RESEARCH ARTICLE

Feasibility Study of Deep Inspiration Breath-Hold Based Volumetric Modulated Arc Therapy for Locally Advanced Left Sided Breast Cancer Patients

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Abstract

Background: The purpose of this study was to assess the feasibility of deep inspiration breath-hold (DIBH) based volumetric modulated arc therapy (VMAT) for locally advanced left sided breast cancer patients undergoing radical mastectomy. DIBH immobilizes the tumor bed providing dosimetric benefits over free breathing (FB). Materials and Methods: Ten left sided post mastectomy patients were immobilized in a supine position with both the arms lifted above the head on a hemi-body vaclock. Two thermoplastic masks were prepared for each patient, one for normal free breathing and a second made with breath-hold to maintain reproducibility. DIBH CT scans were performed in the prospective mode of the Varian real time position management (RPM) system. The planning target volume (PTV) included the left chest wall and supraclavicular nodes and PTV prescription dose was 5000cGy in 25 fractions. DIBH-3DCRT planning was performed with the single iso-centre technique using a 6MV photon beam and the field-in-field technique. VMAT plans for FB and DIBH contained two partial arcs (179°-300°CCW/CW). Dose volume histograms of PTV and OAR's were analyzed for DIBH-VMAT, FB-VMAT and DIBH-3DCRT. In DIBH mode daily orthogonal (0° and 90°) KV images were taken to determine the setup variability and weekly twice CBCT to verify gating threshold level reproducibility. Results: DIBH-VMAT reduced the lung and heart dose compared to FB-VMAT, while maintaining similar PTV coverage. The mean heart $V_{_{30Gv}}$ was 2.3% ±2.7, 5.1% ±3.2 and 3.3% ±7.2 and for left lung V_{20G_V} was 18.57% ±2.9, 21.7% ±3.9 and 23.5% ±5.1 for DIBH-VMAT, FB-VMAT and DIBH-3DCRT respectively. Conclusions: DIBH-VMAT significantly reduced the heart and lung dose for left side chest wall patients compared to FB-VMAT. PTV conformity index, homogeneity index, ipsilateral lung dose and heart dose were better for DIBH-VMAT compared to DIBH-3DCRT. However, contralateral lung and breast volumes exposed to low doses were increased with DIBH-VMAT.

Keywords: Left chest wall - volumetric modulated arc therapy - deep inspiration breath-hold - 3D-CRT

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Introduction

Breast cancer is the most common of all cancers and is the leading cause of cancer deaths in women worldwide. Breast cancer can be treated using a multimodality approach of surgery, chemotherapy, radiotherapy and targeted therapy. The treatment options vary as per the stage of the tumor. The most adopted treatment method for breast cancer patients is breast conservation surgery (BCS), or mastectomy followed by adjuvant radiotherapy. Adjuvant radiotherapy improves local control and improves overall survival (Darby et al., 2011). Large prospective trials and a meta-analysis have shown that adjuvant radiotherapy of the chest wall improves local control and survival in node positive breast cancer patients after mastectomy (Rudat et al., 2011). Many studies have shown a decrease in recurrence using postoperative radiotherapy for breast cancer. The adjuvant radiotherapy of the left chest wall is commonly delivered by three dimensional conformal radiotherapy (3DCRT) with fieldin-field technique (Rahbi et al., 2012). Mcgale et al. (2011) have shown that increased cardiac morbidity and mortality in patients treated with radiotherapy for left-sided breast cancer compared to right-sided, due to the higher cardiac dose for the left-sided patients. This cardiac complication can decrease by reducing dose to the heart, which can be achieved by using deep inspiration breath-hold technique (DIBH) (Prabhkar et al., 2007) and intensity modulated radiotherapy (IMRT) (Mansouri et al., 2014).

DIBH in left chest wall patients increase the distance between left tumor bed and heart. The other advantage of DIBH is that as the tumour bed is immobilized, planning target volume (PTV) margins can be reduced. Korreman et al. (2005) have shown DIBH can substantially reduce

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cardio and pulmonary radiation dose compared to free breathing (FB). Literatures have shown that intensity modulated radiotherapy (IMRT) decreases the high dose to heart and ipsilateral lung for left breast patients compared to 3DCRT (Rudat et al., 2011; Mansouri et al., 2014). In FB motion artifacts and interplay between motion of the leaves of a multi leaf collimator (MLC) degrades the effectiveness of IMRT (Keall et al., 2006). The treatment delivery time of IMRT is often much longer than that 3DCRT treatment. One concern with DBIH-IMRT is that the added time due to DIBH will make the beam delivery time too long. Volumetric modulated arc therapy (VMAT) is a technique which will provide the benefit of IMRT and at the same time it will reduce the treatment time. VMAT-RapidArc (Varian Medical Systems, Palo Alto, CA, USA) belong to rotational IMRT family and there are several literature have shown VMAT can produced dose distribution similar and/or superior to fixed field IMRT. VMAT produces highly conformal dose distribution by simultaneously changing MLC position, dose rate and gantry speed during patient treatment (Subramanian et al., 2012). The most important advantage of VMAT over fixed field IMRT was substantial reduction in treatment time. Very few literatures have investigated the potential of using VMAT technique on breast irradiation (Qiu et al., 2010; Subramanian et al., 2012). In the treatment of left sided chest wall patients, VMAT treatment improves target coverage, homogeneity index and reduces high dose in ipsilateral lung and heart, but increases low dose region for contra lateral organs compared to 3DCRT (Osman et al., 2014). In FB-VMAT, respiratory induced motion can result in substantial intra-fractional dosimetric variation during delivery. DIBH immobilizes the tumor bed and provides superior dosimetric benefits over FB. In this study we have assessed the feasibility of deep inspiration breath-hold in volumetric modulated arc therapy for locally advanced left side breast (chest wall) patients by comparing dose volume histogram (DVH) of DIBH-VMAT with FB-VMAT and DIBH-3DCRT.

Materials and Methods

Image acquisition

Ten locally advanced left-sided breast cancer (stage III) patients who underwent radical mastectomy were chosen for this study. These patients immobilized in supine position with both the arms lifted above head on a hemi-body vaclock. Two thermoplastic masks were prepared for each patient, one for normal free breathing and second mask was made with breath-hold to maintain reproducibility (Figure 1). 3mm slice thicknesses of FB and DIBH CT scans were taken on a Biograph 16 Slice PET-CT scanner (Siemens Medical Systems Concord, CA). DIBH CT scan was performed in prospective mode (amplitude) of Real time position management (RPM) sytem (Varian Medical Systems, Palo Alto, CA, USA). It consists of a six dot marker block, an infrared (IR) light ring that emits IR light, a charge-coupled detector (CCD) as a tracking camera used to visualize the relative position of the block, and a workstation that displays and records the motion data as a waveform. The six dot markers box

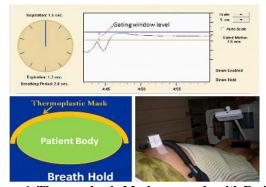


Figure 1. Thermoplastic Mask was made with Patient in Breath-Hold Position. With the help of mask, patients were able to hold breath in predefined gating window level. This gating window level determines the radiation beam to be on (or acquire CT image) only during a pre-specified part of the respiratory cycle

will be placed on the patient's anterior abdominal surface. The six reflecting dots allow the reconstruction of the 3D movements induced by the respiration cycle. In this method, motion of the block was considered as a surrogate for respiratory-induced tumor motion. The gating window can be set either in amplitude based or phase based in the desired portion of the respiratory cycle. This gating window level (Figure 1) determines the radiation beam to on (or acquire CT image) only during a pre-specified part of the respiratory cycle.

Contouring

After CT scan, the DICOM images were transferred to Eclipse treatment planning system (V8.9) (Varian Medical Systems, Palo Alto, CA, USA). Target delineation was performed based Radiation Therapy Oncology Group (RTOG) guidelines. Clinical target volume (CTV) includes left chest wall and supraclavicular nodes. The (PTV) margins were defined according to guidelines of international commission on radiation units and measurement (ICRU) reports 83. A margin of 5-7mm was given from CTV to PTV to account for variation of tumor position due to daily set up and breathing movement. OAR's lungs, contra lateral breast, spinal cord and heart were contoured. Contouring was done by same physician to avoid inter observer variation.

3DCRT planning

In our institute, if the patient is capable of holding the breath for more than 15 seconds, DIBH based 3DCRT is a standard technique for left sided chest wall/ breast patients. PTV prescription dose was 5000cGy in 25 fractions. 3DCRT planning was performed in single iso-centre technique using 6MV photon beam. Two tangential beams for chest wall and single anterior field for supraclavicular nodes. Gantry angles ranged from 300° to 335° for the medial fields and from 120° to 155° for the lateral fields. For anterior field the gantry was rotated laterally by 10 degrees in order to avoid the spinal cord and the esophagus. Field-in-field technique with multi leaf collimators were used to produced adequate dose coverage (95% of the prescribed dose) for target volume while minimize the global hot spot less than 110%. The beam angles and field weights were chosen to optimize coverage of the PTV, while minimizing exposure to the left lung, heart and right breast.

VMAT planning

VMAT treatment planning was performed using 6 MV photon beam in Eclipse TPS (V8.9). Plan contains two partial arcs ranging from 179° to 300° in clock wise and counters clock wise direction. VMAT plan were optimized using Progressive Resolution Optimizer-II (PRO) and final dose calculations were performed using Analytical Anisotropic Algorithm (AAA) with 2.5 mm grid size resolution. Treatment planning was performed to achieve at least 95% of PTV volume (D95) receives 100% of prescription dose (50Gy) and with 2% of PTV volume (D2) receives less than 107% of prescribed dose. Planning and Optimization parameters were kept identical for FB and DIBH.

DVH comparison

Dose volume histogram (DVH) of DIBH-VMAT was compared with FB-VMAT and DIBH-3DCRT. In particular, fractions of PTV or OAR volumes receiving at least a certain dose level (V_{xGy}) or doses computed to at least given volume fractions $(D_{x\%})$ were analyzed. Conformity index (C.I) and homogeneity index (H.I) were compared for PTV. The C.I is defined as the ratio between prescribed dose volume and PTV volume. The H.I is defined as the ratio between dose receiving 2% volume (D $_{2\%})$ and 98% volume (D $_{98\%}).$ For organs at risk, left lung mean dose, $V_{\rm 20Gy}$ and $V_{\rm 10Gy}^{\rm N}$, and for heart maximum dose, $D_{1\%}$, mean dose and V_{20Gy} were compared. For contralateral organs, right breast and right lung mean dose were analyzed. Statistical analyses were performed using the Student's t-test (paired, two-tailed). Differences were considered to be significant for p-value <0.05.

Treatment delivery

Eight patients were treated with DIBH-3DCRT and two patients were treated DIBH-VMAT. Treatment were performed using 6 MV photon beam from dual energy Clinac-iX (Varian Medical Systems, Palo Alto, USA). The machine was equipped with millennium 120 multileaf collimator, on-board imager and maximum dose rate of 600 MU/min. After patient alignment in machine, the gated treatment starts with breath coaching with the help of RPM system. The treatment was delivered at same portion of patient respiratory cycle (gating window), which was kept as reference during image acquisition in CT scan. Therapists were instructed to closely monitor the RPM signal, if the patient breath-hold portion was outside gating window level the treatment should be interrupted. Before the treatment delivery, daily orthogonal (0° and 90°) kilo-volt (KV) images were taken in DIBH mode to know the setup variability and weekly twice cone beam computed tomography (CBCT). In-vivo measurements were performed for the above ten patients using photon field diode (IBA Dosimetry, Schwarzenbruck, Germany) placed over the skin and below the thermoplastic masks. Pretreatment quality assurances (QA) of two VMAT plans were performed using COMPASS 3D dosimetry (V2.0)

(IBA Dosimetry, Schwarzenbruck). This system consists of a gantry angle sensor and MatriXX^{Evolution}. Both were mounted on the gantry using collimator mount to measure fluence. COMPASS reconstructs dose from measured fluence, compares the patient plan with measurements, and provides delivered 3D dose distribution inside the patient's CT scan. The 3D gamma evaluation has performed between Eclipse TPS calculated and COMPASS measured. Average global 3D gamma for PTV and OAR's was calculated using criteria of 3mm distance to agreement (DTA) and 3% dose difference (DD).

Results

For all ten patients DIBH treatments were successfully delivered without any major specific technical or clinical issues. Figure 2 and 3 shows KV-KV orthogonal and CBCT images of a patient taken in DIBH mode before treatment delivery. The ribs and vertebra in breath-hold KV images were used for daily patient position verification (Figure 2). CBCT provides better information about gating threshold level reproducibility, where we observe the surface matching of body as well as lung (Figure 3). Regarding patient positioning, the average vertical, longitudinal and lateral setup error of 10 patients over 225 fractions were ± 1.5 mm (S.D ± 1.4), ± 2.4 mm (S.D ± 2.2) and ± 2.5 mm (S.D ± 2.2) respectively. Table 1 shows the in-vivo dosimetry results for ten patient's using photon field diode. To assess the VMAT delivery quality in pretreatment QA context, VMAT plans along with patient's CT scan, structure set and 3D dose planes were exported to COMPASS in DICOM RT format. The COMPASS uses the measured data and the imported plan file to calculate the dose in the imported patient CT-data using a collapsed cone superposition algorithm. For two VMAT plans, the average 3D gamma between TPS calculated and COMPASS measured for PTV, left lung and heart were less than 0.6, recommend by Visser et al. (2013).

For dosimetric analysis, DVH parameters of PTV and OAR's from DIBH-VMAT was compared with FB-VMAT and DIBH-3DCRT. Figure 4 shows 30Gy isodose distribution for DIBH-VMAT, FB-VMAT and DIBH-3DCRT, DIBH scan shows an increase in distance between chest wall and heart. Due to this distance 30Gy isodose coverage in heart was significantly reduced compared to FB. Table 2 compares DVH parameters of DIBH-VMAT,

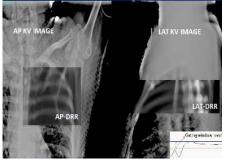


Figure 2. Online Matching of 2D-2D Orthogonal KV Image from OBI with DRR Image from TPS (Inside Box). The ribs and vertebra in breath-hold KV images were used for daily patient position verification



Figure 3. Registration of the Cone-Beam CT (inside Box) with Planning CT Scan for Online Setup Verification. CBCT provides better information about gating threshold level reproducibility, where we can observe the surface matching of body and as well as lung

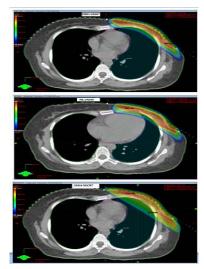


Figure 4. 30Gy Isodose Distributions in the Same Transversal CT-slice for DIBH-VMAT, FB-VMAT and DIBH- 3DCRT. Due to increase in distance between left chest wall and heart, 30Gy isodose coverage in heart was significantly reduced in DIBH-VMAT and DIBH-3DCRT compared to FB-VMAT

Table 1. *In vivo* Dose Measurement using Photon Field Diode (PFD) Placed Over the Skin and Below the Thermoplastic Masks for Ten Left Sided Chest Wall Patients

Pt. ID	Eclipse TPS dose (cGy)	PFD measured dose (cGy)	% variation	
1	202.3	193.6	4.3	
2	201.2	195.9	2.6	
3	199.4	191.4	4.0	
4	195.6	199.1	-1.8	
5	198.4	194.6	1.9	
6	191.2*	185.3	3.1	
7	189.5	193.5	-2.1	
8	199.1	196.7	1.2	
9	200.4*	196.3	2.0	
10	196.7	201.4	-2.4	
Mean			±2.6	

*Two patients treated with DIBH-VMAT plans and other eight patients were DIBH-3DCRT plans

FB-VMAT and DIBH-3DCRT. All values were averaged over ten patients. The mean left lung volume was 1375 cm3 \pm 169 during DIBH whereas in FB it was 781 cm3 \pm 137. On average there is 76% increase in left lung volume for DIBH compared to FB.

 Table 2. Average Dose Volume Histogram Parameters

 of DIBH-VMAT, FB-VMAT and DIBH-3DCRT of Ten

 Locally Advanced Left Sided Chest Wall Patients

Organ parameter	DIBH-VMAT		FB-V	FB-VMAT		DIBH-3DCRT	
	Mean	SD	Mean	SD	Mean	SD	
PTV							
Conformity index	1.07	0.10	1.05	0.06	1.50	0.17	
Homogeneity index	1.13	0.04	1.08	0.07	1.29	0.10	
Heart							
Maximum dose (cG	y) 4344	548	4927	320	4807	396	
D _{1%} (cGy)	3305	738	4160	544	3559	1556	
Mean dose (cGy)	992	208	1197	293	531	305	
V _{30Gy} (%)	2.32	2.7	5.05	3.2	3.27	7.23	
Left lung							
Mean dose (cGy)	1168	159	1302	161	1307	186	
V _{20Gy} (%)	18.6	2.9	21.7	3.9	23.5	4.5	
V_{10Gy}^{200y} (%)	33.7	7.7	37.0	6.8	29.9	5.1	
Right lung mean do	se (cGy)						
	436	70	535	81	35	21	
Right breast mean d	ose (cGy	()					
-	564	117	566	111	103	35	

*DIBH: deep inspiration breath-hold; VMAT: volumetric modulated arc therapy; 3DCRTthree dimensional conformal radiotherapy; SD: standard deviation; D_{rg} ; dose to 1% of the volume; V_{30Gp} , V_{30Gp} , V_{30Gp} , D_{0Gp} ; percentage of volume receiving more than 30Gy, 20Gy and IOGy respectively

DIBH-VMAT vs FB-VMAT

In PTV, there was no much appreciable difference in C.I and H.I, p-value were 0.5932 and 0.0655 respectively. For heart, doses were reduced in DIBH compared to FB, the p-value for maximum dose, $D_{1\%}$, mean dose and V_{30Gy} were 0.0062, 0.0004, 0.0059 and 0.0008 respectively. Concerning left lung, doses were reduced in DIBH compared to FB, the p-value for mean dose, V_{20Gy} and V_{10Gy} , were 0.0002, 0.0006 and 0.0014 respectively. The difference between DIBH and FB was considered to be very statistically significant. Due to increase in lung volume the right lung mean dose was less in DIBH compared to FB (p=0.0032). For right breast, there was no appreciable dose difference between two plans (p=0.8849).

DIBH-VMAT vs DIBH-3DCRT

For PTV, VMAT significantly improved the C.I (p<0.0001) and H.I (p=0.0007) compared to 3DCRT. For heart, maximum doses were reduced in VMAT compared to 3DCRT (p=0.003). On other hand the heart mean dose were significantly increased in VMAT (p<0.0001). The $D_{1\%}$ (p=0.5379) and V_{30Gy} (p=0.0585) were less in VMAT compared to 3DCRT, but not statistically significant. The left lungs V_{20Gy} was improved with VMAT (p=0.0004). There was no statistical difference in left lung mean dose (p=0.0661) and V_{10Gy} (p=0.0842). The mean dose of right lung and right breast were significantly increased in VMAT compared to 3DCRT (p<0.0001).

Discussion

Many studies have shown benefits of DIBH in left breast patients using tangential beams (3DCRT), especially in minimizing the cardiac complications. Few studies have demonstrated a dosimetric benefit of FB-IMRT compared to FB-3DCRT for breast patients. IMRT plans shows better PTV coverage and reduction

of high dose to ipsilateral lung and heart. This study was undertaken to appraise the benefit of DIBH based VMAT for locally advanced left sided chest wall patients (stage III). Eight patients were treated with DIBH-3DCRT and two patients treated with DIBH-VMAT technique. DIBH-3DCRT with field-in-technique produced satisfactory dose distribution for eight patients. However in two patients, due to complex shape of PTV, 3DCRT plan was not able to achieve planning objective. Patient treatment setup errors were in normal clinical acceptable range and it's similar to group of free breathing patients. On average the setup errors were within ±3mm in all three directions (lateral, longitudinal and vertical) and the values were correlating with similar studies (Nakamura et al., 2007; Brost et al., 2010). All patients were treated with mask prepared in DIBH, this mask help the patient to achieve reproducibility in the breath-hold position, which may in turn reduce the respiration related uncertainty of the location of the target. All patients hold breath for 15-25 seconds. Just before the acquisition of the planning CT scan or treatment, the DIBH threshold reproducibility was checked by a dedicated technician with help of RPM system. The delivery of each field for 3DCRT was achieved with single uninterrupted breath-hold, whereas for VMAT, delivery of each arc was achieved with two interruptions. However for CBCT acquisition (364°) 4-5 interruptions were required. During treatment skin coloring was observed for all patients. Nine patients had uniform cosmetic change in skin and one patient had grade two skin reactions. In-vivo dosimetry is the most direct method for monitoring the dose delivered to the patient receiving radiation therapy. Our in-vivo dosimetry results were lesser than AAPM (TG-62) recommend value of ±5% (Vasile et al., 2012). The clinical follow-up available for the ten patients presented here was too short to derive indications on long term toxicity or local recurrences, but it is adequate to outlook early complications occurring within the first months after treatment (as for radiation pneumonitis which have an onset time of typically less than 6 months). With a mean follow-up of about 6 months, no pulmonary and cardiac complications were observed.

Data on the effect of VMAT of the chest wall in postmastectomy breast cancer patients are scarce in literature and as VMAT is a form of rotational IMRT, dosimetric parameters were analyzed with previous IMRT studies. In 3DCRT, numerous studies have compared FB and DIBH and proved that DIBH significantly reduces the dose to lung and heart without compromising the PTV coverage. Thus in this study FB-3DCRT was not included for comparison. Few studies have shown an increased cardiac morbidity and mortality in patients treated with radiotherapy for left-sided breast cancer compared to right-sided (Darby et al., 2011; Mcgale et al., 2011), it was also found that the probability of excess cardiac mortality increased with the relative heart volumes irradiated. DIBH have been used to reduce cardiac and pulmonary doses. Stranzl et al. (2008) reported a significant heart dose reduction using DIBH technique for 22 left-sided breast cancer patients. Korreman et al, (2005) have shown, the DIBH substantially reduced cardiac doses simultaneous with significant pulmonary tissue sparing for nine left sided breast patients. Our study shows, DIBH-VMAT compared to FB-VMAT significantly reduces the lung dose and heart dose (p<0.05).

Sharon et al. (2011) have shown that, DIBH-IMRT reduces the maximum dose to the heart, as well as the fraction of the heart volume receiving 30Gy but it increased the mean dose as compared to DIBH-3DCRT plans. Similar results were observed in our study, on average DIBH-VMAT reduced the heart maximum dose, $D_{_{1\%}}$ and $V_{_{30Gv}}$ by 9.6%, 7.1% and 29% respectively compared to DIBH-3DCRT, on other hand VMAT increases the mean heart dose by an average of 86%. In all three plans the mean left lung V_{20Gv} was lower than 22% The probability of developing Grade 2 radiation pneumonitis was low for patients who had less than 22% of normal lung volume irradiated with more than 20Gy (Tsai et al., 2012). Gagliardi et al. (2010) reported that coronary artery disease risk was much reduced at volume heart receiving doses less than 30Gy. In our study the mean values of heart V_{30Gv} were 2.32%, 5.05% and 3.27% for DIBH-VMAT, FB-VMAT and DIBH-3DCRT respectively; compared to studies reporting V_{30Gv} values in the range of 0.3% to 5%. Mansouri et al. (2014) have shown, FB-IMRT reduces the ipsilateral lung dose-volume (V_{20Gv}) and heart dose-volume (V_{30Gv}) by 32% and 43% respectively compared to FB-3DCRT for left sided whole breast patients. Our study shows, DIBH-VMAT plans reduces left lung (ipsilateral) V_{20Gv} and heart V_{30Gy} by 21% and 29% respectively compared DIBH-3DCRT plans. Rudart et al. (2011); Mansour et al. (2014) and Remoachamps et al. (2003) have shown that IMRT substantially reduces the cardiac dose compared to 3DCRT, but these results were for normal breathing. In our study we observe that was there is no statistical difference (p>0.05) in heart dose parameters between DIBH-VMAT and DIBH-3DCRT plans, this may due to deep inspiration breath-hold technique. DIBH-VMAT technique in this study demonstrates promising results with respect to improved target coverage and high dose avoidance in left lung and heart. Meanwhile, there was an increased volume of right lung and right breast exposed to low doses (5Gy) in the VMAT plans. The low dose bath was usually greater in these advanced techniques (VMAT) as a result of multiple beam directions passing through regions outside the PTV. Problem of low dose volume in contralateral breast and lung is still unknown for potential risk of secondary cancers.

In conclusion, significant dose-sparing to the heart and lung can be achieved using DIBH without compromising the target coverage. As a result of this dose sparing, the cardiac and pulmonary complication probability can be reduced. DIBH-VMAT provides better target coverage and reduces the high doses to heart and left lung as compared to DIBH-3DCRT. However, right lung and right breast volumes exposed to low doses were increased with VMAT and will need to be reviewed in future studies.

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