The Role of Active Breathing Control-Moderate Deep Inspiration Breath-Hold (ABC-mDIBH) Usage in non-Mastectomized Left-sided Breast Cancer Radiotherapy: A Dosimetric Evaluation

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ABSTRACT

The aim of this study is to evaluate the dosimetric impact of utilizing Active Breathing Control-moderate deep inspiration breath-hold (ABC-mDIBH) technique in early-stage left-sided breast cancer radiotherapy (RT). Twenty-five patients with left-sided early-stage breast cancer undergoing breast-conserving surgery referred to our department for adjuvant radiotherapy between October 2010 and October 2011 were scanned with computed tomography (CT)-simulator at free breathing (FB) and ABC-mDIBH for radiation treatment planning. Two separate treatment plans were generated for each patient, with and without ABC-mDIBH to comparatively evaluate dose-volume parameters of both plans. Dose-volume parameters of lung, heart, left anterior descending artery (LAD), contralateral breast and spinal cord were significantly reduced with ABC-mDIBH compared to free breathing (p< 0.001). The use of ABC-mDIBH technique in the practice of early-stage left-sided breast cancer radiotherapy improves critical organ sparing with the dosimetrically-confirmed potential to decrease treatment-related morbidity and mortality. This respiratory management strategy is a promising tool that may be routinely used for the treatment of patients with early-stage left-sided breast cancer.
Keywords: Breast cancer, Breast-conserving surgery, Radiotherapy, Active breathing control, Breath-hold

ÖZET

Non-Mastektomize Sol Meme Kanseri Radyoterapisinde Aktif Nefes Kontrolü-Orta Derin İnspirasyonda Nefes Tutma Kullanımının Rolü: Dozimetrik Bir Değerlendirme

Bu çalışmanın amacı erken evre sol meme kanseri radyoterapisinde aktif nefes kontrolü-orta derin inspirasyonda nefes tutma tekniğinin dozimetrik olarak değerlendirilmesidir. Ekim 2010 ile Ekim 2011 tarihleri arasında erken evre sol meme kanserli, meme koruyucu cerrahi uygulanmış 25 hastanın, 2 ayrı solunum fazında radyasyon tedavisinin çevre kritik organlara olan etkisinin dozimetrik değerlendirmesine yönelik olarak serbest solunum ve aktif nefes kontrollü tomografik simulasyon planlama görüntüleri alınmış ve her hasta için 2 ayrı tedavi planı oluşturularak her iki plandan elde edilen kritik organların doz-volüm parametreleri karşılaştırmalı olarak değerlendirilmiştir. Aktif nefes kontrolü-orta derin inspirasyonda nefes tutma tekniğinin eklenmesiyle kritik organlar olan akciğerler, kalp, sol ön inen arter, karşı meme ve spinal kordun aldığı dozlarda serbest solunuma göre anlamlı azalma saptanmıştır (p< 0.001). Erken evre sol meme kanseri radyoterapisinde aktif nefes kontrolü-orta derin inspirasyonda nefes tutma tekniğinin kullanılması, tedaviyle ilişkili beklenen morbidite ve mortaliteyi azaltma potansiyeli açısından dozimetrik olarak kritik organ korumasını iyileştirmiştir. Bu solunum manajmanı stratejisi erken evre korunmuş sol meme kanserli hastaların tedavisinde rutin olarak kullanılabilecek umut vadeden bir yöntemdir.
Anahtar Kelimeler: Meme kanseri, Meme koruyucu cerrahi, Radyoterapi, Aktif nefes kontrolü, Nefes tutma

INTRODUCTION

Breast cancer comprises the most common type of cancer in females worldwide.[1] Radiation therapy is an integral part of breast cancer management utilized after breast conserving surgery or mastectomy.[2,3] Postoperative radiotherapy (RT) has been shown to reduce local recurrence and improve overall survival.[4-9] Despite the reduction in local failure with the use of RT, some trials have failed to show an improvement in overall survival.[10,11] Failure to achieve improved overall survival may not be explained by RT toxicity alone, however, the use of RT along with surgery, hormonotherapy and chemotherapy in the multimodality management of breast cancer may lead to a resultant toxicity that may compromise survival in long-term follow-up. Comprehensive RT for breast cancer targets the breast or chest wall and lymph nodes when indicated. The close proximity of these targets to critical structures poses the risk of radiation-induced toxicity with the potential to compromise long-term survival. Moreover, besides treatment-related mortality, radiomorbidity and secondary cancers have been important concerns and areas of active investigation recently due to the increased life expectancy in breast cancer patients with more effective therapies as well as diagnostic improvements allowing earlier detection. The role of RT in breast cancer management is rapidly evolving since more patients are now diagnosed with early-stage disease which is increasingly being treated with breast conserving surgery. The trend towards favoring breast conserving surgery plus radiotherapy versus mastectomy in the management of early-stage breast cancer has been based on the results of trials showing comparable survival outcomes with both strategies but improved quality of life in terms of cosmesis and patient satisfaction with breast conserving treatment.[5,10,12-14] Since radiotherapy is being more increasingly utilized in the management of breast cancer, long-term complications of irradiation have to be considered thoroughly. Side effects of RT for breast cancer include skin irritation, changes in skin color, tenderness in treated area, fatigue, arm edema, swelling, radiation pneumonitis, and cardiotoxicity. Among these, cardiotoxicity composes the most serious side effect since it may lead to significant mortality besides morbidity. Second malignancies also deserve utmost attention particularly in long-term survivors of breast cancer.[15,16] In many studies conducted so far, particularly deaths from cardiac events contributed to the increase in non-breast cancer mortality.[5,10,11,17-25] Cardiac morbidity and mortality is an important concern particularly in left-sided breast cancer patients who have a higher risk of having coronary artery disease, chest pain, and myocardial infarction.[22,25,26] The dose to the left anterior descending artery (LAD), which is suggested to be radiosensitive, may play a role in lethal cardiotoxicity.[22,27,28] RT-related cardiotoxicity may be affected by several factors including the volume of heart within the RT field, dose, fraction size, and systemic therapy.[29-32] Although modern RT techniques offer improved cardiac sparing to minimize toxicity, it has been suggested that even low doses of 4-5 Gray (Gy) could contribute to cardiotoxicity.[33-36] Moreover, cardiotoxicity of RT in breast cancer patients may further be enhanced by the use of some chemotherapeutic agents.[37-39] Consequently, cardiac dose-volume parameters should be thoroughly optimized in breast cancer RT to avoid potential cardiotoxicity of treatment. Another concern in breast cancer radiotherapy is the sparing of lungs as much as possible to avoid pulmonary complications.[40] Besides three-dimensional computed tomography (CT)-based planning and intensity modulation, incorporation of respiratory management strategies is increasingly being used to improve critical organ sparing in breast cancer RT.[41-56] Active Breathing Control system, first developed by Wong et al. offers an effective respiratory management strategy used to improve normal tissue sparing in breast cancer RT with the advantages of separating the target and heart by changing the internal anatomy with moderate deep inspiration breath-hold (mDIBH) and minimizing breathing-induced motion through temporarily suspending the air flow at 75% of maximum inspiration capacity.[57]

In this study, we evaluated the dosimetric impact of ABC-mDIBH in early-stage left-sided breast cancer radiotherapy.

PATIENTS AND METHODS

Patient Selection: Twenty-five consecutive patients with left-sided early-stage breast cancer meeting the eligibility criteria of ≤ 65 years of age, Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, no previous radiotherapy to the breast and no disorders hampering patient compliance (hearing impairment, mental illness etc.) referred to our department between October 2010 and October 2011 for adjuvant radiotherapy after breast conserving surgery were studied. Informed consents of all participants were obtained prior to study enrollment.

Instructions and Training for the ABC Procedure: Before CT-simulation, all patients underwent a thirty-minute-long training session with the ABC device (ABC, Elekta, UK) to enhance patient compliance and to determine individual mDIBH levels set at 75% of maximum inspiratory capacity. The training session included a brief introduction to the ABC procedure with explanation of potential benefits. Verbal instructions were given in an attempt to motivate patients to achieve a constant breathing pattern. Patients practiced breath-holding at moderate deep inspiration until they reached a steady and reproducible breathing pattern. Signaling for interruption of ABC process due to discomfort was taught to the patients. Duration of breath-hold and threshold for mDIBH of each patient was documented in order to use during treatment. Patients with a comfortable breath-hold duration of ≥ 20 seconds were considered eligible to undergo treatment with ABC-mDIBH. Breathing traces of the patients were monitored with the ABC system through the patient mouthpiece connected to the device.

Simulation, Treatment Planning and Delivery: Two sets of CT images were acquired for each patient in order to evaluate the dosimetric impact of routinely utilized ABC procedure. All patients were immobilized in supine position with both arms above head, using an angled breast-board. Radiopaque wires were used to locate the palpable breast tissue and visible surgical scar to assist in target definition. The mirror enabled patients to see their breathing trace on the monitor attached to the ABC system helping them achieve a steady and reproducible breathing pattern necessary for simulation and treatment. Nose clip was used to ensure breathing through the mouth only. After positioning and immobilization was completed and a steady breathing pattern achieved by the patient, first scan was acquired at mDIBH with the ABC system at CT-simulator (GE Lightspeed RT, GE Healthcare, Chalfont St. Giles, UK) to use for actual treatment. This was followed by a second scan at FB without ABC to use for comparative dosimetric analysis. Both scans were acquired with 5 mm slice thickness. The acquired images were sent to the contouring workstation via network. Advantage Sim MD simulation and localization software (Advantage SimMD, GE, UK) was used for contouring treatment volumes and critical organs on both FB and ABC-mDIBH scans at the same window level. To improve consistency, the same physician performed all contouring procedures and the same physicist the treatment planning procedures. Clinical target volume-breast, lungs, heart, LAD, contralateral breast and spinal cord were delineated on both scans. A recent validated cardiac atlas was used for contouring the heart and LAD to improve contouring accuracy and concordance.[58] PrecisePLAN (Elekta, UK) Treatment Planning System was used in generating the 2 separate three-dimensional conformal RT plans for each patient. Beam organizations, wedges, and the beam angles were identical in both plans of the patients. Multileaf collimators were used to shape treatment fields when necessary. The clinical target volume-breast coverage was between 90% and 110% of the prescribed dose. All patients were planned to receive a whole breast dose of 50 Gy in 25 fractions followed by a tumor bed boost of additional 10 Gy in five fractions. Dose-volume histograms were generated for all delineated structures. Treatment was delivered using a linear accelerator (Synergy, Elekta, UK) allowing on-line set-up verification under image guidance with kilo-Voltage Cone Beam Computed Tomography (kV-CBCT) (X-ray Volumetric Imaging (XVI), Elekta, UK) mounted on the LINAC gantry. Treatment duration of patients for each treatment session was documented. Follow-up visits were scheduled for every patient routinely at 3-month intervals.

Dose-Volume Parameters and Statistical Analysis: Dose-volume histograms were generated for all delineated structures in both plans of each patient. For the LAD, contralateral breast and spinal cord; mean dose (Dmean) and maximum dose (Dmax) were calculated. For the heart; Dmean, Dmax and percentage volumes receiving doses ≥ 5 Gy (V5), 10 Gy (V10), 15 Gy (V15), 20 Gy (V20), 25 Gy

Table 1. Patient and tumor characteristics

Patient No	Age	TNM	Stage	Threshold for mDIBH (liters)	Breath-hold duration (seconds)	Treatment Duration (minutes)
1	38	T2N0M0	IIA	1.4	31	21
2	63	T1bN0M0	I	2.2	28	17
3	41	T1cN0M0	I	1.6	27	14
4	50	T1cN0M0	I	1.5	25	16
5	45	T1cN0M0	I	2.4	32	13
6	56	T2N0M0	IIA	2.3	34	15
7	41	T2N0M0	IIA	2.6	33	14
8	43	T1cN0M0	I	1.8	23	14
9	35	T1cN0M0	I	2.4	30	16
10	36	T2N0M0	IIA	1.3	24	18
11	65	T1cN0M0	I	2.1	28	19
12	46	T1cN0M0	I	1.7	29	17
13	32	T2N0M0	IIA	1.5	27	15
14	39	T2N0M0	IIA	1.4	24	16
15	41	T2N0M0	IIA	1.9	31	19
16	60	T1cN0M0	I	1.6	23	18
17	56	T2N0M0	IIA	1.3	25	17
18	43	T1cN0M0	I	1.5	22	18
19	65	T2N0M0	IIA	1.7	26	17
20	41	T2N0M0	IIA	1.8	29	18
21	57	T2N0M0	IIA	1.6	31	18
22	62	T1cN0M0	I	1.2	32	17
23	30	T2N0M0	IIA	1.7	27	16
24	36	T1cN0M0	I	1.3	30	14
25	56	T1cN0M0	I	2.1	33	13
Mean	47.08			1.76	28.16	16.40
STD	10.95			0.40	3.52	2.04

mDIBH: moderate deep inspiration breath-hold; STD: Standard deviation

(V25), 30 Gy (V30), 35 Gy (V35), 40 Gy (V40), 45 Gy (V45), 50 Gy (V50) were calculated. For the ipsilateral lung; Dmean and percentage volumes receiving doses ≥ 5 Gy (V5), 10 Gy (V10), 15 Gy (V15), 20 Gy (V20), 25 Gy (V25), 30 Gy (V30), 35 Gy (V35), 40 Gy (V40), 45 Gy (V45), 50 Gy (V50) were calculated. V20 and mean lung dose (MLD) was calculated for both lungs. MLD was defined as the average dose of the CT-defined residual total lung volume. Aforementioned dose-volume parameters acquired from both plans were compared with each other using statistical tests. The Kolmogorov-Smirnov test was used to detect whether the variables were normally distributed or not. After assessment of all variables for normal distribution, variables with normal distribution were analyzed using paired t test while variables with non-normal distributions were analyzed using Wil-

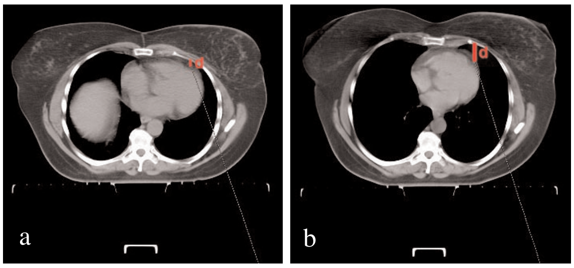

Figure 1 a, b: Axial planning CT images showing the distance (d) between LAD and left chest wall (FB vs. ABC-mDIBH), 1a) Axial planning CT image measuring 5.7 mm distance (d) between LAD and left chest wall (FB), 1b) Axial planning CT image measuring 25.4 mm distance (d) between LAD and left chest wall (ABC-mDIBH)

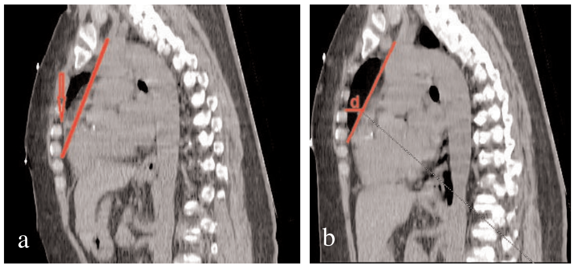

Figure 2 a, b: Sagittal planning CT images showing the distance (d) between heart and left chest wall (FB vs.ABC-mDIBH), 2a) Sagittal planning CT image measuring no distance (d) between heart and left chest wall (FB), 2b) Sagittal planning CT image measuring 15.7 mm distance (d) between LAD and chest wall (ABC-mDIBH)

coxon signed rank test. In descriptive statistics, mean and standard deviation (STD) was used for normally distributed variables which were analyzed using the paired t test, and median (minimum-maximum) was used for non-normally distributed variables which were analyzed using the Wilcoxon signed rank test. Statistical Package for the Social Sciences, version 15.0 (SPSS, Inc., Chicago, IL) software was used for analysis and the level of significance was set at $p < 0.05$.

RESULTS

Between October 2010 and October 2011, twenty-five consecutive patients with left-sided early-stage breast cancer (pT1-2N0M0) referred to our department for adjuvant radiotherapy after breast conserving surgery were enrolled in the study. Mean age was 47.08 years. Mean breath-hold duration was 28.16 seconds. Mean treatment duration per fraction was 16.40 minutes and mean threshold for breath-holding was 1.76 liters. 13 patients (52%) had stage I, 12 patients (48%) had stage IIA breast cancer. Patient and tumor characteristics are shown in Tale 1.

All participating patients succeeded the whole course of the prescribed radiotherapy with ABC. The training session including a brief introduction to the ABC system, explanation of the rationale, verbal instructions and practice breath-holds resulted in excellent patient compliance. Attentive attitude of the treating team towards the patients was appreciated.

Mean lung volume was 4570.24 cc with ABC-mDIBH and 3036.28 cc with FB ($p< 0.001$). Mean increase in the whole lung volumes with ABC-mDIBH was 54.98%. Axial and sagittal planning CT images of a patient with FB and ABC-mDIBH are shown in figures 1 and 2, respectively.

Dose-volume parameters of the heart, left lung and both lungs, LAD, contralateral breast and spinal cord acquired from the dose-volume histograms of the 2 plans with and without ABC-mDIBH are shown in table 2, 3 and 4, respectively. All critical organ dose-volumes were significantly improved with ABC-mDIBH compared to free breathing ($p< 0.001$). Heart V50 was the only variable with non-normal distribution and median heart V50 was 0 (0 - 2.90) with ABC-mDIBH while it was 0.3 (0 – 6.90) with free breathing ($p< 0.001$).

DISCUSSION

Improving the toxicity profile of radiation delivery in breast cancer has gained utmost priority recently thanks to the increased public awareness, enhanced screening programs, technological developments in imaging and more effective therapies leading to earlier detection and longer overall survival. More patients are being diagnosed with early-stage breast cancer and there is a growing trend towards favoring conservative surgery resulting in increased use of RT. Patients with early-stage breast cancer are younger and have an extended life expectancy further substantiating the importance of normal tissue sparing. RT-induced second malignancies are also of great concern in this patient group given the young average age at diagnosis and excellent survival.[15,16] Integrating respiratory management strate-

Table 2. Cardiac dose-volume parameters

		Cardiac volume irradiated (%)											
		≥5 Gy	≥10 Gy	≥15 Gy	≥20 Gy	≥25 Gy	≥30 Gy	≥35 Gy	≥40 Gy	≥45 Gy	≥50 (**) Gy	Dmean (cGy)	Dmax (cGy)
FB	**Mean**	17.77	12.89	11.14	9.98	9.12	8.34	7.48	6.30	4.61	1.08	660.04	5151.92
	STD	6.80	5.52	5.08	4.90	4.80	4.52	4.32	4.04	3.59	1.81	241.22	151.95
ABC-mDIBH	**Mean**	7.57	4.61	3.67	3.12	2.74	2.38	2.04	1.62	0.97	0.18	324.68	4388.16
	STD	6.40	4.51	3.95	3.55	3.29	2.99	2.73	2.31	1.51	0.58	190.53	941.17
p (*)		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
% decrease with ABC-mDIBH	**Mean**	60.99	68.27	71.49	73.36	74.73	76.30	77.94	79.62	84.44	82.34	51.81	14.68
	STD	24.13	24.28	24.54	24.72	25.10	25.46	25.75	26.17	23.36	31.03	17.95	18.62

(*) : Comparison of FB and ABC-mDIBH for cardiac sparing ; FB: free breathing; mDIBH: moderate deep inspiration breath-hold; Dmean: mean dose; Dmax: maximum dose; STD: Standard deviation; (**) : Median heart V50 was 0 (0 - 2.90) with ABC-mDIBH while it was 0.3 (0 – 6.90) with free breathing (p<0.001).

gies into breast cancer RT has been widely studied in the past few years.[41-56] Our study primarily aimed at investigating the dosimetric impact of ABC-mDIBH on critical organ dose-volume parameters, and we found statistically significant reductions in heart, LAD, lung, and contralateral breast doses. It is worthy of note that we also reported doses to the spinal cord which is poorly considered in many studies. Although the dose to the spinal cord either with or without ABC was low, ABC-mDIBH reduced the spinal cord dose in all patients and eliminated the exposure of the spinal cord in three patients which may have further implications grounding on the fact that radiation carcinogenesis is a stochastic effect without a dose threshold. Clearly, future studies with long-term follow-up are warranted to determine the clinical relevance of these dose reductions. However, incidental irradiation should be considered thoroughly since the late effects of radiation have yet to be defined.

Compliancewise observation of all the twenty-five patients revealed 100% success in completing the

Table 3. Left lung dose-volume parameters

		Left lung volume irradiated (%)										MLD (cGy)
		≥5 Gy	≥10 Gy	≥15 Gy	≥20 Gy	≥25 Gy	≥30 Gy	≥35 Gy	≥40 Gy	≥45 Gy	≥50 Gy	
FB	**Mean**	28.44	23.82	22.15	21.10	20.08	19.22	18.22	17.02	15.36	10.24	1156.84
	STD	5.02	4.88	4.63	4.40	4.35	4.25	4.21	4.18	4.01	4.81	229.73
ABC-mDIBH	**Mean**	21.86	18.16	16.69	15.52	14.80	14.02	13.24	12.40	11.18	7.33	894.68
	STD	5.60	5.08	4.93	4.79	4.60	4.48	4.32	4.16	3.94	3.99	233.85
p (*)		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
% decrease with ABC-mDIBH	**Mean**	23.44	23.93	25.03	26.98	26.76	27.52	27.94	27.69	28.36	27.35	22.93
	STD	12.84	14.13	14.64	15.36	15.73	16.41	15.89	16.59	15.87	24.39	12.97

(*) : Comparison of FB and ABC-mDIBH for left lung sparing; FB: free breathing; mDIBH: moderate deep inspiration breath-hold ; MLD: mean lung dose; STD: Standard deviation

Table 4. Dose-volume parameters of both lungs, LAD, contralateral breast and spinal cord

		Both Lungs		LAD		Contralateral Breast		Spinal Cord	
		MLD (cGy)	V20 (%)	Dmean (cGy)	Dmax (cGy)	Dmean (cGy)	Dmax (cGy)	Dmean (cGy)	Dmax (cGy)
FB	**Mean**	542.68	9.69	3626.56	4895.84	62.20	420.16	9.68	80.00
	STD	104.07	2.07	1319.65	441.69	19.99	134.46	4.60	18.33
ABC-	**Mean**	427.72	7.37	1590.00	2659.28	53.92	333.48	4.88	56.16
mDIBH	**STD**	109.32	2.12	1435.97	1683.49	15.39	96.55	4.48	28.16
p (*)		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
% decrerease	**Mean**	21.58	23.97	53.21	44.61	8.63	17.24	53.97	31.32
with ABC-	**STD**	12.81	16.39	49.21	38.00	29.69	20.47	28.83	27.86
mDIBH									

(*) : Comparison of FB and ABC-mDIBH for lung (both lungs), LAD, contralateral breast and spinal cord sparing; FB: free breathing; mDIBH: moderate deep inspiration breath-hold ; Dmean: mean dose; Dmax: maximum dose; STD: Standard deviation

whole course of radiotherapy with ABC. We would also like to draw special attention to patient training. Using ABC-mDIBH is a well-established method of respiratory management with promising results and patients with early-stage breast cancer are generally quite fit to tolerate the treatment with breathing control unlike their counterparts with lung cancer. We believe a vast majority of early-stage left-sided breast cancer patients may routinely be treated using ABC-mDIBH with adequate training. The rationale of ABC-mDIBH must clearly be explained to the patient with an attentive attitude and practicing breath-holds should be instructed to achieve a steady, reproducible breathing pattern. Additional studies with long-term follow-up comparing or compounding ABC-mDIBH with other normal tissue sparing techniques and documenting the clinical relevance of critical organ dose reductions are needed.

CONCLUSION

The use of ABC-mDIBH in the practice of early-stage left-sided breast cancer radiotherapy improves normal tissue sparing with the potential to decrease treatment-related morbidity and mortality. This respiratory management strategy is a promising tool that may be routinely used for the treatment of patients with early-stage left-sided breast cancer.

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