

The Advantages of Active Breathing Coordinator Device During Left-Sided Breast Cancer Radiation Therapy: A Dosimetric Comparison Study

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Research

Keywords: Moderate deep inspiration breath-hold, ABC, Breast cancer, Radiotherapy

Posted Date: July 9th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-40352/v1>

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Abstract

Background: Radiotherapy (RT) improves local control and survival in breast cancer (BC) patients. However, risk of heart and lung side effects after post-operative left breast RT for breast cancer remain despite technological and technical RT advances. In a retrospective cohort we investigated if Active Breathing Coordinator (ABC) device can reduce risk of cardiopulmonary morbidity.

Methods: we performed two different dosimetric analyses by Normal Tissue Complication Probability (NTCP) and Bio-Dose-Volume Histograms (Bio-DVH) in order to determine whether left breast RT using moderating deep inspiration breath-hold (mDIBH) with the Active Breathing Coordinator (ABC) device, may significantly reduce heart, left anterior descending coronary artery (LADCA) and lung radiation exposure during left breast RT performed with 3d-CRT technique.

Results: Several dosimetric parameters were used in the present study to compare the treatment plans generated by FB and mDIBH images of sixty-nine consecutive patients treated between May 2012 and April 2016 at the Istituto del Radio Radiation Oncology Dept. All data derived by Bio-DVH and the heart NTCP calculation showed that ABC led to significant sparing of organs at risk compared with FB, especially for the heart and LADCA. We also showed that the mDIBH technique significantly reduced left lung dose: in fact, through inflation, only low density lung tissue remains within the tangential field, thus avoiding its deterioration.

Conclusions: Use of mDIBH gives a real advantage on breast cancer RT by reducing the radiation to the organs at risk (OARs) and consequently, the risk of cardiac and pulmonary late side effects.

Introduction

Radiation therapy (RT) improves local control and survival in breast cancer (BC) patients [1]. However, incidental radiation dose to heart and lung during post-operative left breast radiation therapy for breast cancer has been associated with an increased risk of cardiopulmonary morbidity, especially in patients undergoing Anthracyclines as neoadjuvant or adjuvant chemotherapy schedules along with surgery [2]. Improvements in radiation techniques continue to be of interest to radiation oncologists, to achieve enhanced sparing of organs at risk, especially the heart, without compromising tumor volume coverage. Despite the improving in RT technology and techniques, 3 dimensional conformal Radiation Therapy (3d-CRT) still remains the standard approach. Intensity Modulated Radiation Therapy (IMRT) can improve the target dose coverage, delivering a higher low-dose exposure of organs at risk (OARs), with the subsequently potential risk of RT-related malignancies. Thus, the IMRT clinical applicability in daily practice for breast remains to be defined, except for unfavorable or strictly selected situations [3]. Apart from the adoption of IMRT (eg, volumetric-modulated arc therapy) that is potentially able to better reduce high doses to the heart, other approaches could be able to minimize heart radiation exposure in BC patients. For example, in other thoracic diseases, breathing-adapted RT delivery could reduce the dose to the heart and left coronary artery [4]. Therefore, we performed two different dosimetric analyses by

Normal Tissue Complication Probability (NTCP) and Bio-Dose-Volume Histograms (Bio-DVH) in order to determine whether left breast RT using moderating deep inspiration breath-hold (mDIBH) with the Active Breathing Coordinator (ABC) device, may significantly reduce the organs at risk (OARs) radiation exposure. More specifically, we have investigated heart, left anterior descending coronary artery (LADCA) and lung radiation exposure during left breast radiotherapy performed with 3d-CRT technique.

Methods

Patient population

Between May 2012 to April 2016 at the Istituto del Radio Radiation Oncology Dept, seventy-two consecutive patients (pts) presenting for adjuvant RT after resected left breast cancer were retrospectively reviewed. However, as three of them revealed poor compliance towards mDIBH procedure, the population in the study was finally made of sixty-nine patients (68 female, 1 male), mainly staging TNM 0-Ib (45 pts = 65.2%) [5]. The characteristics of our patients are summarized in Table 1. Median age ranged between 31 and 60 years. Forty patients underwent concomitant sentinel node biopsy, while axillary node dissection was performed in 22 pts, only 7 pts received surgical treatment of the primitive tumor. The immunohistochemical pattern was above all positive for estrogen and progesterin receptors (ER + and PgR+), as well as negative C-erb-B2 expression and Ki67 index ≤ 20 . Because of the anatomopathological and immunohistochemical tumor features, 7 pts received neoadjuvant anthracycline-based chemotherapy and/or sequential taxanes scheme, while 29 subjects underwent post-operative chemotherapy before breast irradiation, mainly using the EC (Epirubicin and Cyclophosphamide) regimen.

Table 1
Descriptive patient characteristics of the study cohort

			PATIENTS (n.) 69	PATIENTS (%) 100
SEX	F		68	98.55%
	M		1	1.45%
AGE	≤ 30		0	0%
	31–60		54	78.26%
	> 60		15	21.74%
MENOPAUSE	YES		39	56.55%
	NO		29	42%
	NOT APPLICABLE		1	1.45%
STAGING sec. TNM	ST 0		8	11.6%
	ST Ia-Ib		37	53.6%
	ST IIa-IIb		13	18.85%
	ST IIIa-IIIb-IIIc		10	14.5%
	ST IV		1	1.45%
SURGERY	QUADRANTECTOMY		56	81.2%
	MASTECTOMY		11	15.9%
	RECURRENCE EXCISION		2	2.9%
NODAL SURGERY	SENTINEL LYMPH NODE		40	58%
	AXILLARY DISSECTION		22	32%
	NONE		7	10%
	NODAL RATIO	< 0,5	28	82.35%
		≥ 0,5	6	17.65%
	EXTRACAPSULAR SPREAD	YES	6	17.65%
		NO	28	82.35%
HORMONAL THERAPY	NO		16	23.2%
	YES		53	76.8%

			PATIENTS (n.) 69	PATIENTS (%) 100
NEOADJUVANT CHEMOTHERAPY	YES *	ANTHRACYCLINES	7	100%
	*7 pts (10%)			
	NO		62	90%
ADJUVANT CHEMOTHERAPY	YES *	ANTHRACYCLINES	21	30.4%
	*29 pts (42%)			
		OTHER REGIMENS	8	11.6%
	NO		40	58%
TRASTUZUMAB	YES		7	10%
	NO		62	90%

Table 1: Descriptive patient characteristics of the study cohort

Breath-holding training

All patients were trained with the Active Breathing Coordination™ device (ABC®, Elekta Oncology System Ltd, Crawley, UK) before CT simulation. This kind of device was designed to provide the same level of forced inspiration during the treatment planning phase and during RT as the radiation beam delivery would occur only during a specific breathing phase. The ABC device allows to monitor the patient's breathing and to evaluate how many seconds pts is able to hold the breathing, with the aim to reduce the thoracic movement caused by a normal respiratory cycle.

Computed tomography (CT) simulation

For all patients, set-up was performed in supine position on a commercial breast board and CT simulation consisted of a nominal 5-mm slice thickness and the field of view was set to include the whole lungs. For each patients, both image acquisition of standard free-breathing (FB) and blocked breathing by the ABC device were performed for dosimetric comparison.

Target volume and organs at risk (OAR) delineation

The breast or chest wall clinical target volume (CTV) was defined according to RTOG guidelines [6]: for 11 pts delineation of supraclavicular lymph nodes was necessary, and similarly they were contoured according to the RTOG guidelines. The planning treatment volume (PTV) was generated by adding a 10-mm cranio-caudal expansion and a 5-mm expansion in the remaining directions around the CTV except for the skin surface, keeping into account the set-up margin and patient movement. For 30 pts a sequential boost over the lumpectomy cavity was prescribed, and delineated using surgical clips as fiducial markers. As OARs, the heart (the pericardial sac starting from the pulmonary artery bifurcation), the LADCA, the ipsilateral and contralateral lung were contoured. Target volume and OARs delineation

were performed by the same operator in order to ensure a better homogeneity and reduce inter-operator variability.

Plan design

For all patients, 3d-CRT technique using a tangential field was performed. For each patient, two treatment plans were generated (Oncentra MasterPlan®), using two tangential fields, applying the following dose constraints: left lung $V_{20\text{Gy}} < 20\%$ (lower than standard QUANTEC constraint, referring to a cumulative $V_{20\text{Gy}}$ for both lungs), heart $V_{25\text{Gy}} < 10\%$ as QUANTEC reports [7]. The PTV prescribed dose for whole breast irradiation was 50 Gy in 25 daily fractions (78% of cases) or 44 Gy in 16 daily fractions (internal Institute schedule) (22%). For each patient, two DVHs for heart, LADCA and lungs, using FB and ABC respectively, were generated. Then, they were compared and analyzed using two kinds of software (SW): 1. a homemade Planning Reporting Orienteering (PRO)-DVH SW, which elaborates Bio-DVH (that is the Equivalent DVH for 25 fractions) and so allowed comparison between the two different treatment schedules in the present study. 2. The BIOlogical Evaluation of radiotherapy treatment PLANs (Bioplan) SW [8] for NTCP calculation of cardiac mortality, according to the relative seriality model (Fig. 1) [9]:

where D_i is the absorbed dose in each dose bin, i , of the different DVH, D_{50} is the dose resulting in 50% complication probability, γ is the maximum relative slope of the dose-response curve, n is the number of DVH dose bins, $DV_i = V_i/V$ where V_i is the volume of each dose bin and V is the total volume of the organ. The relative seriality factor s (range 0–1), describes the tissue architecture. In the present study $D_{50} = 52.3$ Gy, $\gamma = 1.28$, $s = 1$ were used as benchmarks, taken from Gagliardi et al. [10]. The primary study endpoint was to determine any potential dosimetric (and consequently clinical) advantages provided by mDIBH in terms of LADCA, heart and left lung protection and the effect on cardiac NTCP. Standard statistical assessment of the significance of the results was performed. Two tailed paired t-test was used to estimate the statistical significance of the differences between groups. A p-value less than 0.05 was considered statistically significant.

Results

Dosimetric Analysis

Several dosimetric parameters were used in the present study to compare the treatment plans generated by FB and mDIBH images of all the patients. We have determined relative and absolute DVHs for LADCA and heart and relative DVH for lung, and we have calculated heart NCTP. Figure 2 shows the analyses of the DVH relative and absolute mean for the LADCA in the FB and DIBH plans showing statistically significant advantage by ABC use to reduce LADCA exposure.

The NTCP calculation (Fig. 3) showed that there was a significant reduction in the heart NTCP calculation of cardiac mortality in the DIBH plans as compared to the FB plans: 0.40% vs 1.83% (p value < 0.01).

The analyses of the DVH absolute for the 5 ml of LADCA receiving the maximum dose in the ABC and FB plans (Fig. 4) highlighted that ABC curves tend to shift left to low doses, while FB curves tend to shift right towards high doses. Thus, the use of the DIBH technique resulted in a significant reduction in doses to the LADCA.

Also in the heart DVH relative mean, our study showed that there was a significant reduction in dose to the entire heart in the DIBH plans compared to the FB plans, with a p value < 0.01 (Fig. 5).

Finally, we have assessed the DVH relative mean for the left lung (Fig. 6): although there is a statistically significant difference with the ABC technique, an increased irradiated lung volume corresponds to a reduction in lung density which results in an absence of correlation with clinical damage.

Discussion

Currently, the management of breast cancer requires a combined-modality treatment approach. This has led to an improvement in local control and overall survival, but the gain in survival allowed clinicians to observe a higher probability of late toxicity onset [11]. Cardiac sequelae attributed to radiotherapy in breast cancer usually represent late side effects and the clinical evidence may occur several years after the treatment. Technological improvements in breast treatment radiation techniques (IMRT, use of collimation and gantry angles, patients set-up...) have decreased late complications rates, also including cardiac morbidities [12]. In addition, the need for sparing the heart during irradiation represents a crucial issue, due to the increasing use of modern systemic agents, such as trastuzumab and anthracyclines, known for their intrinsic cardiotoxicity in breast cancer patients, as also long-term aromatase inhibitors use relates to an increased cardiovascular risk [13]. Of note, since the risk of cardiac mortality is multifactorial, the association of genetic factors, eating habits, age, smoking, etc. with current therapies may worsen the outcome of these patients. These considerations have led the radiation oncology community to increase the caution for heart exposure during breast radiotherapy. One of the most cited studies examining the potential impact of breast radiation treatment on ischemic heart disease evaluated an association with major coronary events (coronary re-vascularization, myocardial infarction and death from ischemic heart disease), suggesting that there was no safe dose threshold that would not increase future cardiac events and found an association with pre-existing cardiac risk factors and higher absolute increases in RT risk [14]. Notably, the retrospective design and the inclusion of obsolete RT techniques may have affected the power of the study. More recently, a publication by Killander et al. presented long-term follow-up data from a randomized trial started in 1991 regarding many different clinical endpoints such as total mortality, cause-specific mortality and morbidity, and cardiovascular interventions after radiotherapy in breast conserving surgery patients [15]. The authors reported no increased cardiac mortality in patients receiving breast radiotherapy, with no detrimental effect in terms of morbidity. Study limitations are the lack of data on risk factors for cardiac disease or stroke (such as hypertension, smoking, diabetes mellitus, or obesity) and on less serious morbidity that could not be taken into account. In addition, within the study, most of the patients had not undergone chemotherapy or endocrine treatment. Individual baseline cardiac risks within the setting of patients undergoing left-breast irradiation

have not yet been systematically investigated and very few studies have addressed the influence and significance of these factors [16]. Baseline cardiac risk estimation could be a parameter to refer to for the indication of mDIBH use, in order to achieve a superior cardiac protection during breast radiation therapy as reported by Gaasch A. et al. [17]. The growing evidence in support of the long-term risks provided by breast radiotherapy along with systemic therapy stress out the need to keep into account the accurate optimization of radiotherapy to decrease the probability of heart sequelae. To achieve this goal, mDIBH radiotherapy techniques represent one of the most effective, reproducible and widely studied methods for left-sided breast cancer treatment [18–20]. Breath-hold treatments using Active Breathing Coordinator provide the ability to reduce the low-dose exposure of critical structures such as heart: more specifically, ABC expands the lung volume, increasing the distance between the chest wall and the heart, thus reducing the heart dose. mDIBH also reduces heart and lung doses in locoregional breast irradiation, including internal mammary nodes (IMNs), demonstrating that the ABC device plays a role not only in patients with early stage disease but also in the case of advanced breast cancer [21]. The evaluation of the impact of the ABC technique on IMNs coverage and organs at risk protection in patients planned for post-mastectomy radiation therapy (PMRT) was equally analysed by Barry A. et al. [22] who reported their results concerning fifty left-sided postmastectomy patients supporting the use of ABC for breast cancer patients receiving left-sided PMRT plus regional nodal irradiation, also including the IMNs. Our study was performed to evaluate the efficacy of the mDIBH technique and its dosimetric advantages over the FB technique in cardiac (heart and LADCA) and ipsilateral lung sparing in left-sided breast conformal radiotherapy. We showed that ABC led to significant sparing of organs at risk compared with FB, reporting a statistically significant sparing of the heart as documented by the DVH comparison analysis. This significant advantage was also recorded for the LADCA sub-structure with a statistically significant p-value that further supports the role of mDIBH for cardiac sparing during breast post-operative RT. During left-sided breast cancer irradiation, LADCA and the anterior part of the heart, are the sides that receive the maximum dose while the tangential fields are used. The risk of developing radiation-induced ischemic heart disease is directly proportional to the doses received by LADCA [23]. Besides heart radiation exposure, lungs dose represents another relevant endpoint when considering acute and late toxicities (like radiation pneumonitis and fibrosis) during and after breast cancer irradiation. In agreement with previous studies [24–26], we also showed that the mDIBH technique significantly reduced left lung dose. This might seem counterintuitive at first, since more lung volume is within the tangential beam when the heart moves out of the treatment field during mDIBH, but through inflation, only low density lung tissue remains within the tangential field, thus avoiding its deterioration. Our study has some limitations, first of all the retrospective nature of the series and the relatively small sample size may limit the statistical power of our analysis. Furthermore, we did not perform a baseline estimate of cardiac events risk, which may represent a tool to better select ideal candidates for the use of this technique. In fact, not all patients may benefit from mDIBH, since tolerance and compliance are two mandatory factors for ABC device use. Nonetheless, we believe that the implementation of this technique may be of major impact especially for patients at a higher baseline risk for cardiac events.

Conclusion

Currently, a wide range of post-operative therapeutic options for breast cancer are available, thanks to not only conformal radiation techniques but also giving the chance of mDIBH with devices like the ABC Elekta. The results about studies on innovative irradiation techniques, on dosimetric comparison and the adequate follow-up period to understand clinical impact of mDIBH techniques are today disposable. Use of mDIBH gives a real advantage on breast cancer RT by reducing the radiation to heart and LADCA and the risk of cardiac late side effects: correct training with ABC system regarding patients and operators is obligatory to reach this goal.

Abbreviations

RT

Radiation therapy

BC

breast cancer

3d-CRT

3 dimensional Conformal Radiation Therapy

IMRT

Intensity Modulated Radiation Therapy

OARs

organs at risk

NTCP

Normal Tissue Complication Probability

DVHs

Dose-Volume Histograms

mDIBH

moderating deep inspiration breath-hold

ABC

Active Breathing Coordinator

LADCA

left anterior descending coronary artery

PTS

patients

CTV

clinical target volume

PTV

planning treatment volume

FB

free breathing

IMNs

internal mammary nodes

PMRT

post-mastectomy radiation therapy

Declarations

Ethics approval and consent to participate: The study was performed according to ASST Spedali Civili di Brescia Ethic Committee principles. The study was conducted in agreement with the Declaration of Helsinki. All the patients signed a consent to share their clinical data and information for clinical studies.

Consent for publication: All the patients signed a consent to share their clinical data and information for publication.

Availability of data and materials: Data are stored according to our Institutional protocols and are available upon request.

Competing interests: The authors declare that they have no competing interests

Funding: None to declare

Authors' contributions: PN and BL analysed and interpreted the patients data. SL and GB performed the dosimetric analyses. PS, PL, MM, CL, BM, TL, BP contributed to data collection and to review of current literature. PN, BL, CF, AF, FV and SMM were a major contributors in writing the manuscript. All authors read and approved the final manuscript.

Acknowledgements: Not applicable

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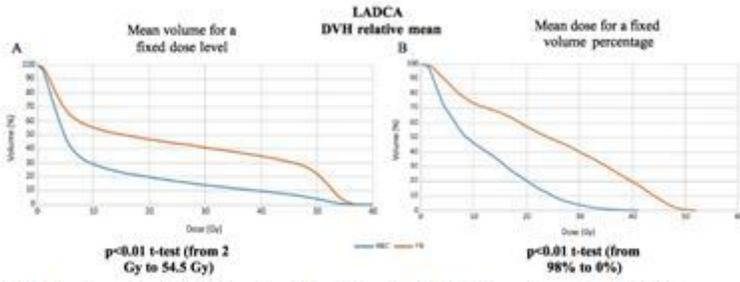
Figures

$$NTCP = \left\{ 1 - \prod_{i=1}^n [1 - P(D_i)]^{AV_i} \right\}^{1/\alpha} \quad (1)$$

$$P(D_i) = 2^{-\exp(\sigma(1 - D_i/D_{50}))} \quad (2)$$

Figure 1

Heart NTCP



DIBH plans showing statistically significant advantage by ABC use to reduce LADCA exposure.

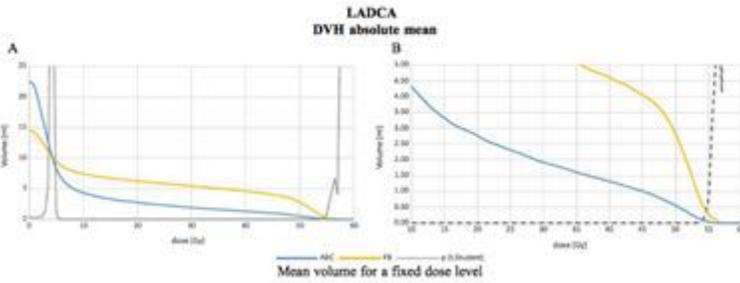


Figure 2

Protective effects of ABC on LADCA protection.

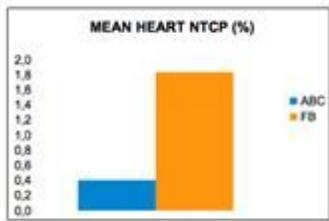


Figure 3

Heart NTCP.

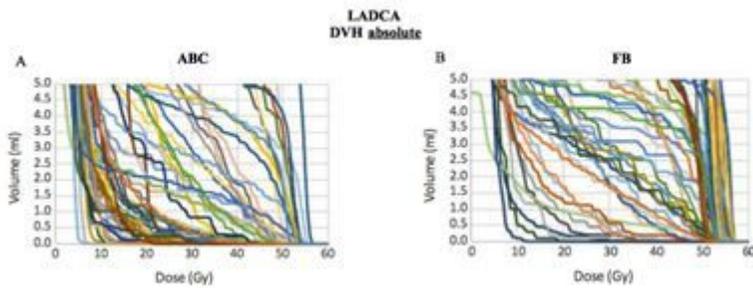


Figure 4

DVH absolute for the 5 ml of LADCA receiving the maximum dose.

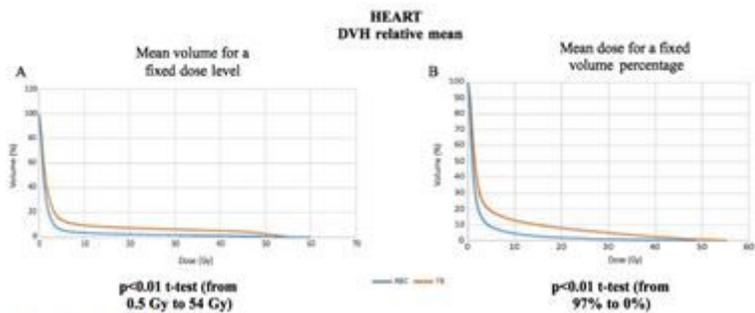


Figure 5

Heart DVH relative mean.

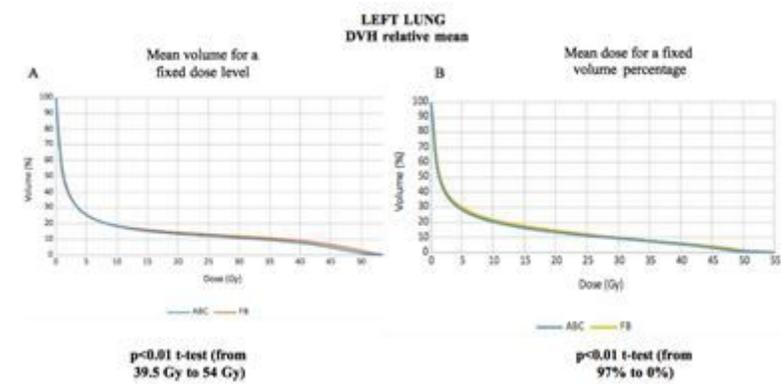


Figure 6

Left lung DVH relative mean. Although the differences are statistically significant, they are not clinically relevant.