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Original Article

A Prospective Study on the Use of Deep Inspiration Breath-Hold Technique in External Beam Radiotherapy for Breast Cancer

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Abstract

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Background Breast cancer is the most common cancer and the leading cause of death in women. The deep inspiration breath-hold (DIBH) technique helps reduce the dose received by the heart and lungs in breast cancers during adjuvant radiotherapy (RT). We present the dosimetry of heart and lungs with DIBH technique, reproducibility, and ease of execution.

Materials and Methods This is a prospective study among breast cancer patients planned for adjuvant RT following either breast conservation or mastectomy. Patients received adjuvant RT to a dose of 42.5 Gy/16 Fr to the chest wall/whole breast followed by a boost of 10 Gy/5 Fr for breast conservation surgery patients with either three-dimensional conformal RT or volumetric modulated arc therapy technique. The dosimetric parameters such as lung mean dose, heart mean dose, and V25 Gy were compared between DIBH and free-breathing (FB) scans. Data were analyzed using SPSS software, and p-value <0.05 was considered statistically significant.

Results The study was conducted from September 2018 to August 2020, and 32 patients were included. The compliance to the DIBH technique was good. The dose received by ipsilateral lung V20 (17 vs. 25%) and mean dose (9 vs. 12 Gy) were significantly lower in DIBH compared with FB ($p < 0.001$). The V5 (31 vs. 15%), V25 (9 vs. 2%), and mean dose (7 vs. 3.3 Gy) to the heart were much higher in FB compared with DIBH ($p < 0.001$).

Conclusion DIBH-based RT treatment delivery for breast cancer patients requiring adjuvant RT showed good compliance and offers a significant reduction in radiation dose to the heart and lung.

Keywords
- breast cancer
- adjuvant radiotherapy
- deep inspiration breath hold
- radiation
- toxicities

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Introduction

Carcinoma of the breast is the commonest cancer in women worldwide and its incidence in India is steadily increasing.[1] Adjuvant radiotherapy (RT) is a standard treatment for breast cancer and significantly improves local control up to 8% in postmastectomy for locally advanced breast cancers and up to 25% in women undergoing breast conservation surgery (BCS).[2–4] The incidence of breast cancer is on the rise in younger women. Patients with breast cancers are long-term survivors and as a result, live with various treatment-related toxicities such as radiation pneumonitis due to lung fibrosis and radiation-induced cardiac disease.[5–10]

Cardiac toxicity, particularly those receiving radiation for left-sided breast cancer, is associated with risks of cardiac mortality and coronary events.[11,12] The toxicity is strongly correlated with the mean heart dose. It is estimated that for every 1 Gy increase in mean heart dose, the risk of ischemic heart disease increased by 4 to 7%.[13] Hence, reducing the mean heart dose during radiation planning is essential. Various methods include intensity-modulated RT, prone position, protons, and deep inspiration breath-hold (DIBH) technique.[14]

DIBH is a recent technique that helps reduce the dose received by the underlying heart and ipsilateral lung during RT treatment delivery. During the inspiratory effort, the heart is displaced downward and backward, distancing itself from the chest wall and thereby helps reduce the volume of heart receiving radiation without compromising the dose distribution to the breast or chest wall.[15–18] Several studies have shown beneficial cardiac sparing with DIBH, and the UK consensus statement on postoperative RT for breast cancer recommends using the breath-hold technique for maximal cardiac sparing.[19–22]

The routine implementation of DIBH is resource intensive and is not uniformly adapted across all institutions.[23,24] In the present study, we report on our initial experience of implementing DIBH for breast cancer in terms of dosimetry comparing free-breathing (FB) and DIBH techniques, reproducibility, compliance, ease of execution, and acute toxicities.

Materials and Methods

This is a prospective study conducted at a tertiary cancer hospital and approved by the institutional ethics committee (IEC no.: 632/2018). Patients who presented to the RT OPD following either BCS or mastectomy requiring adjuvant RT, able to comprehend and follow the instructions that are required to execute a DIBH treatment, and willing to provide informed consent were included in the study. Patients with preexisting lung or heart pathology that prevents the patient from adequately holding her breath in inspiration for the reasonable time required (around 20 seconds) to execute DIBH, metastatic disease at presentation, and prior RT for breast cancers or other cancers of the thoracic region were excluded from the study.

Patients satisfying the inclusion criteria underwent trial runs where they were assessed for their ability to hold breath in inspiration, at least 20 seconds at a stretch. The patients then underwent a planning computed tomography (CT) scan where two sets of CT images were acquired for all patients, one during FB and the other one in DIBH (►Fig. 1). The planning CT images were transferred to the Monaco planning system. The clinical target volume (CTV) and organs at risk (OAR), heart, lungs, and spinal cord were delineated on the CT images. CTV delineation was done using Radiation Therapy Oncology Group (RTOG) guidelines, and the left anterior descending (LAD) artery was contoured with the help of cardiac contouring guidelines for RT by Duane et al and heart atlas by Feng et al.[25,26] The treatment planning was done using either the three-dimensional conformal RT (3DCRT) technique or volumetric modulated arc therapy (VMAT) technique on the treatment planning system. Patients were planned for the total RT dose of 42.5 Gy/16 Fr for postmastectomy and 42.5 Gy/16 Fr followed by 10 Gy/5 Fr boost in breast conservation cases. The planning target volume (PTV) for the FB technique was taken as 1 cm (as per institutional protocol), and the PTV margin for DIBH was taken as 0.5 cm. In the event of any breathing difficulty, the patient is equipped with a safety button which on activation can terminate the treatment cycle. As a safety measure, the treating physician also monitors that patient's breathing from the console.

Demographic data and clinical details were collected from the outpatient records of the patients. RT treatment details, including volumes of lung and heart irradiated, adequacy of tumor volume coverage, OAR parameters such as lung mean dose, lung V20 Gy, heart mean dose and V25 of heart, and LAD artery mean dose and maximum dose were recorded. The patients were monitored for acute toxicities (typically, radiation dermatitis, acute dysphagia, and hematological toxicities) during treatment as per routine practice. On follow-up, they were assessed for any evidence of recurrence, treatment toxicities, specifically radiation pneumonitis, and other toxicities that might have potentially occurred due to RT.

Data collected were entered in MS Excel, analyzed using the trial version of Statistical Package for Social Sciences (SPSS) software and a p-value <0.05 was considered statistically significant. All quantitative variables were expressed as mean and standard deviation (SD) and qualitative variables as percentages. The distribution of dose–volume parameters

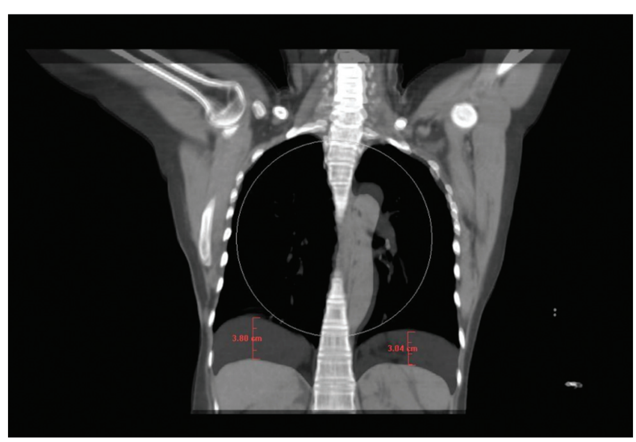

Fig. 1 An overlay to compare lung and heart volume between free-breathing and deep inspiration breath-hold techniques.

was tested for normality. If normally distributed, parametric test such as paired t-test was applied, and if not normally distributed, a nonparametric test was used. Pearson's correlation was done to test the association between the categorical variables.

The sample size was calculated using formula,

$$N = \frac{2\left(z1-\frac{\alpha}{2}+z1-\beta\right)^2\sigma^2}{d^2}.$$

With 5% alpha error, 80% power of the study, and a clinically significant difference of 1.5 Gy in the dose received by heart with the use of DIBH, the sample size calculated was 32.

Results

The study was conducted from September 2018 to August 2020, and 32 patients were included. The demographic variables are shown in ►Table 1. The mean age of patients was 49.5 years (SD ± 11.3). Three percent of our patients had a history of bronchial asthma which was mild and did not require any treatment; 81% of patients had left-sided breast cancer. The most common stage at presentation was stage II (65%) followed by stage III (26%). While majority of the patients underwent upfront surgery (72%), 28% patients received neoadjuvant chemotherapy prior to surgery, and 31% underwent BCS.

Patient Compliance

The compliance rate was high with 93.5% patients completing the entire radiation course with the DIBH plan. About 6.5% could not continue DIBH plan, and had to be changed to treatment in FB. Of the 6.5% (two patients), one patient had difficulty in comprehending the technique and usage of the spirometer. In contrast, the second patient understood the technique but could not achieve the breathing threshold during treatment. An interesting observation was that both the noncompliant patients were older than 65 years. The average breath-holding time for all patients was 27 seconds (range 20–36). The breath-hold parameters are summarized in ►Table 2.

As treatment progressed, there was an overall improvement in total time taken for completion of the cycle by 25% (7–40%), that is, patients required 25% less time toward the completion of treatment as compared with the first week. On assessing the mean time during the first and the last weeks of treatment, the mean time and the number of breath-hold cycles required for each treatment decreased toward the

Table 1 Demographic variables of patients

Characteristics	Categories (%)	Categories (%)
Age	< 40 y	> 40 y
	8 (25%)	24 (75%)
Education	< Metric	≥ Secondary education
	4 (12.5%)	28 (87.5%)
Occupation	Homemaker	Employed
	27 (84.4%)	5 (6.3%)
Comorbidities	Nil	Diabetes mellitus/hypertension/ hypothyroidism
	24 (75%)	8 (25%)
Cardio/respiratory illness	None	Bronchial asthma
	31 (97%)	1 (3%)
Personal habits	None	Pan chewers
	30 (94%)	2 (6%)
Tumor laterality	Right sided	Left sided
	6 (19%)	26 (81%)
Quadrants	Outer	Inner and central
	22 (68.75%)	10 (31.25%)
Histopathological grade	Grade I—1 (3%)	
	Grade II—23 (72%)	Grade III—8 (25%)
Histopathological type	Infiltrating ductal carcinoma	Metaplastic carcinoma
	31 (97%)	1 (3%)
Hormone status	Luminal A—4 (12.5%)	Luminal B Her2 −ve—10 (31.3%), Her2 +ve—8 (25%)
	TNBC/basal like—4 (12.5%)	Her2 enriched—6 (18.8%)

(*Continued*)

Table 1 (*Continued*)

Characteristics	Categories (%)	Categories (%)
Clinical stage	I—3 (9.37%)	≥ III—8 (25%)
	II—21 (65.6%)	
Pathological stage	0—4 (12.5%)	I—8 (25%)
	II—14 (43.75%)	≥ III—6 (18.75%)
NACT	Upfront surgery	NACT
	23 (71.875%)	9 (28.125%)
Lymph nodes dissected	Adequate	< 10 nodes
	24 (75%)	8 (25%)
Nodal status	N0—13 (41%)	N1—6 (18.8%)
	N2—4 (12.5%)	N3—2 (6.3%)
	pNx—3 (9.3%)	pN0(i+)—4 (12.5%)
Extracapsular extension	No	Yes
	30 (94%)	2 (6%)
Margin status	Positive	Negative
	1 (3%)	31 (97%)
Treatment details Surgery	BCS	MRM
	22 (69%)	10 (31%)
Chemotherapy	4AC→4 Taxol 9 (28%)	4AC→12 paclitaxel + trastuzumab →maintenance trastuzumab 13 (40.8%)
	4AC→12 paclitaxel 7 (22%)	No chemo/stopped chemo—3 (9.3%)
Radiotherapy	42.15 Gy/16 Fr—10 (31.3%)	40 Gy/15 Fr f/b boost—1 (3%)
	42.5 Gy/16 Fr f/b 10 Gy/5 Fr boost—21 (65.6%)	
Treated areas	Breast only—11 (34%)	Chest wall only—3 (9.4%)
	Breast + SCF—11 (34%)	Chest wall + SCF—6 (18.8%)
		Chest wall + SCF + IMN—1 (3.1%)
RT technique	3DCRT	VMAT
	25 (78%)	7 (22%)

Abbreviations: 3DCRT, three-dimensional conformal radiotherapy; AC, adriamycin + cyclophosphamide; BCS, breast conservation surgery; f/b, followed by; IMN, internal mammary node; MRM, modified radical mastectomy; NACT, neoadjuvant chemotherapy; RT, radiotherapy; SCF, supraclavicular fossa; TNBC, triple-negative breast cancer; VMAT, volumetric modulated arc therapy.

Table 2 Breath-hold parameters

Breath-hold parameters	Mean ± SD	Range
Breathing threshold (L)	1.08 ± 0.11	0.8–1.2
Breath-hold seconds (s)	27.42 ± 3.71	20–36
Breath-hold cycles to complete treatment	5.78 ± 1.17	4–8
Minimum time taken (min)	15.5 ± 6.21	10–45
Maximum time taken (min)	29.6 ± 10.2	20–60
Mean time taken (min)	18.91 ± 6.58	14.2–51.4

Abbreviation: SD, standard deviation.

completion, indicating better compliance after the initial few fractions of RT. The mean time taken for delivery of 3DCRT was 18.46 seconds and 23.7 seconds for VMAT.

The mean ipsilateral lung volume in DIBH was significantly higher than FB (1,312.74 ± 239.24 vs. 954.28 ± 150.74 mL). Lung expansion had a positive correlation to breathing threshold with patients with good lung expansion having good breathing threshold and breath-hold time in seconds. There was a moderately positive correlation between age and mean time taken ($p = 0.09$).

Dosimetry

Target Volume

The mean values of V95 of the CTV in FB (88.26 ± 4.56%) and DIBH (89.53 ± 4.65%) were comparable ($p = 0.196$). The mean values of D95, D2, and D98 were comparable, with no significant difference between the two techniques.

Organs at Risk

The ipsilateral lung V20 and mean lung dose were significantly higher in FB ($p < 0.001$). The contralateral lung V20 and mean dose in FB were not significantly different. The V5, V25, and mean heart dose were significantly higher in FB compared with DIBH ($p < 0.001$). The mean dose received by LAD was significantly higher in FB compared with DIBH, with an average difference of 12.276 Gy ($p < 0.001$). LAD D_{max} in FB was higher with a difference of 11.95 Gy ($p < 0.001$), and the LAD planning organ at risk volume (PRV) D_{max} dose was higher in FB. The dosimetric parameters for OARs in FB and DIBH are tabulated and compared in ►Table 3. For patients undergoing VMAT, mean heart dose was 10.9 Gy in FB plans versus 6.2 Gy with DIBH.

With increased lung expansion, there was a decrease in ipsilateral lung mean and LAD mean doses (►Fig. 2). For every percentage increase in lung expansion, the ipsilateral lung mean dose reduces by 12%, and the LAD mean dose reduces by 15%. The acute toxicities consisted of dermatitis and dysphagia; 86.7% developed grade 1 dermatitis, while 13.3% developed grade II. Grade I dysphagia was seen in only 30%, while rest were asymptomatic. Of these nine patients, seven received RT to supraclavicular fossa. The average mean dose to esophagus was 8.7 ± 1.4 Gy and mean D_{max} dose was 26.76 ± 14.28 Gy. However, the esophageal mean ($p = 0.045$) and D_{max} ($p = 0.249$) doses did not correlate significantly with dysphagia.

Discussion

The present study aimed to assess the dosimetric benefit of DIBH compared with FB, compliance, and toxicities. We found that DIBH showed a significant decrease in ipsilateral lung and heart mean dose and volume parameters. DIBH was well tolerated, with a compliance rate of 93.5%, and patients completed treatment faster in the last week of treatment. The acute toxicities were minimal.

In the present study, we found that DIBH contributed to a significant dose reduction in the heart. There was reduction in V5, V25, and mean heart dose. This was in agreement with studies done by Bruzzaniti et al, where the mean dose to the heart was significantly lower in DIBH, and another conducted by Darapu et al, where 46% reduction in V25 for heart was seen as compared with the FB plan.[27,28] Mean dose to the heart in DIBH in their study was much higher (4.78 Gy), whereas we achieved a mean heart dose of 3.3 Gy similar to the study by Swamy et al.[29]

The LAD artery is in the anterior most part of the heart and is at direct risk of developing radiation-induced ischemic heart diseases as it is maximum exposed to radiation while using the tangential fields. Bruzzaniti et al reported

Table 3 Dosimetric parameters of organs at risk with free breathing and DIBH

Organ/parameter	Free breathing	DIBH	Mean difference (SD)	*p*-Value
Ipsilateral lung				
V20 (%)	25.96 ± 8.03	17.44 ± 5.03	8.50 ± 7.57	<0.001
Mean dose (Gy)	12.06 ± 3.14	8.9 ± 2.29	3.14 ± 2.76	<0.001
Contralateral lung				
V20 (%)	0.09 ± 0.23	0.06 ± 0.26	0.03 ± 0.35	0.615
Mean dose (Gy)	1.41 ± 1.88	1.28 ± 1.94	0.13 ± 1.94	0.326
Heart (for left-sided tumors only)				
Mean dose (Gy)	7.01 ± 3.76	3.34 ± 3.16	3.68 ± 2.33	<0.001
V25 (%)	9.24 ± 5.62	1.88 ± 2.66	7.36 ± 4.72	<0.001
V5 (%)	31.25 ± 27.17	15.98 ± 24.55	15.26 ± 15.32	<0.001
Left anterior descending artery				
Mean dose (Gy)	23.96 ± 7.27	11.68 ± 6.85	12.28 ± 7.36	<0.001
D_{max} (Gy)	42.2 ± 4.82	30.24 ± 10.51	11.96 ± 9.27	<0.001
PRV D_{max} (Gy)	43.67 ± 2.69	36.88 ± 7.13	6.79 ± 5.97	<0.001

Abbreviations: DIBH, deep inspiration breath hold; PRV, planning risk volume; SD, standard deviation.

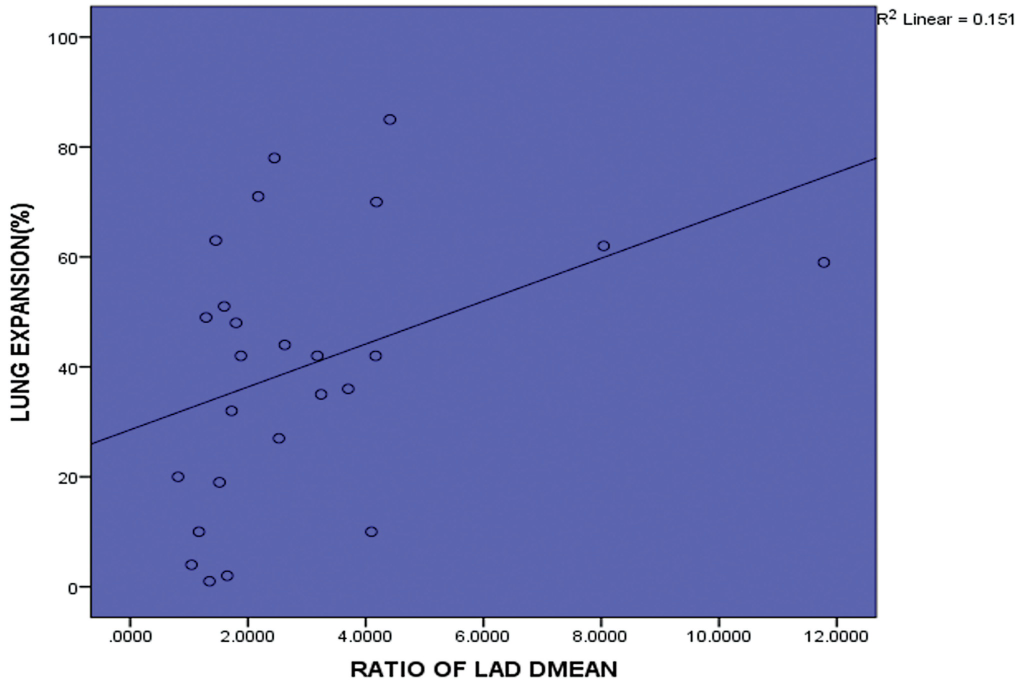

Fig. 2 Correlation of lung expansion with left anterior descending (LAD) artery mean dose.

reduction in heart and LAD dose by 78% with DIBH and normal tissue complication probability (NTCP) values for pericarditis were zero. In our study, we found that LAD mean dose, D_{max}, LAD PRV D_{max} all to be statistically significantly lower in DIBH compared with FB. These studies also report significantly lower lung mean doses, 16% in the study by Bruzzaniti et al, 15.7% lower in the study by Darapu et al and Swamy et al. The present study also showed a statistically significant difference in lung mean dose and V20 doses. Many similar studies have shown dosimetric benefit of DIBH; however, they lack information on compliance and breath-hold parameters.[30,31] A systematic review and meta-analysis by Lu et al analyzed 41 studies with 3,599 left-sided breast cancer patients comparing DIBH with FB. They found that DIBH significantly reduced heart dose (D_{mean}, D_{max}, V30, V10, V5), LAD dose (D_{mean}, D_{max}), ipsilateral lung dose (D_{mean}, V20, V10, V5), and heart volume.[32]

Although there is significant dosimetric benefit of DIBH in breast cancer, its implementation in routine practice varies. A survey among European Organization for Research and Treatment of Cancer–affiliated institutions in 2010 showed only 19% implemented DIBH.[24] However, a recent survey conducted in the United States by Desai et al showed that 73% used a cardiac-sparing technique with DIBH accounting for 43%.[33] They also found patient tolerance to be the most important determinant for DIBH in left-sided breast cancer. Our study found majority of the patients to be compliant with the DIBH technique. The patients who were unable to continue the DIBH-based treatment were aged more than 65 years. This was in agreement with the study conducted by Latty et al and Nissen and Appelt.[34,35] Desai et al also found 23% of physicians using DIBH for right-sided breast cancer patient with lung and heart sparing. Demiral et al showed DIBH for right-sided breast cancer patients resulted in decrease in mean lung, heart, and liver dose.[36] In the present study as well, six right-sided patients were treated wherein DIBH resulted in lung sparing.

We analyzed the correlation between various breath-hold parameters such as breathing threshold and breath-hold seconds with lung expansion and found that lung expansion had a good correlation concerning breathing threshold and breath-hold seconds. With lung expansion, there was decrease in lung and LAD mean dose. This is consistent with the results published by Cao et al.[37] Vuong et al reported inverse correlation with increase in DIBH left lung volume and inspiratory volume with maximum heart dose and lung V20.[38]

This study explores routine implementation of DIBH in clinical practice for left- and right-sided breast cancer patients with good compliance. Our study was limited by sample size, lack of long-term toxicities, and clinical impact of reduced normal tissue doses. We did not report the setup reproducibility of DIBH compared with FB.

Conclusion

The use of DIBH for delivering adjuvant RT can significantly reduce dose exposure to critical OARs such as heart, lung, LAD especially in left-sided breast cancers and should be implemented in all patients who are compliant with the technique.

Authors' Contribution

There is equal contribution from both first authors hence, put as first coauthors. As well as, equal contribution from both corresponding authors, hence as corresponding coauthors. N.J. and K.S. conceptualized, designed, and analyzed the study. J.N.P. and S.L. prepared the manuscript. All authors reviewed the manuscript.

Note

This study was performed in line with the Declaration of Helsinki; approval was obtained from the Institutional Ethics Committee (IEC no.: 632/2018).

Conference Presentations

WALTCON 2023.

Informed Consent

Informed consent was taken from the participants for participation in the study.

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None.

Conflict of Interest

None declared.

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