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Voluntary breath-hold reduces dose to organs at risk in radiotherapy of left-sided breast cancer☆

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ABSTRACT

Aim: To compare the dose to organs at risk with free breathing (FB) or voluntary breath-hold (VBH) during radiotherapy of patients with left sided breast cancer.
Background: Radiotherapy reduces the risk of breast-cancer-specific mortality but the effects on other organs increase non-cancer-specific mortality. Radiation exposure to the heart, in particular in patients with left sided breast cancer, can be reduced by breath hold methods that increase the distance between the heart and the radiation field.
Materials and Methods: Three-dimensional conformal radiotherapy (3D-CRT) dose plans for the left breast and organs at risk including the heart, left anterior descending coronary artery (LAD) and ipsilateral lung were compared with FB and VBH in ten patients with left sided breast cancer.
Results: The mean doses to the heart and LAD were reduced by 50.4 % ($p < 0.001$) and 58.8 % ($p = 0.006$), respectively, in VBH relative to FB. The mean dose to the ipsilateral lung was reduced by 13.8 % ($p = 0.11$) in VBH relative to FB. The planning target volume (PTV) coverage was at least 95 % in both FB and VBH ($p = 0.78$).
Conclusion: The VBH technique significantly reduces the dose to organs at risk in 3D-CRT treatment plans of left sided breast cancer.

1. Introduction

The Early Breast Cancer Trialists' Collaborative Group reported that radiotherapy reduces the absolute risk of breast cancer mortality in selected patients with early breast cancer.[1]

However, the treatment usually involves incidental radiation to the heart and lungs that may increase the risk of future heart disease and lung cancer increasing the risk of mortality for patients with left sided breast cancer that begins within a few years of exposure and continues for at least 20 years when compared to right breast radiation.[2]

Whole breast radiation following conservative surgery has been a standard of treatment for decades, with similar results to mastectomy. The technique uses two opposing tangential fields to uniformly treat the entire breast. Careful dosimetric planning spares organs at risk, such as the heart, LAD and lungs. Over time, the risk of radiation-induced heart disease has been recognised as the cause of a 1 % increase in non-cancer related deaths.[3] Recent imaging studies have shown consistent perfusion defects; micro-vascular disease, stenosis and atherosclerosis in the heart and arteries that were included in the radiation fields.[4] Therefore, sparing techniques are justified.

Various solutions have been developed to modify dose delivery to organs at risk in these patients. The use of multileaf collimators (MLC) and intensity-modulated radiotherapy (IMRT) can potentially reduce the cardiac dose; however, MLC may shield the breast tissue preventing adequate treatment and IMRT may increase low dose radiation to healthy tissue depending on the parameters established in the planning process. Proton therapy, although promising, is unavailable in many parts of the world due to high cost and logistic difficulties.

Another solution is breath holding during dose delivery as it reduces radiation exposure to the heart by increasing the distance between the thoracic wall and the heart.[5] The risk of cardiac-related death is decreased by reducing the volume of cardiac tissue in the

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radiation field and the dose to the LAD.[6] Breath holding protects the heart without increasing treatment time per session, which is routinely less than 20 min.

There are various techniques available for breath holding. Most require additional equipment to the standard linear accelerator, such as the Active Breathing Coordinator (ABC, Elekta, Stockholm, Sweden), where automated gated breath-hold treatments can be delivered by means of a spirometer that monitors airflow throughout the respiratory cycle. A predetermined volume cut-off causes the patient to hold breath to maintain this volume.

Another approach is Real-time Position Management™ (RPM) Respiratory Gating (Varian® Medical Systems Inc., Palo Alto, CA). Using an infrared camera and a reflective marker placed on the patient's thorax to track the rise and fall of the chest wall during breathing. The gating thresholds are set when the target volume reaches the desired portion of the respiratory cycle. These techniques, however, are not widely utilised in spite of their cardiac sparing benefits, likely due to the need for specialised equipment, such as the reflective marker with attendant capital investment together with on-going costs, such as disposable mouthpieces.[4,7,8]

A less sophisticated and cheaper alternative is the voluntary breath hold (VBH) technique in which the patient holds breath for about 20 s while the beam is on. Voluntary inspiration is monitored visually by the light field or by laser alignment with reference marks on the skin. This technique compares favourably to the others in terms of reproducibility and reduction of cardiac dose.[4,8,9]

The objective of this study was to compare the dose to the heart and other organs at risk in patients with left sided breast cancer treated with tangential fields with either FB or VBH.

2. Materials and methods

Twenty treatment plans compared CT scans acquired with FB and VBH in 10 patients with left sided breast cancer treated with 50 Gy to the whole breast. The radiation dose delivered to the ipsilateral lung (V10, V20, V30, Dmean, Dmin, Dmax), heart (Dmean, Dmax, V5, V25), LAD (D2 %, Dmean, Dmax), and the planning treatment volume (D2, V98, V95) were documented.

2.1. Patient selection

Patients with left sided breast cancer were selected if they had undergone conservative surgery with no axillary lymph node involvement and were able to hold their breath for 20 s. CT images were acquired in accordance with our treatment protocol from the lower jaw as the upper limit, to one vertebra below the inferior limit of the tangential field in scout view. Acquisition time is approximately 20 s, although it may vary according to patient height. All patients signed a letter of informed consent.

2.2. CT simulation

Patients were placed in a supine position on a 15° breast board with both arms extended and holding fastening bars (AIO Breast and lung board solution, Orfit Industries NV, Belgium). Patients were aligned using three positioning lasers. CT markers were placed on the patient's midline in free breathing, approximately half way along the limits of the tangential fields. The lateral markers were added to each side of the patient in FB in line with the midline marker. The anterior and lateral marks were placed in relation to the lasers in breath-hold and the height of the lateral mark above the couch top recorded before proceeding with the CT scan.[9] Two sequential CT scans were acquired on a GE Optima (CT580 RT, GE Healthcare), according to the RT Breast protocol that includes rotation time 1.0 s, 2.5 mm slice thicknesses, 120 kV and automA during FB and VBH. During VBH the reference marks were placed as in FB.

2.3. Contouring of treatment volumes and organs at risk

The planning target volume (PTV) was the CTV with a 5 mm margin up to the midline and cropped 5 mm beneath the skin surface. The clinical target volume (CTV) of the whole breast with FB and VBH was contoured by the radiation oncologist on the CT scans following the RTOG (Radiation Therapy Oncology Group) atlas.[10] Organs at risk, such as the heart, LAD, left lung and spinal cord were also contoured by the radiation oncologist in the FB and VBH mode. When required the LAD was contoured by the radiologist. The heart was contoured using the cardiac atlas published by Duane et al.[11]

2.4. Treatment planning

The images acquired during breath hold were used for treatment planning and for daily treatment verification. One of the treatment objectives was to achieve the coverage of at least 95 % of the PTV with 95 % of the prescription dose (V95 %>95 %). The doses to the heart, LAD and ipsilateral lung were recorded and compared in the FB and VBH plans. 3D-CRT dose planning was done on Eclipse, (Varian Medical Systems (Palo Alto, CA) planning software using the Analytical Anisotropic Algorithm (AAA) version 11. The prescription dose was 50 Gy in 25 daily fractions of 2 Gy. Two opposing tangential fields were used and complemented if a better dosimetric plan was achieved with 3 or 4 low weighted sub fields. The beam quality of the main fields was 6 MV and the sub fields reached 18 MV. All cases received a boost of 15 Gy to the surgical bed using an electron beam of 6 to 9 MeV.

2.5. Initial patient positioning and daily treatment

The patient was positioned in the linear accelerator with the lasers aligned to the inspiration tattoos. From the control room the patient was instructed to breathe in and hold and this was continuously verified on the cameras. The real-time portal verification image was acquired. The digitally reconstructed images were co-registered with the simulation VBH images. The table was adjusted as required from the plan and the patient was instructed to breathe in and under continuous verification by the cameras, the treatment was delivered assuring that it did not exceed 20 s. In the case of subfields, the patient was asked to rest for a few seconds before resuming treatment.

2.6. Statistical analyses

Twenty dose volume histograms (DVH) from the FB and VBH treatment plans of ten patients were compared with paired T-tests using SPSS version 22. The variables analysed were the mean dose (Dmean) and maximum (Dmax) to the heart, the D2 %, Dmean and Dmax to the LAD, the V10, V20, V30, Dmean, Dmax and dose minimum (Dmin) to the ipsilateral lung, and the D2 %, D98 % and V95 of the PTV.

3. Results

The dose to organs at risk and the PTV for the FB and VBH treatment plans are shown in Table 1. All treatment plans satisfied the coverage criteria of the PTV with 96.9 % and 97.1 % mean dose coverage in the FB and VBH plans, respectively. All of the organs at risk showed a reduced dose in VBH relative to FB. The Dmin of the ipsilateral lung showed a significant reduction of 49.1 % ($p < 0.001$). The mean (min-max) volumes of the lungs were 1141 cc (790–1484) in FB and 1964 cc (1595–2378) in VBH ($p < 0.001$). The mean doses to

Table 1
Dosimetry summary for 50 Gy prescription dose in 10 patients during free breathing (FB) or voluntary breath hold (VBH).

	FB			VBH					
	Mean	Min	Max	Mean	Min	Max	% reduction	p	
Heart	V5 Gy (%)	9.1	3.9	21.2	2.5	0.0	7.7	72.0	<0.001
	V25 Gy (%)	3.2	0.8	8.7	0.3	0.0	1.5	91.5	0.003
	Dmean (Gy)	3.3	1.7	5.8	1.6	1.2	2.6	50.4	<0.001
	Dmax (Gy)	51.7	46.8	55.4	32.4	4.8	51.0	37.3	0.004
LAD	D2 % (Gy)	43.2	9.5	54.3	19.3	3.8	50.7	55.4	0.003
	Dmean (Gy)	15.6	4.1	27.7	6.4	2.2	21.2	58.8	0.006
	Dmax (Gy)	46.4	11.9	54.9	23.1	4.1	51.6	50.3	0.003
Ipsilateral lung	V30 (%)	12.5	4.1	16.0	10.6	5.3	14.9	15.8	0.201
	V20 (%)	14.7	9.7	17.7	12.2	6.2	16.3	17.2	0.086
	V10 (%)	18.6	13.6	24.4	15.7	7.6	21.1	15.9	0.088
	Dmean (Gy)	8.6	6.2	10.1	7.4	4.4	9.2	13.8	0.109
PTV	Dmin (Gy)	0.3	0.2	0.4	0.2	0.0	0.3	49.1	<0.001
	Dmax (Gy)	53.5	51.5	57.9	53.5	50.5	55.3	−0.1	0.933
	Coverage (%)	96.9	95.0	99.5	97.1	95.0	99.3	−0.2	0.781
	D2 % (Gy)	55.4	54.0	57.8	55.6	54.2	57.9	−0.4	0.489
	D98 % (Gy)	45.5	35.4	49.1	44.9	35.1	49.4	1.4	0.629

PTV: Planning target volume. V30, V25, V20, V10, V5: volume that receives 30, 25, 20, 10 and 5 % of prescribed dose respectively. Dmean, Dmax, Dmin: dose mean, minimum and maximum respectively. D2 %, D98 %: dose received by 2 % and 98 % of the target volume respectively. Gy : Gray.

the heart ranged from 1.7 to 5.8 Gy with an average of 3.26 Gy in FB, whereas in VBH the range was from 1.2 to 2.6 Gy and an average of 1.6 Gy. This corresponded to a 50.4 % reduction in the dose in VBH ($p < 0.001$). Heart V5 and V25 were also significantly reduced from 9.1%–2.5 % ($p < 0.001$) and 3.2 % to 0.3 % ($p = 0.003$) in FB relative to VBH, respectively. The mean Dmax to the heart was 51.7 Gy with FB and 32.4 Gy with VBH ($p = 0.004$). The mean dose to the LAD showed a significant reduction from 15.6 Gy to 6.4 Gy in FB and VBH, respectively ($p = 0.006$).

The mean values in the shifts of patient positioning between treatment fractions were 0.34 cm, 0.38 cm and 0.26 cm in the vertical, longitudinal and lateral directions respectively.

Fig. 1 compares treatment plans FB and VBH showing reduced radiation delivery to the heart. Posterior and inferior displacement of the heart and the increased distance to the border of the tangent field can be observed here and in Fig. 2 that shows the image co-registration of sagittal sections and the digitally reconstructed CT image.

4. Discussion

Radiotherapy improves overall survival after breast conserving surgery or radical mastectomy after positive lymph node disease and reduces the risk of death by 4 %.[12]

However, radiotherapy involves incidental radiation of normal tissues, such as the heart, which can lead to cardiac morbidity. There are numerous reports in the literature that describe cardiac dose following breast irradiation. The cardiac risk is the highest after irradiation to the left breast. A review of world literature by Taylor et al.[13] reported a mean cardiac dose of 5.4 (range 0.1–28.6) Gy. The mean dose during free breathing in our series was 3.3 Gy (range 1.7–5.8).

In Mexico, there have been no reports so far that demonstrate the benefits of VBH. This is the first report that shows the dose reduction to organs at risk, low cost, ease of adoption and time considerations of using the technique. One limitation of our series is the small number of patients ($N = 10$) with breast conserving surgery and conventional dose of 50 Gy without treating the lymph nodes. Cases of hypo-fractionation, radical mastectomy and positive lymph nodes were also excluded from the series.

Our findings are in agreement with previous studies showing that VBH reduces the dosimetric values, especially to the heart (mean and maximum dose). In our series, the mean cardiac dose was reduced by 50.4 % from 3.3 to 1.6 Gy using the VBH technique. Similarly, Swanson et al.[14] reported a 40 % reduction in mean cardiac dose from 4.2 Gy with free breathing to 2.5 Gy with VBH.

Radiation related heart disease was reported by Bartlett et al. where the mean dose was 4.9 Gy (range 0.03–27.72)..[9] The rate of major coronary events was proportional to the mean cardiac dose at 7.4 % per Gy (IC 95 %, 2.9–14.5; $P < 0.001$) without an apparent threshold. The increase started within the first 5 years after radiotherapy and continued into the third decade after radiotherapy.

Respiratory gating described by Becker-Schiebe[15] reduced the mean dose to the heart from 2.7 Gy (range 0.8–5.2) in FB to 2.4 Gy (range 1.1–4.6) and the Dmean to the LAD decreased from 11.1 Gy (range 1.3–28.6) to 9.3 Gy (range 2.2–19.9). The heart V25 mean was 3.6 % with free breathing or gated monitoring. In our own study the mean dose to the LAD ranged from 4.1–27.7 Gy in FB and from 2.2–21.2 Gy with VBH. The mean V25 to the heart was significantly reduced from 3.2 % in FB to 0.3 % in VBH.

Modern radiotherapy techniques treat a relatively distal part of the LAD that irrigates a small area of the myocardium and, therefore, is associated with a lower risk of clinically relevant radiation induced coronary disease. Thus, modern tangential radiation effect on the heart may be less pronounced than with older techniques. Our dosimetrist performs the contouring of normal anatomical structures, such as the heart and lung. The LAD is a structure that is difficult to visualise; therefore, contouring requires considerable expertise and should preferably be performed by a radiation oncologist or radiologist. The study by Evans et al. reported a mean dose to the LAD of 17.98 Gy with free breathing.[16] In our study the mean dose to the LAD was 6.4 Gy with VBH and 15.6 with FB.

Simonetto et al.[17] reported a mean cardiac dose with free breathing of 2.5 Gy (range 0.9–9.1). With VBH the mean cardiac dose was reduced to 0.9 Gy (range 0.6–5.1). The mean cardiac dose with VBH was reduced by 35 % (IQR: 23%–46%), when compared to free breathing. The absolute risk of radiation-induced mortality at 10 years was 0.14 % with free breathing. Mean expected years of life lost due to radiation induced ischaemic heart disease were 0.11 years in free breathing and 0.07 years in IVS ($p < 0.001$, Wilcoxon signed-rank test).

In view of these results, the VBH techniques should be offered to all patients with left sided breast cancer who require radiotherapy. There are various strategies for the implementation of a breath-hold technique. Success relies on patient's ability to maintain uniform breath-holds and on the verification of

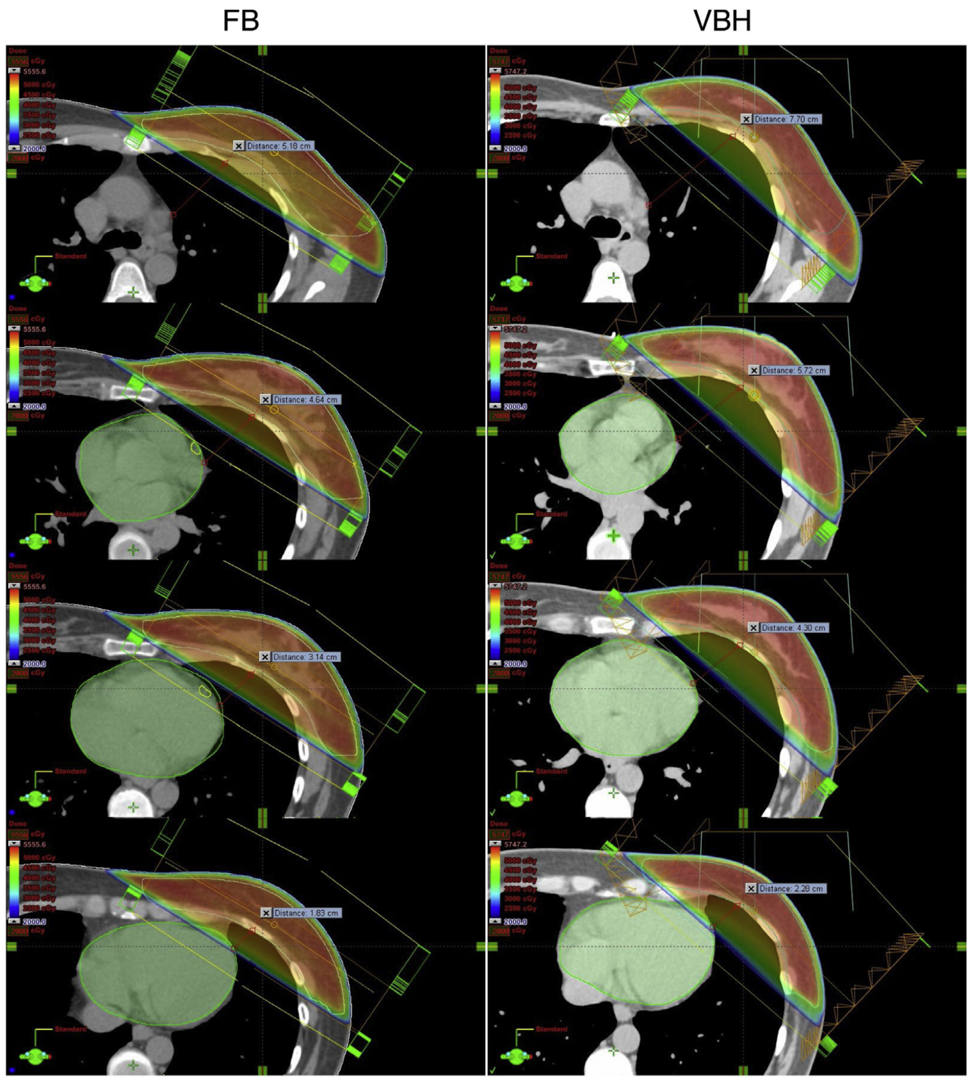

Fig. 1. Dose distribution with free breathing (FB – left panels) and voluntary breath-hold (VBH – right panels). Voluntary breath-hold results in posterior and inferior displacement of the heart and an increase in the distance from the heart to the field tangent.

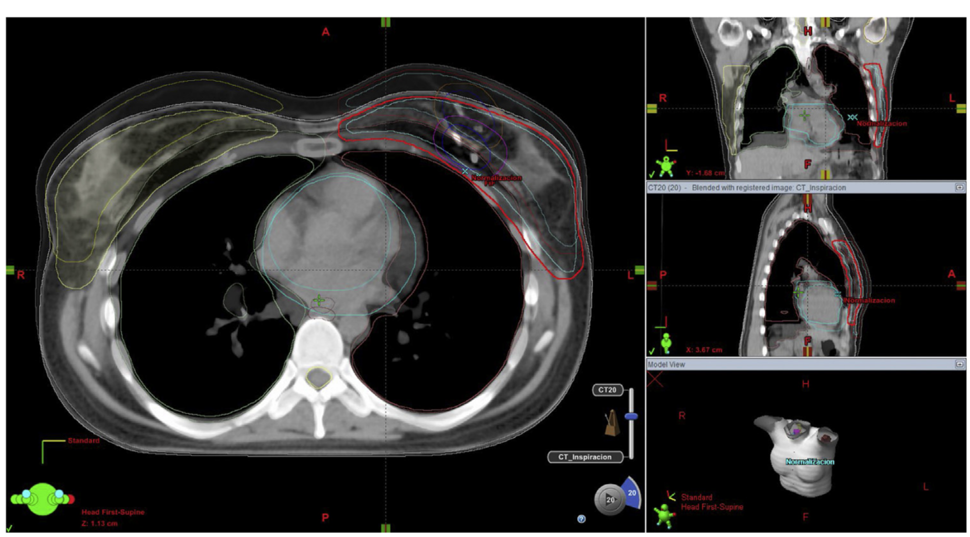

Fig. 2. Co-registered CT images showing the posterior and inferior displacement of the heart.

treatment delivery with various skin references (tattoos) and image guidance.

In conclusion, 3D-CRT treatment planning with VBH in patients with left sided breast cancer reduces dose to organs at risk, especially the heart and LAD, without compromising the coverage of the PTV. Voluntary breath-hold is a reproducible technique.

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Declaration of interest

The authors declare that there is no conflict of interest.

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