB scan plans. Both NB and DIBH scans produce the best homogeneous plan in the 6MV FB and FFFB VMAT technique (HI ≤ 0.14, p ≤ 0.452) as compared to 3DCRT (0.15, p = 0.808). Similarly, the highly conformal plan is generated in 6MV FFFB VMAT DIBH, the value is 1.00 ± 0.2 (p = 0.345) due to the modulation of VMAT beams. In the present study, the 6MV 3DCRT NB scan plans gives a poor conformity index, the value is ≤ 1.63 (p = 0.002), as a 7 mm field margin around PTV is given in all the beams to obtain adequate coverage. The DIBH plans produce higher HGI and LGI in all the techniques; however, the 3DCRT plans produce lesser HGI (≤ 1.33) and LGI (≤ 1.20) as compared to VMAT (HGI ≤ 1.98, LGI ≤ 1.86) as 3DCRT plans have a minimum number of beams and beam passing through non-target PTV was lesser. The dosimetric advantage of the DIBH technique is observed in sparing OARs , such as the heart, common lung and liver, the values were mentioned in Table 2.The DIBH plan spareed the heart $V_{25\ Gy,}$ the values were 5.07 *vs.* 1.17% (p = 0.00), 2.27 *vs.* 0.48% (p = 0.00) and 2.77% *vs.* 0.81% (p = 0.00) for 3DCRT, FB VMAT and FFFB VMAT as compered to NB scan. Similarly, DIBH plan spared the heart Dmean, the value were 4.38 *vs.* 2.24 Gy (p = 0.00) for 3DCRT, 9.0 *vs.* 7.01 Gy (p = 0.010) for 6MV FB VMAT and 9.6 *vs.* 7.4Gy (p = 0.00) for 6MV FFFB VMAT, respectively. The heart $V_{5\ Gy}$, $V_{10\ Gy}$, $V_{15\ Gy}$, $V_{20\ Gy}$, $V_{25\ Gy}$, $V_{30\ Gy}$, $V_{40\ Gy}$ and Dmean value is 48–81% in 3DCRT, 25–100% in 6MV FB VMAT and in 7.6–27.8% 6MV FFFB VMAT lower in DIBH scan as compared to FB scan.

The DIBH plan spared the common lung $V_{20\ Gy,}$ the values were 16.19 *vs.* 12.48 % (p = 0.012) for 3DCRT, 19.29 *vs.* 16.16% (p = 0.122) for 6MV FB VMAT and 20.41 ± 6.90 % *vs.* 18.46% (p = 0.251) for 6MV FFFB VMAT as compared to the NB scan. Similarly, DIBH spared the common lung Dmean, the values were 9.2 *vs.* 7.53 Gy (p = 0.011) for 3DCRT. 13.85 *vs.* 12.74 (p=0.007) for 6MV FFFB VMAT and 14.26 *vs.* 13.03Gy (p = 0.005) for 6MV FFFB VMAT as compared to the NB scan, respectively. The common lung $V_{5\ Gy}$, $V_{10\ Gy}$, $V_{15\ Gy}$, $V_{20\ Gy}$, $V_{30\ Gy}$, $V_{40\ Gy}$ and Dmean values were 10–27% in 3DCRT, 7.6–27.8% in 6MV FB VMAT and 7.4–23.3% in 6MV FFFB VMAT, lower in DIBH scan as compared to FB scan.

The DIBH scan reduced the liver mean dose about 42% in 3DCRT (2.29 *vs.* 1.33 Gy, p = 0.162), 54% in 6MV FB VMAT, (6.37 *vs.* 2.93 Gy, p = 0.094) and 52% in 6MV FFFB VMAT (6.43 *vs.* 3.07, p = 0.092) as compared to the NB Scan.

In all the techniques, there is no significant p value noted when comparing NB *vs.* DIBH. No monitor unit (MU) difference was observed in 3DCRT plans of NB and DIBH scans, the MU was 478 (p = 0.817). In the case of 6MV FB VMAT the MU were 1366 for the NB scan and 1299 MU (p = 0.183) for the DIBH Scan. The MU for 6MV FFFB VMAT is 1853 for NB scan and 1788 (p = 0.335) for DIBH Scan.

The body V105%, body-PTV mean dose and out of field dose, i.e. normal tissue exposed to 1 Gy to 40 Gy dose contribution is reduced in DIBH scan plans due to the lesser volume of the PTV (1329 cc

Table 1. Planning target volume (PTV) and organ at risk (OAR) dose comparison between normal breathing (NB) and deep nspiration breath hold (DIBH) scan for three-dimensional conformal radiation therapy (3DCRT) and VMAT plans

Target and OARs	Parameters	Average ± standard deviation (SD)						p-value		
		Normal breathing (NB)			Deep inspiration breath hold (DIBH)			NB *vs.* DIBH		
		3DCRT	6MV VMAT FB	6MV VMAT FFFB	3DCRT	6MV VMAT FB	6MV VMAT FFFB	3DCRT	6MV FB	6MV FFFB
PTV	$D_{98\%}$ [Gy]	46.2 ± 0.67	46.47 ± 0.19	46.38 ± 0.25	46.12 ± 0.73	46.49 ± 0.33	46.42 ± 0.33	0.609	0.877	0.630
	$D_{95\%}$ [Gy]	47.5 ± 0.0	47.5 ± 0.00	47.5 ± 0.00	47.5 ± 0.10	47.5 ± 0.01	47.5 ± 0.01	0.213	0.660	0.330
	$D_{50\%}$ [Gy]	50.86 ± 0.80	50.63 ± 0.64	51.02 ± 0.76	50.8 ± 0.88	50.54 ± 0.63	50.78 ± 0.59	0.798	0.574	0.181
	$D_{2\%}$ [Gy]	53.19 ± 1.74	52.76 ± 1.76	53.27 ± 1.88	53.14 ± 1.87	52.54 ± 1.67	52.93 ± 1.63	0.840	0.464	0.269
	V90% [cc]	2491 ± 736	1584 ± 442	1602 ± 444	2236 ± 559	1548 ± 468	1561 ± 468	0.009	0.432	0.380
	V50% [cc]	3284 ± 905	3059 ± 711	3063 ± 743	3088 ± 685	3012 ± 743	3028 ± 758	0.093	0.550	0.679
	V25% [cc]	3866 ± 1043	5468 ± 1430	5526 ± 1415	3691 ± 825	5530 ± 1207	5585 ± 1222	0.167	0.724	0.718
	Dmax (%)	110.7 ± 2.63	112.5 ± 2.96	113.2 ± 3.18	110.7 ± 2.96	112.4 ± 3.42	113.7 ± 3.16	0.926	0.866	0.560
	$V_{95\%}$ [cc]	2089 ± 628	1368.75 ± 395	1384.9 ± 401	1867.65 ± 505	1330.79 ± 422	1259.09 ± 505	0.040	0.378	0.194
	HI	0.15 ± 0.03	0.13 ± 0.02	0.14 ± 0.03	0.15 ± 0.03	0.13 ± 0.03	0.14 ± 0.02	0.808	0.452	0.223
	CI	1.63 ± 0.21	1.04 ± 0.04	1.05 ± 0.04	1.47 ± 0.28	1.04 ± 0.05	1.00 ± 0.24	0.002	1.000	0.345
	HGI	1.33 ± 0.04	1.96 ± 0.14	1.93 ± 0.14	1.39 ± 0.06	1.98 ± 0.15	1.97 ± 0.16	0.000	0.330	0.110
	LGI	1.18 ± 0.02	1.78 ± 0.11	1.8 ± 0.12	1.2 ± 0.02	1.86 ± 0.17	1.86 ± 0.16	0.000	0.048	0.058
Body	$V_{105\%}$ [cc]	340.45 ± 267	131.6 ± 130	247 ± 204	274 ± 258	109.76 ± 122	152.4 ± 130	0.397	0.495	0.074
Body-PTV	Mean [Gy]	5.99 ± 1.28	7.72 ± 0.93	7.88 ± 1.03	5.43 ± 0.91	7.56 ± 0.90	7.59 ± 0.93	0.454	0.440	0.340
	$V_{1\,Gy}$ (%)	42.22 ± 7.54	64.67 ± 5.65	61.49 ± 12.51	40.42 ± 5.77	63.55 ± 5.57	62.92 ± 5.47	0.219	0.338	0.633
	$V_{2\,Gy}$ (%)	26.06 ± 5.36	53.68 ± 5.25	53.07 ± 5.19	24.76 ± 3.77	53.29 ± 4.77	52.81 ± 4.61	0.151	0.707	0.780
	$V_{3\,Gy}$ (%)	20.1 ± 4.27	48.14 ± 5.03	47.81 ± 4.98	19.46 ± 3.22	47.9 ± 4.65	47.71 ± 4.54	0.361	0.816	0.911
	$V_{4\,Gy}$ (%)	17.36 ± 3.68	44.01 ± 4.89	43.87 ± 4.92	16.92 ± 2.92	43.66 ± 4.74	43.56 ± 4.75	0.481	0.750	0.749
	$V_{5\,Gy}$ (%)	15.97 ± 3.39	40.29 ± 4.97	40.33 ± 4.93	15.27 ± 2.46	39.92 ± 4.74	39.88 ± 4.82	0.241	0.760	0.669
	$V_{10\,Gy}$ (%)	13.21 ± 2.60	25.4 ± 3.87	25.96 ± 3.69	12.05 ± 1.84	25.07 ± 3.69	25.37 ± 3.76	0.032	0.730	0.434
	$V_{20\,Gy}$ (%)	10.85 ± 2.58	12.17 ± 1.73	12.48 ± 2.08	9.5 ± 1.59	11.76 ± 1.80	12.01 ± 1.92	0.012	0.287	0.200
	$V_{30\,Gy}$ (%)	9.28 ± 2.32	6.55 ± 0.97	6.85 ± 1.49	8.06 ± 1.38	6.19 ± 1.03	6.23 ± 1.10	0.018	0.114	0.019
	$V_{40\,Gy}$ (%)	7.71 ± 2.04	3.08 ± 0.58	3.47 ± 1.36	6.16 ± 1.60	2.92 ± 0.60	2.98 ± 0.62	0.090	0.316	0.043
MU		478 ± 19	1366 ± 184	1853 ± 240	477 ± 20	1299 ± 174	1788 ± 234	0.817	0.183	0.335

Dmax — maximum dose; Dmean — mean dose; FB — flattened beam; FFFB — flattening filter free beam; HI — homogeneity index; CI — conformity index; HGI — high-gradient index; LGI — low gradient index; MU — monitor units

Table 2. Organ at risk (OAR) comparison between normal breathing (NB) and deep inspiration breath hold (DIBH) scan for three-dimensional conformal radiation therapy (3DCRT) and volumetric modulated arc therapy (VMAT) plans

OARs	Parameters	Average ± standard deviation (SD)						p-value		
		Normal breathing (NB)			Deep inspiration breath hold (DIBH)			NB *vs.* DIBH		
		3DCRT	6MV VMAT FB	6MV VMAT FFFB	3DCRT	6MV VMAT FB	6MV VMAT FFFB	3DCRT	6MV FB	6MV FFFB
Common lung	$V_{5\,Gy}$ (%)	30.1 ± 9.35	91.51 ± 5.65	92.19 ± 5.62	27.13 ± 8.15	84.55 ± 7.99	85.36 ± 7.86	0.092	0.000	0.000
	$V_{10\,Gy}$ (%)	20.8 ± 8.35	58.17 ± 13.02	60.93 ± 13.18	17.18 ± 6.54	52.64 ± 8.91	54.42 ± 9.55	0.023	0.026	0.006
	$V_{15\,Gy}$ (%)	17.89 ± 7.95	32.77 ± 8.43	34.89 ± 9.69	14.05 ± 5.85	30.13 ± 7.20	32.31 ± 6.85	0.013	0.219	0.171
	$V_{20\,Gy}$ (%)	16.19 ± 7.56	19.29 ± 5.71	20.41 ± 6.90	12.48 ± 5.48	16.16 ± 5.92	18.46 ± 4.48	0.012	0.122	0.251
	$V_{30\,Gy}$ (%)	13.75 ± 7.01	7.33 ± 3.41	7.37 ± 3.69	10.36 ± 5.03	5.92 ± 2.62	6.53 ± 3.19	0.018	0.039	0.353
	$V_{40\,Gy}$ (%)	10.6 ± 6.33	2.01 ± 1.67	2.23 ± 2.29	7.73 ± 4.55	1.45 ± 1.76	1.71 ± 1.70	0.031	0.129	0.354
	Dmean [Gy]	9.2 ± 3.43	13.85 ± 1.82	14.26 ± 1.97	7.53 ± 2.56	12.74 ± 1.61	13.03 ± 1.68	0.011	0.007	0.005
Heart	$V_{5\,Gy}$ (%)	11.05 ± 6.52	74.17 ± 13.99	75.57 ± 13.80	3.97 ± 3.39	55.59 ± 13.07	56.26 ± 14.57	0.000	0.000	0.000
	$V_{10\,Gy}$ (%)	7.14 ± 5.08	31.69 ± 17.45	36.73 ± 17.56	2.01 ± 2.57	20.78 ± 8.11	23.7 ± 9.65	0.000	0.013	0.007
	$V_{15\,Gy}$ (%)	6.16 ± 4.51	13.18 ± 9.17	16.77 ± 10.58	1.62 ± 2.24	7.97 ± 4.80	10.88 ± 7.08	0.000	0.032	0.056
	$V_{20\,Gy}$ (%)	5.54 ± 4.17	5.16 ± 3.25	6.85 ± 4.20	1.37 ± 2.02	2.62 ± 2.13	3.66 ± 3.46	0.000	0.008	0.019
	$V_{25\,Gy}$ (%)	5.07 ± 3.93	2.27 ± 1.75	2.77 ± 2.04	1.17 ± 1.78	0.48 ± 0.62	0.81 ± 0.92	0.000	0.000	0.000
	$V_{30\,Gy}$ (%)	4.63 ± 3.68	1.14 ± 1.20	1.18 ± 1.24	0.97 ± 1.55	0.1 ± 0.20	0.14 ± 0.29	0.000	0.000	0.000
	$V_{40\,Gy}$ (%)	3.61 ± 3.03	0.15 ± 0.30	0.16 ± 0.33	0.67 ± 1.17	0.00± 0.00	0.00± 0.00	0.000	0.038	0.037
	Dmean [Gy]	4.38 ± 1.30	9.00 ± 2.05	9.6 ±2.27	2.24 ± 1.06	7.01 ± 1.32	7.42 ± 1.59	0.000	0.010	0.010
Liver	Dmean [Gy]	2.29 ± 0.73	6.37 ± 3.14	6.43 ± 3.08	1.33 ± 0.69	2.93 ± 1.70	3.07 ± 1.70	0.162	0.094	0.092
Spinal cord	Dmax [Gy]	0.93 ± 0.23	21.32 ± 5.95	20.4 ± 5.22	1.02 ± 0.18	18.67 ± 6.04	16.73 ± 7.84	0.079	0.129	0.056

Dmax — maximum dose; Dmean — mean dose; FB — flattened beam; FFFB — flattening filter free beam

Table 3. Hounsfield units (HUs) and electron density for the common lung for normal breathing (NB) and deep inspiration breath hold (DIBH) scan

Scan	Common lung [average ± standard deviation (SD)]	
	HU	Electron density
NB scan	652 ± 168	0.355 ± 0.176
DIBH scan	794 ± 167	0.233 ± 0.160

for the NB Scan and 1289 cc for DIBH), The graph is plotted between dose *vs.* volume as shown in Figures 7–9, from the plot as by increasing the dose the volume decreases gradually. This lesser volume of PTV in DIBH scan will reduce the patient scatter and collimator scatter contribution. However, in our study, 3DCRT plans will reduce the low dose volume (1 Gy to 40 Gy) in the body-PTV region,

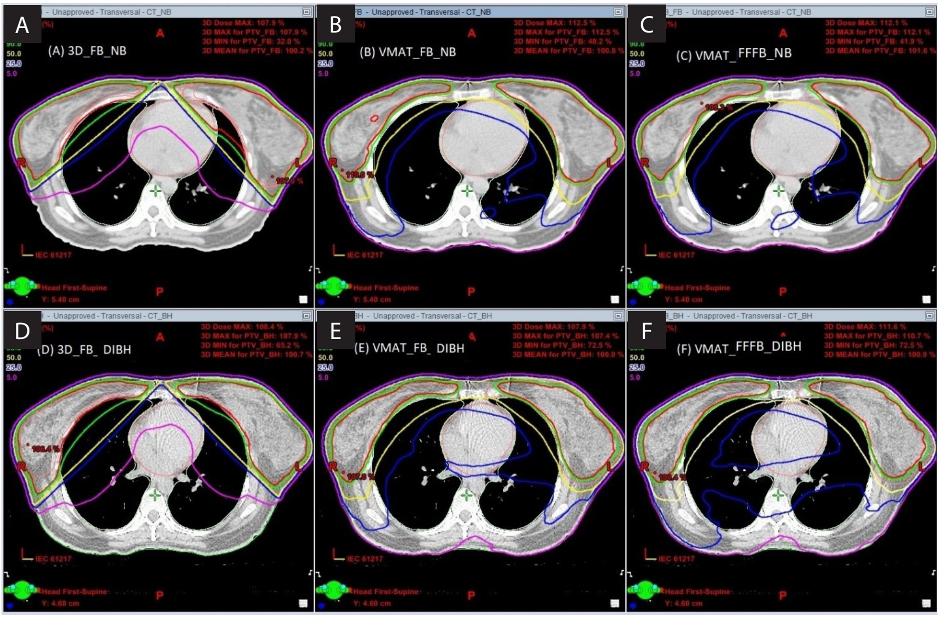

Figure 2. Transverse plane isodose distribution for one patient in all six plans. **A.** Three-dimensional conformal radiation therapy (3DCRT) — normal breathing (NB); **B.** 6MV flattened beam (FB) volumetric modulated arc therapy (VMAT) — NB; **C.** 6MV VMAT flattening filter free beam (FFFB) — NB; **D.** 3DCRT — deep inspiration breath hold (DIBH); **E.** 6MV FB VMAT — DIBH; **F.** 6MV VMAT FFFB — DIBH

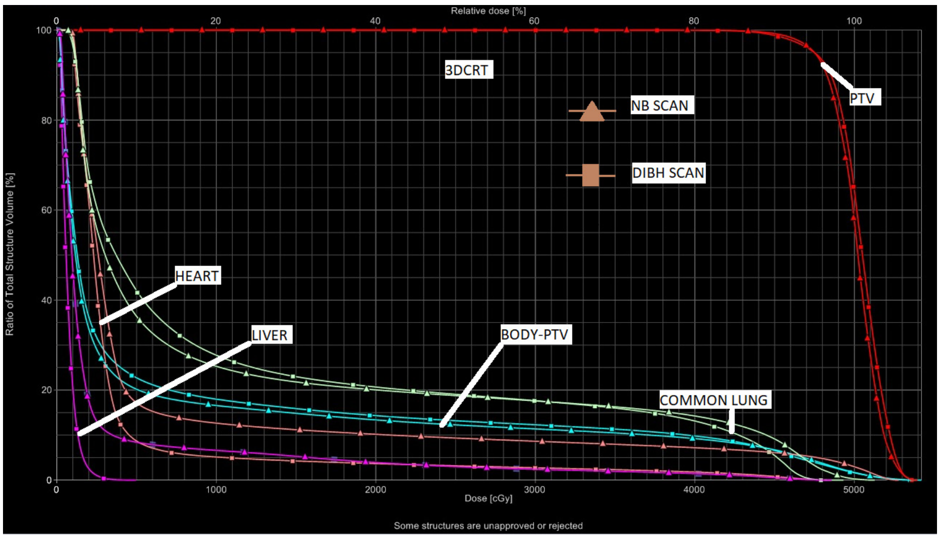

Figure 3. Planning target volume (PTV) and organ at risk (OAR's) dose comparison for between normal breathing (NB) and deep inspiration breath hold (DIBH) scan for three-dimensional conformal radiation therapy (3DCRT) plan of one patient

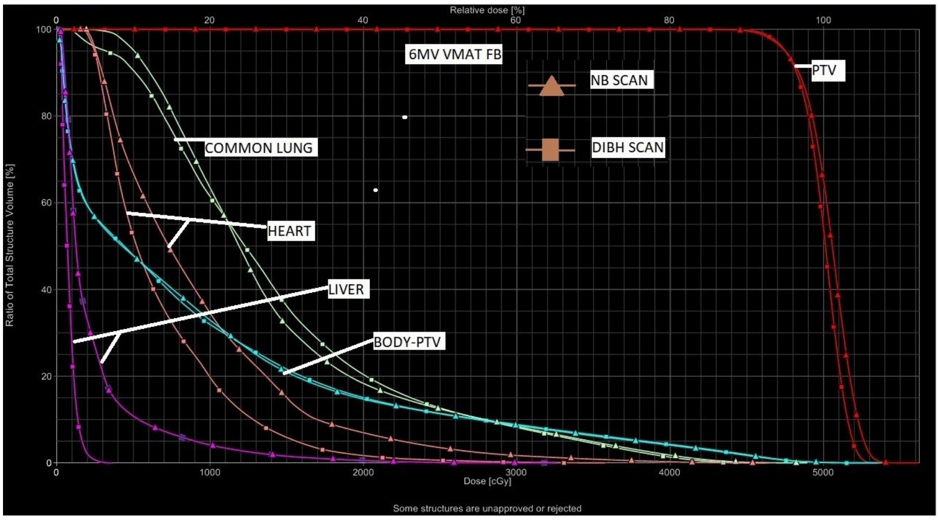

Figure 4. Planning target volume (PTV) and organ at risk (OAR's) dose comparison between normal breathing (NB) and deep inspiration breath hold (DIBH) scan for 6MV volumetric modulated arc therapy (VMAT) flattened beam (FB) plan of one patient

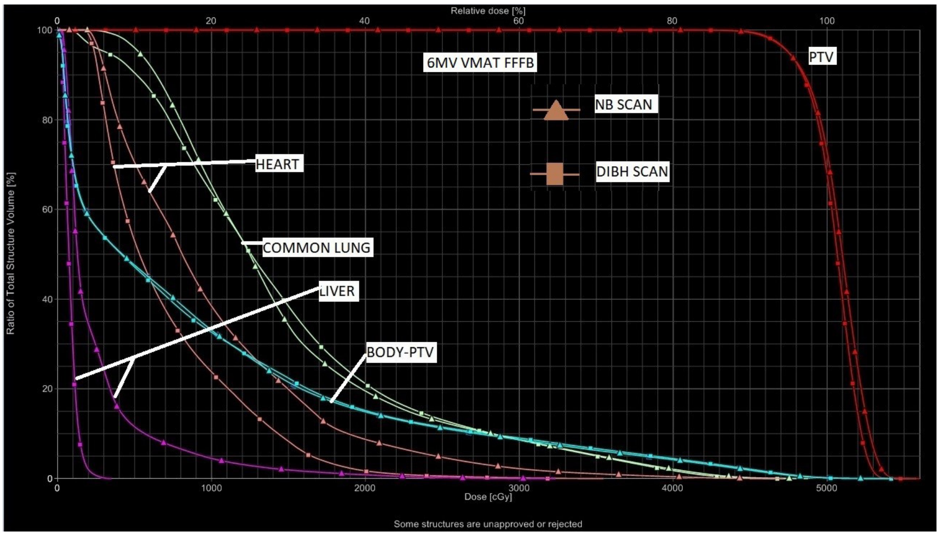

Figure 5. Planning target volume (PTV) and organ at risk (OAR's) dose comparison between normal breathing (NB) and deep inspiration breath hold (DIBH) scan for 6MV volumetric modulated arc therapy (VMAT) flattening filter free beam (FFFB) plan of one patient

the reason was parallel opposed minimum number of tangential beams around the PTV as compared to VMAT (see beam placement in Fig. 1), the values were represented in Table 1.

Discussion

In our study DIBH scan plans spared the common lung, heart, liver, body-PTV mean dose and low dose volume in normal tissue is lower as compared to NB scan plans. Kalef-ezra et al. [15] reported that the electron density of the lung reflects the relative volumes of air, lung tissue, interstitial fluid and blood. However, the mean densities of the lung in women were 8% and 16% higher than in men in the whole lung and lung close to the chest wall. The mean CT number for women was –722 and for men, –746; the mean relative electron densities were 0.297 and 0.275 for women and men, respectively. Rotstelen et al. [16] reported that the relative electron density of the lung varied from the anterior to posterior direction, the anterior-latera1

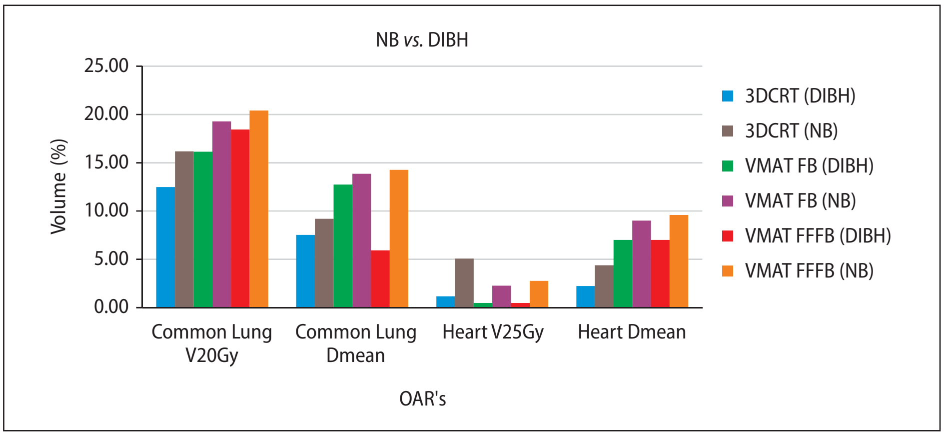

Figure 6. Common lung (Dmean and V20 Gy) and heart dose (Dmean and V25 Gy) in normal breathing (NB) and deep inspiration breath hold (DIBH) scan for three-dimensional conformal radiation therapy (3DCRT) and volumetric modulated arc therapy (VMAT) technique; Dmean — mean dose; FB — flattened beam; FFFB — flattening filter free beam

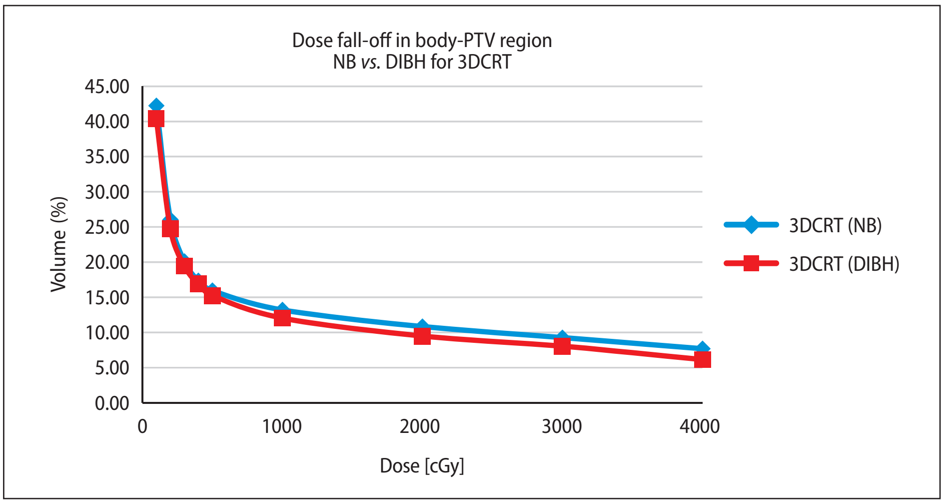

Figure 7. Dose fall off (1 Gy to 40 Gy) in BODY — planning target volume (PTV) region normal breathing (NB) and deep inspiration breath hold (DIBH) scan for three-dimensional conformal radiation therapy (3DCRT) technique

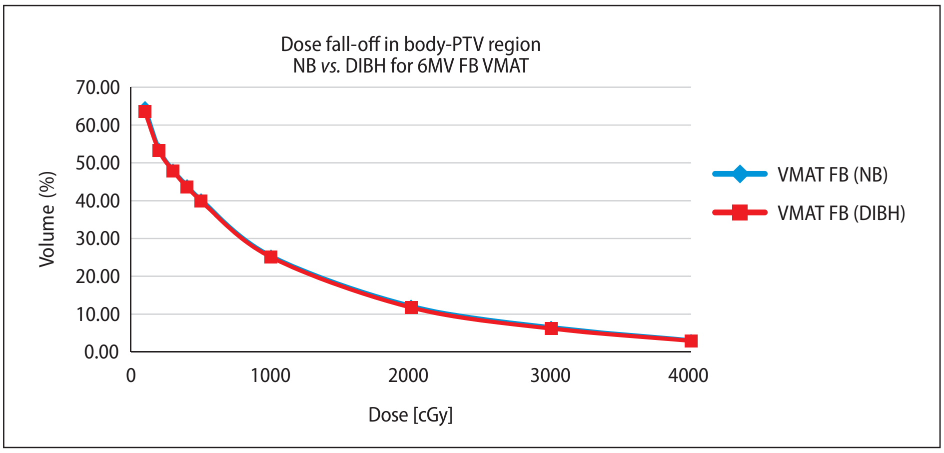

Figure 8. Low dose fall off (1 Gy to 5 Gy) in BODY — planning target volume (PTV) region normal breathing (NB) and deep inspiration breath hold (DIBH) scan for 6MV flattened beam (FB) volumetric modulated arc therapy (VMAT) technique

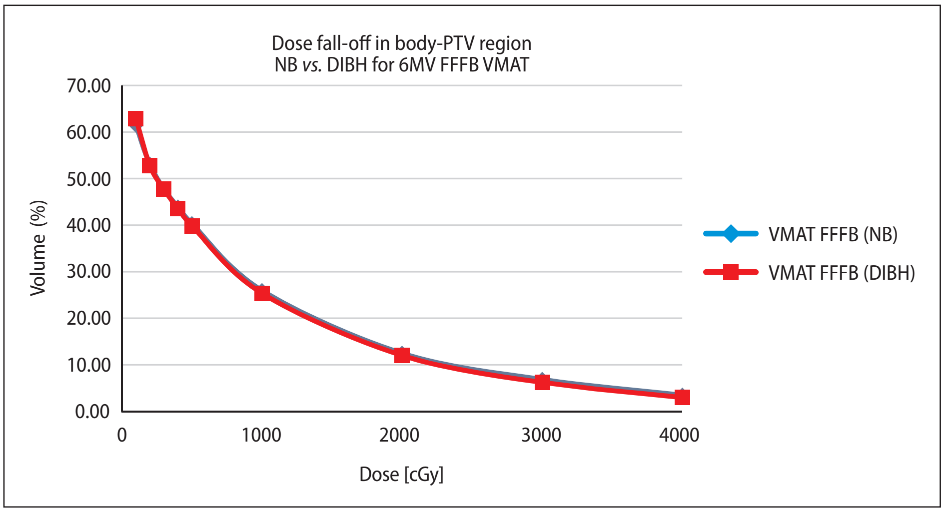

Figure 9. Dose fall off (1 Gy to 40 Gy) in BODY — planning target volume (PTV) region normal breathing (NB) and deep inspiration breath hold (DIBH) for flattening filter free beam (FFFB) volumetric modulated arc therapy (VMAT) technique

quarter of the lung is 0.17 and the whole lung is 0.25. Fogliata et al. [17] reported that the mean HU and mean density (gcm^{-3}) for the NB scan is –709 HU and 0.27. In the case of DIBH scans, the value is –822 HU and 0.16, respectively.

Oechsner et al. [18] reported that the application of DIBH resulted in the left lung mean dose being reduced to 8.1 ± 1.6 Gy (DIBH) *vs.* 10.0 ± 1.7 Gy (NB) and the left lung $V_{20\ Gy}$ to 18.9 ± 3.6% *vs.* 14.4 ± 3.3%. Similarly, heart mean dose decreased from 4.0 ± 1.9 Gy (NB) to 1.7 ± 1.0 Gy (DIBH). Heart $V_{20\ Gy}$ is 6.2 ± 4.2% *vs.* 1.2 ± 1.0% and $V_{40\ (\%)}$ 3.6 ± 2.7% *vs.* 0.4 ± 0.9%. Significant changes in mean lung density were noted, 0.31 ± 0.05 g/cm^3 for NB CT scan and 0.17 ± 0.03 g/cm^3 for DIBH scan. Due to the expansion of the lung in DIBH scan, the irradiated lung volumes were larger; however, the total relative irradiated lung volume was small.

In our study, the common lung HU for NB and DIBH scans were 652HU and 794HU, respectively, and the corresponding electron densities were 0.355 and 0.233, respectively. The changes are due to air filling in the common lung. The DIBH scan reduced the common lung mean dose and the values were 9.2 ± 3.43 Gy *vs.* 7.53 ± 2.56 Gy for 3DCRT, 13.85 ± 1.82 Gy *vs.* 12.74 ± 1.61 Gy for VMAT FB and 14.26 ± 1.97 Gy *vs.* 13.03 ± 1.68 Gy for VMAT FFFB as compared to NB scan. Similarly, DIBH scan reduced the heart mean dose: 4.38 ± 1.30 Gy *vs.* 2.24 ± 1.06 Gy (for 3DCRT), 9.00 ± 2.05 Gy *vs.* 7.01 ± 1.32 Gy (VMAT FB plan) and 9.6 ± 2.27 Gy *vs.* 7.42 ± 1.59 Gy for VMAT FFFB as compared to the NB scan.

Kim et al.[19] compared the 3DCRT, IMRT and VMAT treatment plans for 10 synchronous bilateral breast cancer (SBBC) patients. The MU of 3DCRT, IMRT and VMAT plans were 458 MU, 1194 MU and 1205 MU, the delivery time was 55 secs, 764 secs and 389 secs. The 3DCRT, IMRT and VMAT plans generated the liver mean doses of 4.66 Gy, 5.83 Gy and 8.10 Gy, respectively. Similarly the heart mean doses were 8.18 Gy, 9.46Gy and 14.47 Gy, respectively. In our study the NB scan plan gave the maximum MU, the values were 478 MU, 1366 MU and 1853 MU in 3DCRT, VMAT FB and FFFB plans, respectively. The corresponding beam ON time was 0.8 min, 3.1 min and 2.8 min, respectively.

In our study the VMAT FFFB needed 37% higher monitor units to achieve the plan goal; however, the FFF beam reduced the beam ON time by 10% in the FB scan plan and by 7% in the DIBH plan as compared to the VMAT FB plan. The reason being that the FFF beam profile is non-uniform, the dose is maximum at the center and decreases towards the periphery. The linear accelerator is calibrated (1 cGy = 1MU) at the central axis of the beam under reference condition (10 × 10cm^2 filed sized at dmax). The additional MU is required in the off axis part of the FFF beam to maintain the same dose away from the central axis.

Yeona Cho et al. [20] studied the synchronous bilateral breast cancer (SBCC) of 15 patients, single isocenter was used for the whole PTV, and two

240° arcs placed in the clockwise and clockwise direction, the VMAT plans produced the common lung mean dose, $V_{5\,Gy}$, $V_{10\,Gy}$ and $V_{20\,Gy}$ of 14.4Gy, 67.9%, 41.1% and 27.5%, respectively. The heart mean dose, $V_{25\,Gy}$, and $V_{30\,Gy}$ were 13.2 Gy, 11.5% and 6.4%, respectively. The CI and HI were 1.5 and 1.07. The treatment MU was 795 and beam on time was 115.3 secs.

In our study the CI of 3DCRT (1.63) was high compared to VMAT (1.05) in both NB and DIBH scans. The NB scan of all plans gives more MU (478 MU for 3DCRT, 1366 MU for VMAT FB and 1853 MU for VMAT FFFB) and the beam ON times were 0.8 min, 3.1 min and 2.8 minutes, respectively. In our earlier study [21] the VMAT plan of 6MV FB and FFF beam gave MU values of 1214 and 1638, the corresponding beam ON times were 3.0 minutes and 2.5 minutes, respectively. The heart mean dose was less than 10.8 Gy and $V_{25\,Gy}$ was 10.8%. The common lung mean dose was less than 15.8 Gy and $V_{20\,Gy}$ was 26.9%.

Gagliardi et al. [22] reported that less than 1% of cardiac moralities occur 15 years after completion of radiotherapy, with the dose to the heart limited to $V_{25\,Gy}$ < 10%. Sun et al. [23] reported that the single isocenter VMAT plan gave the common lung $V_{5\,Gy}$, $V_{10\,Gy}$, $V_{20\,Gy\%}$, $V_{30\,Gy}$,$V_{40\,Gy}$ and mean dose of 35%, 23.5% 15%, 10.3%, 7.4% and 8.95 Gy, respectively. Similarly, heart mean dose, $V_{5\,Gy}$, $V_{10\,Gy}$, $V_{20\,Gy\%}$, $V_{30\,Gy}$ and $V_{40\,Gy}$ were 4.85 Gy, 16.9%, 10.1%, 6.2%, 3.8% and 1.7%, respectively. The liver mean dose was 4.04 Gy and treatment MU was 987.

Gunel Haji et al. [24] compared in their study the NB *vs.* DIBH scan, in the right breast patients. The liver mean dose was reduced (5.59 ± 2.07 Gy *vs.* 2.54 ± 1.40 Gy). Rice et al. [25] also reported that the DIBH method reduced the liver mean dose to 2.6Gy in comparison to normal breath (4.8 Gy). Huang et al. [26] reported that fixed jaw IMRT plan gave the liver mean dose of 3.07 ± 1.23 Gy and 4.39 ± 1.25 Gy for partial VMAT. The prescription dose was 42.56 Gy delivered in 16 fractions. In our study DIBH plan reduced the liver mean dose of 48% in 3DCRT and 22% in VMAT as compared to the NB scan, the doses were 2.29 Gy *vs.* 1.33 Gy (3DCRT), 6.37 *vs.* 2.93Gy (VMAT FB) and 6.43 *vs.* 3.07 Gy for the VMAT FFFB plan.

Shaitelman et al. [27] noted grade 3 pneumonitis after radiotherapy for non-small cell lung cancer, the incidence rate was 2%, 4% and 24% of bilateral lung volumes receiving $V_{5\,Gy}$ < 35%, $V_{5\,Gy}$ = 35–50%, and $V_{5\,Gy}$ > 50%, respectively. In our analysis the DIBH scan plans reduced the V5Gy as compared to the NB scan (30.1% *vs.* 27.1% in 3DCRT, 91.5% *vs.* 84.5% in VMAT FB and 92.1% *vs.* 85.3% in VMAT FFFB plan, respectively). Graham et al. [28] reported that the common lung $V_{20\,Gy}$ is the predictor of pneumonitis severity. There was no grade 2 pneumonitis noted, when the common lung V20 ≤ 22% and V20 = 22–31%. Grade 3 pneumonitis was observed with $V_{20\,Gy}$ > 40%. In our study all plans generated for the common lung $V_{20\,Gy}$ was less than 18.4% noted in the DIBH scan and 20.4% in the FB scan. Grantzau et al. [29] observed the incidence of secondary lung cancer after 12 years from breast irradiation. The lung cancer risk was 8.5% per gray and 17.3% of smokers. To avoid this risk, advanced normal tissue sparing technique is needed.

Paddick et al. [10] proposed the dose gradient index (GI) to compare equal conformity plans and to measure the dose falloff outside the target. The lower isodose volume covers normal tissue, which is responsible for normal tissue complication. The recommended value of GI is less than 3 for the radiosurgery plan because of the steep dose falloff outside the target. In our analysis the GI was less than 2. In both NB and DIBH CT scans, 3DCRT (GI ≥ 1.4) plan gave higher dose fall in normal tissue compared to VMAT (GI ≥ 1.9).

American Society for Radiation Oncology (ASTRO-2018)[30] evidence-based guidelines reported that $V_{105\%}$ volume should be minimized to reduce the body toxicity for unilateral breast cancer. To avoid desquamation $V_{105\%}$ < 200 cc. In our study the volume received by 105% is less in the DIBH scan as compared to the FB scan plans, the values were 340 cc *vs.* 274 cc for 3DCRT, 131 cc *vs.* 109 cc for VMAT FB and 247 cc *vs.* 152 cc for VMAT FFFB plan, respectively.

AAPM TG 158 report [31] defined the in-field non-target dose, which is located near the field border and out-field non-target dose which is away from the field border due to irradiation of non-tumor tissue by treatment beams. The out-field dose was classified into the high dose region [> 50% of the prescription dose (> 30 Gy)], the intermediate dose region [≤ 5–50% of the prescription dose (3–30 Gy)] and low dose volume [≤ 5% of the prescription dose (3 Gy)].

In our study, DIBH scan reduced the out-field dose in 3DCRT and VMAT planning technique; however, the high dose (30–50 Gy) component in the body-PTV region is 25–80% higher in the 3DCRT technique as compared to VMAT in both NB/DIBH scans.

Conclusions

In our analysis 3DCRT and VMAT plans achieved the target coverage and OAR sparing in both NB and DIBH scans. However, a better OAR sparing is achieved in DIBH scan plans. This purely treatment planning study will be used as future reference for determining the best plan for bilateral breast patients under the DIBH technique.

Conflicts of interest

None declared.

Funding

None declared.

References

1. Kheirelseid EAH, Jumustafa H, Miller N, et al. Bilateral breast cancer: analysis of incidence, outcome, survival and disease characteristics. Breast Cancer Res Treat. 2011; 126(1): 131–140, doi: 10.1007/s10549-010-1057-y, indexed in Pubmed: 20665107.
2. Schubert LK, Gondi V, Sengbusch E, et al. Dosimetric comparison of left-sided whole breast irradiation with 3DCRT, forward-planned IMRT, inverse-planned IMRT, helical tomotherapy, and topotherapy. Radiother Oncol. 2011; 100(2): 241–246, doi: 10.1016/j.radonc.2011.01.004, indexed in Pubmed: 21316783.
3. Thilmann C, Zabel A, Kuhn S, et al. [Inversely planned intensity modulated radiotherapy for irradiation of a woman with breast cancer and funnel chest]. Strahlenther Onkol. 2002; 178(11): 637–643, doi: 10.1007/s00066-002-0955-2, indexed in Pubmed: 12426675.
4. Teoh M, Clark CH, Wood K, et al. Volumetric modulated arc therapy: a review of current literature and clinical use in practice. Br J Radiol. 2011; 84(1007): 967–996, doi: 10.1259/bjr/22373346, indexed in Pubmed: 22011829.
5. Otto K. Volumetric modulated arc therapy: IMRT in a single gantry arc. Med Phys. 2008; 35(1): 310–317, doi: 10.1118/1.2818738, indexed in Pubmed: 18293586.
6. Lind P, Wennberg B, Gagliardi G, et al. Pulmonary complications following different radiotherapy techniques for breast cancer, and the association to irradiated lung volume and dose. Breast Cancer Res Treat. 2001; 68(3): 199–210, doi: 10.1023/a:1012292019599, indexed in Pubmed: 11727957.
7. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013; 368(11): 987–998, doi: 10.1056/NEJMoa1209825, indexed in Pubmed: 23484825.
8. Tanguturi SK, Lyatskaya Y, Chen Y, et al. Prospective assessment of deep inspiration breath-hold using 3-dimensional surface tracking for irradiation of left-sided breast cancer. Pract Radiat Oncol. 2015; 5(6): 358–365, doi: 10.1016/j.prro.2015.06.002, indexed in Pubmed: 26231594.
9. Parkes MJ, Green S, Stevens AM, et al. Safely prolonging single breath-holds to >5 min in patients with cancer; feasibility and applications for radiotherapy. Br J Radiol. 2016; 89(1063): 20160194, doi: 10.1259/bjr.20160194, indexed in Pubmed: 27168468.
10. Parkes MJ, Green S, Kilby W, et al. The feasibility, safety and optimization of multiple prolonged breath-holds for radiotherapy. Radiother Oncol. 2019; 141: 296–303, doi: 10.1016/j.radonc.2019.06.014, indexed in Pubmed: 31540744.
11. Osman SOS, Hol S, Poortmans PM, et al. Volumetric modulated arc therapy and breath-hold in image-guided locoregional left-sided breast irradiation. Radiother Oncol. 2014; 112(1): 17–22, doi: 10.1016/j.radonc.2014.04.004, indexed in Pubmed: 24825176.
12. Georg D, Knöös T, McClean B. Current status and future perspective of flattening filter free photon beams. Med Phys. 2011; 38(3): 1280–1293, doi: 10.1118/1.3554643, indexed in Pubmed: 21520840.
13. Hodapp N. [The ICRU Report 83: prescribing, recording and reporting photon-beam intensity-modulated radiation therapy (IMRT)]. Strahlenther Onkol. 2012; 188(1): 97–99, doi: 10.1007/s00066-011-0015-x, indexed in Pubmed: 22234506.
14. Paddick I, Lippitz B. A simple dose gradient measurement tool to complement the conformity index. J Neurosurg. 2006; 105 Suppl: 194–201, doi: 10.3171/sup.2006.105.7.194, indexed in Pubmed: 18503356.
15. Kalef-Ezra J, Karantanas A, Tsekeris P. CT measurement of lung density. Acta Radiol. 1999; 40(3): 333–337, doi: 10.3109/02841859909175564, indexed in Pubmed: 10335975.
16. Rotstein S, Lax I, Svane G. Influence of radiation therapy on the lung-tissue in breast cancer patients: CT-assessed density changes and associated symptoms. Int J Radiat Oncol Biol Phys . 1990; 18(1): 173–180, doi: 10.1016/0360-3016(90)90281-n, indexed in Pubmed: 2298619.
17. Fogliata A, Nicolini G, Vanetti E, et al. The impact of photon dose calculation algorithms on expected dose distributions in lungs under different respiratory phases. Phys Med Biol. 2008; 53(9): 2375–2390, doi: 10.1088/0031-9155/53/9/011, indexed in Pubmed: 18421117.
18. Oechsner M, Düsberg M, Borm KJ, et al. Deep inspiration breath-hold for left-sided breast irradiation: Analysis of dose-mass histograms and the impact of lung expansion. Radiat Oncol. 2019; 14(1): 109, doi: 10.1186/s13014-019-1293-1, indexed in Pubmed: 31215458.
19. Kim SJ, Lee MiJo, Youn SM. Radiation therapy of synchronous bilateral breast carcinoma (SBBC) using multiple techniques. Med Dosim. 2018; 43(1): 55–68, doi: 10.1016/j.meddos.2017.08.003, indexed in Pubmed: 28988893.
20. Cho Y, Cho YJ, Chang WS, et al. Evaluation of optimal treatment planning for radiotherapy of synchronous bilateral breast cancer including regional lymph node irradiation. Radiat Oncol. 2019; 14(1): 56, doi: 10.1186/s13014-019-1257-5, indexed in Pubmed: 30935400.

21. Tamilarasu S, Saminathan M, Sharma SK, et al. Treatment Planning With Unflattened as Compared to Flattened Beams for Bilateral Carcinoma of the Breast. Asian Pac J Cancer Prev. 2017; 18(5): 1377–1381, doi: 10.22034/APJCP.2017.18.5.1377, indexed in Pubmed: 28612590.
22. Gagliardi G, Constine LS, Moiseenko V, et al. Radiation dose-volume effects in the heart. Int J Radiat Oncol Biol Phys. 2010; 76(3 Suppl): S77–S85, doi: 10.1016/j.ijrobp.2009.04.093, indexed in Pubmed: 20171522.
23. Sun T, Lin X, Tong Y, et al. Heart and Cardiac Substructure Dose Sparing in Synchronous Bilateral Breast Radiotherapy: A Dosimetric Study of Proton and Photon Radiation Therapy. Front Oncol. 2019; 9: 1456, doi: 10.3389/fonc.2019.01456, indexed in Pubmed: 31998635.
24. Haji G, Nabizade U, Kazimov K, et al. Liver dose reduction by deep inspiration breath hold technique in right-sided breast irradiation. Radiat Oncol J. 2019; 37(4): 254–258, doi: 10.3857/roj.2019.00206, indexed in Pubmed: 31918462.
25. Rice L, Harris S, Green MML, et al. Deep inspiration breath-hold (DIBH) technique applied in right breast radiotherapy to minimize liver radiation. BJR Case Rep. 2015; 1(2): 20150038, doi: 10.1259/bjrcr.20150038, indexed in Pubmed: 30363168.
26. Huang JH, Wu XX, Lin X, et al. Evaluation of fixed-jaw IMRT and tangential partial-VMAT radiotherapy plans for synchronous bilateral breast cancer irradiation based on a dosimetric study. J Appl Clin Med Phys. 2019; 20(9): 31–41, doi: 10.1002/acm2.12688, indexed in Pubmed: 31483573.
27. Shaitelman SF, Grills IS, Liang J, et al. A Comprehensive Dose-volume Analysis of Predictors of Pneumonitis and Esophagitis following Radiotherapy for Non–small Cell Lung Cancer (NSCLC). Int J Radiat Oncol Biol Phys. 2009; 75(3): S468, doi: 10.1016/j.ijrobp.2009.07.1068.
28. Graham M, Purdy J, Emami B, et al. Clinical dose–volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys . 1999; 45(2): 323–329, doi: 10.1016/s0360-3016(99)00183-2, indexed in Pubmed: 10487552.
29. Grantzau T, Thomsen MS, Væth M, et al. Risk of second primary lung cancer in women after radiotherapy for breast cancer. Radiother Oncol. 2014; 111(3): 366–373, doi: 10.1016/j.radonc.2014.05.004, indexed in Pubmed: 24909095.
30. Smith BD, Bellon JR, Blitzblau R, et al. Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Pract Radiat Oncol. 2018; 8(3): 145–152, doi: 10.1016/j.prro.2018.01.012, indexed in Pubmed: 29545124.
31. Kry SF, Bednarz B, Howell RM, et al. AAPM TG 158: Measurement and calculation of doses outside the treated volume from external-beam radiation therapy. Med Phys. 2017; 44(10): e391–e429, doi: 10.1002/mp.12462, indexed in Pubmed: 28688159.