Tumori, 96: 417-423, 2010

Active Breathing Coordinator in adjuvant three-dimensional conformal radiotherapy of early stage breast cancer: a feasibility study

Mariangela Massaccesi[1], Luciana Caravatta[1], Savino Cilla[2], Cinzia Digesù[1], Francesco Deodato[1], Gabriella Macchia[1], Vincenzo Picardi[1], Adele Piscopo[1], Gilbert DA Padula[3], Gabriella Ferrandina[4], Giovanni Scambia[5], Vincenzo Valentini[6], Numa Cellini[6], Angelo Piermattei[2], and Alessio G Morganti[1]

[1]Radiotherapy Unit, Department of Oncology, and [2]Physics Unit, "John Paul II" Center for High Technology Research and Education in Biomedical Sciences, Catholic University, Campobasso, Italy; [3]Department of Radiation Oncology, The Lacks Cancer Center Saint Mary's Health Care, Grand Rapids, Michigan, USA; [4]Gynecologic Oncology Unit, Department of Oncology, "John Paul II" Center for High Technology Research and Education in Biomedical Sciences, Catholic University, Campobasso, Italy; [5]Gynecology/Obstetrics Department, and [6]Radiotherapy Department, Policlinico A. Gemelli, Catholic University, Rome, Italy

ABSTRACT

Aims. To investigate the technical feasibility of utilizing the Active Breathing Coordinator for planning of postoperative three-dimensional conformal radiation therapy in patients with early stage breast cancer undergoing breast conservation therapy.

Methods. Patients with early stage breast cancer for whom adjuvant radiotherapy after breast-conserving surgery was planned were consecutively enrolled. Five sessions of simulation with the Active Breathing Coordinator were planned for each patient. Computed tomography for simulation was not acquired until a good level of compliance with the procedure was achieved by the patient. Patients who did not show a satisfactory level of compliance after the planned fifth session were defined as noncompliant. Two simulation computed tomography scans were acquired: the first without the Active Breathing Coordinator during free breathing, the second with the Active Breathing Coordinator. Forward intensity-modulated treatment plans were calculated. Mean lung dose ($MLD_{ipsilateral}$) and V30 ($V30_{lung}$) for the ipsilateral lung and V30 for the heart ($V30_{heart}$), were evaluated.

Results. Twenty consecutive patients were enrolled (6 with left-sided breast cancer and 14 with right-sided breast cancer). Eighteen of the patients completed the simulation computed tomography with the Active Breathing Coordinator after 1-5 sessions (median, 3). In 16 of the 18 patients, a reduction of $V30_{lung}$ was observed with the Active Breathing Coordinator. In 15 of the 18 patients, a reduction of $MLD_{ipsilateral}$ was also observed. In 5 of the 6 patients with left-sided breast cancer, a reduction of $V30_{heart}$ was noted.

Conclusions. Routine application of the Active Breathing Coordinator in clinical practice is feasible, even though it requires an increased workload. Dosimetric results are encouraging in terms of a better sparing of the ipsilateral lung and the heart. Free full text available at www.tumorionline.it

Key words: Active Breathing Coordinator, adjuvant radiotherapy, breast cancer.

Correspondence to: Gabriella Macchia, MD, Radiotherapy Unit, Department of Oncology, "John Paul II" Center for High Technology Research and Education in Biomedical Sciences, Catholic University, Largo A Gemelli 1, 86100 Campobasso, Italy.
Tel +39-0874-312261;
fax +39-0874-312720;
e-mail gmacchia@rm.unicatt.it

Received October 14, 2009;
accepted January 13, 2010.

Introduction

After breast-conserving surgery, adjuvant radiotherapy delivered to the whole breast is known to be the current standard of care for early stage breast cancer[1]. The most commonly used technique to treat the whole residual breast consists of two opposite beams with an arrangement that is tangent to the chest wall. This is done in order to minimize radiation exposure to the heart and lung. However, due to the curvature of the chest wall, some volume of lung and heart (in left-sided breast cancers) is included in the radiation beam. Moreover, to take into account setup and organ motion variations, a margin needs to be added to the whole residual breast to obtain the planning target volume (PTV). Thus, a larger amount of lung and heart is in the radiation field.

Movement of the breast is mainly due to breath-related chest wall motion. Several studies have reported that breathing adaptation techniques, particularly those that allow the immobilization of breast motion during inspiration, can be used to reduce the volume of heart and lung that is irradiated[2-6]. These techniques allow for a spatial separation of the heart from the target and for an inflation of lung, and thus a reduction of density, during irradiation. Furthermore, the procedures could be applied to reduce the margin for conformal treatment by minimizing breathing motion[7].

The Active Breathing Coordinator™ (ABC, Elekta, UK) has been tested to reduce the negative impact of organ motion due to breathing in various cancers[8]. It consists of a portable computerized device which allows for a temporary controlled interruption of patient breathing. Many authors have reported a potential advantage of the ABC in reducing normal tissue irradiation in breast cancer[7,9,10]. However, an evaluation of feasibility of ABC application in a sufficient sample of patients is still lacking.

The aim of the present study was to investigate the technical feasibility of utilizing the ABC for postoperative three-dimensional conformal radiation therapy (3D-CRT) planning in unselected patients with early stage breast cancer. A preliminary dosimetric evaluation, in terms of healthy organ sparing, was also performed.

Materials and methods

Study end points and design

The primary end point of the study was to evaluate the feasibility of the use of the ABC for controlled inspiration breath hold in adjuvant 3D-CRT for early stage breast cancer in unselected patients. The secondary end point was to evaluate the dosimetric impact on organs at risk with the use of the ABC in the same population of patients. The study was planned to enroll 20 consecutive unselected patients. To investigate the clinical feasibility of the use of the ABC, the following parameters were evaluated: number of patients who completed the treatment planning procedure, and number of simulation sessions needed to reach a satisfactory level of compliance of the patients to the procedure. In order to compare dosimetric results, the following parameters were considered: the mean dose to the ipsilateral lung ($MLD_{ipsilateral}$), volume of the ipsilateral lung that receives at least 30 Gy ($V30_{lung}$), and volume of heart that receives at least 30 Gy ($V30_{heart}$). The statistical analysis was carried out using a *t* test.

Patient selection criteria

The study was approved by the local Institutional Review Board. Written consent was obtained from all participating patients. Eligibility criteria included patients with unilateral breast cancer undergoing breast conservation therapy. Patients requiring prophylactic irradiation of nodal regions were excluded from the study. The following conditions were also considered to be exclusion criteria: previous radiotherapy delivered to the breast; Eastern Cooperative Oncology Group performance score[11] >3; mental disorders precluding study participation.

Treatment planning

Before starting treatment planning, all patients were informed regarding the rationale of the ABC. Patients were also advised to avoid generous meals and gaseous drinks before each phase of treatment planning and delivery. An in-house designed angled board was used as an immobilization device. Patients were placed in the supine position, with the ipsilateral arm placed above their head. This position was kept during computed tomography (CT) simulation, each radiation session, and for the acquisition of electronic portal images for setup verification.

Five sessions of simulation with the ABC were planned for each patient (one session a day for five consecutive days). That was done in order to make the patients progressively more confident with the system. CT simulation for treatment planning was not acquired until the patient had achieved a good level of compliance to the procedure, as judged by the radiation oncologist and the radiation therapist. Once deemed compliant, the remaining sessions were cancelled. The patients who did not show a satisfactory level of compliance after the fifth planned session were defined as noncompliant and treated without the ABC.

In order to investigate the dosimetric impact of the ABC, two sets of CT images were acquired. The first was performed during free breathing (FB), without ABC. The movements of chest wall due to respiration were measured by means of three series of slices, i.e., dynamic scans, at the level of the sterno-clavicular joint, nipple, and lower border of breast. Each of these was obtained with 10 CT slices for 10 seconds, while keeping the couch still. The second CT simulation scan was acquired using the ABC during the breath-hold period. In the first 10 patients, the threshold was set near the end of normal inspiration (top of the tidal volume), according to the best patient tolerance. In the following 10 patients, the threshold was set at deep inspiration. In order to further promote patient cooperation, the scanning period was subdivided into shorter periods, each lasting 10 seconds.

Both FB and ABC CT studies were performed with 5 mm thickness and a pitch of 1, without intravenous contrast administration. A radio-opaque wire was placed in order to delimitate the palpable breast and to assist in target delineation. This method was chosen to reduce inter-individual variability[12].

The heart and ipsilateral lung were considered organs at risk. The heart was defined as all the visible myocardium and pericardium, from the apex to the right auricle, atrium, and ventricular infundibulum, excluding the pulmonary trunk, root of the ascending aorta, superior vena cava, and pericardium. The ipsilateral lung contours were defined using an automated threshold-contouring tool.

The clinical target volume (CTV) was defined as the whole breast excluding 5 mm from body surface unless infiltration of the skin had been documented. In all patients, a margin of 5 mm was added to the CTV to account for setup variation[13]. Since the chest wall motion during breath hold with the ABC was found to be almost negligible (less than 1 mm)[14], in case of ABC use, no internal margin was considered and the PTV was derived from the CTV plus a 5-mm margin. In FB treatment plans, individualized internal margins were derived from "dynamic" CT scan, as previously described. The PTV was obtained by adding to the CTV a uniform margin resulting from the square root of the sum of the squares of internal margins and set-up margins.

Dose was prescribed according to the ICRU 62 report. The treatment was performed with the tangential technique and slight beam angulation (gantry angles optimized to match divergence of the posterior edges of the beam) to reduce the dose to the organs at risk. Beam angulation was adapted to avoid contralateral breast irradiation. Forward intensity-modulated treatment plans were processed. This modality of treatment planning showed dosimetric advantages over the traditional one with wedge filters[15-17]. The contribution of each of the two tangential beams was divided into two different segments. One segment was designed to include the whole breast without filters (6 MV photons). This configuration, in the absence of filters, results in a volume of under dosage in the thickest region of the breast. A second segment was directed to this area of under dosage to compensate for dose loss (15 MV photons). The dose distribution was recalculated, assigning approximately 8 to 10% of the prescription dose to the reduced fields. Successive multileaf collimator manipulations were iterated to optimize the tangential treatment with respect to target coverage and dose uniformity.

Recently, the authors have proposed a practical method to obtain the in-vivo isocenter dose in patients using a signal obtained by the central pixels of the beam central axis of the electronic portal imaging device, when irradiated by the X-ray beam transmitted through the patient, for every beam gantry angle[18,19]. This method makes use of: a) the correlation function between the middle dose in a cylindrical water phantom, and the signal due the transmitted X-ray beam from the patient; b) the water-equivalent thickness of the patient along the beam central axis, determined by the treatment planning system, that uses the information supplied by CT scanners. In-vivo dosimetry was performed daily for all the patients enrolled in the study and treated with the ABC.

Results

Twenty consecutive patients with early stage breast cancer (pT1b-cN0M0) submitted to conservative surgery were enrolled in our feasibility study. Characteristics of patients are reported in Table 1.

Eighteen of 20 patients completed the CT simulation scan with the ABC after 1-5 sessions (median, 3). Table 2 shows some details about the compliance of the patients.

Table 1 - Patient characteristics

Number	20
Median age, yr (range)	58 (38-80)
Side of primary tumor	
Right breast	14
Left breast	6

Table 2 - Compliance to the Active Breathing Coordinator (ABC) for CT simulation in 20 patients with early stage breast cancer

Patient no.	No. of sessions*	Breath hold period (s)	Threshold volume for breath hold (L)°	Simulation with ABC completed
1	5	10	0.4	Yes
2	3	10	0.8	Yes
3	2	10	0.8	Yes
4	3	10	0.5	Yes
5	1	8	0.6	Yes
6	3	15	0.6	Yes
7	3	10	0.35	No
8	4	10	0.5	Yes
9	3	10	0.65	Yes
10	2	15	0.6	Yes
11	3	20	1.9	Yes
12	2	15	1.4	Yes
13	2	18	1.6	Yes
14	3	20	1.5	Yes
15	3	16	1.5	Yes
16	3	20	1.6	Yes
17	2	20	1.9	Yes
18	3	20	1.6	Yes
19	2	15	1.2	No
20	3	15	1.4	Yes
Median	3	15	1	

*Number of sessions needed to obtain a good compliance, as judged by the radiation oncologist and the radiation therapist.
°Residual functional capacity as baseline.

The median values of the displacement of the chest wall in FB condition (internal margin), as measured from "dynamic" scans, were 3.0, 3.0 and 2.0 mm in the cranio-caudal, lateral, and antero-posterior direction, respectively. Therefore, in FB plans, the median values of CTV expansion to PTV were 5.8 mm (range, 5.1-7.07) in the cranio-caudal and lateral directions and 5.4 mm (range, 5.1-8.6) in the antero-posterior direction.

In 15 of 18 patients, a reduction of $MLD_{ipsilateral}$ was observed with the ABC compared with FB. In one patient, no improvement of $MLD_{ipsilateral}$ with the ABC was found, whereas in 2 other patients the $MLD_{ipsilateral}$ slightly increased with the ABC. Mean values of $MLD_{ipsilateral}$ were 5.8 Gy (range, 1.1–10.2) and 4.2 Gy (range, 1.0–6.5), in FB and ABC treatment plans, respectively (mean difference, 1.6 Gy; 95% CI, 0.8-2.5; P = 0.001, paired t test). The mean relative variation of $MLD_{ipsilateral}$ with the ABC consisted of a 25.3% reduction (ranging from a relative increase of 25.0% and a relative decrease of 65.0%).

In 16 of 18 patients, a reduction of $V30_{lung}$ was observed with the ABC. Mean values of $V30_{lung}$ were 10.3% (range, 2.0-23.0) and 5.9% (range, 1.0-15.5) in FB and ABC treatment plans respectively (mean difference, 4.3%; 95% CI, 1.2-7.5; p = 0.009, paired T test). The mean relative variation of $V30_{lung}$ with the ABC consisted of a 31.4% reduction (ranging from a relative increase of 77.7% and a relative decrease of 100.0%).

In 5 of 6 patients with left-sided breast cancer, a reduction of $V30_{heart}$ was also recorded. In the other patient, the heart was completely outside of the 30 Gy isodose region, both in FB and ABC treatment plans. Mean values of $V30_{heart}$ were 3.1% (range, 0.0–7.6) and 0.2% (range, 0.0-0.6) in FB and ABC treatment plans, respectively (P = 0.04, Wilcoxon signed ranks test). The mean relative reduction of $V30_{heart}$ with the ABC was 91.0% (range, 66.6-100% reduction).

Figures 1, 2, and 3 show variation of $MLD_{ipsilateral}$, $V30_{lung}$, and $V30_{heart}$, respectively, in FB and ABC treatment plans.

Patients who showed dosimetric advantage with the ABC (15/18) underwent radiotherapy with the ABC and completed all the planned sessions.

In vivo dosimetry during breath hold was used to determine the interfraction isocenter dose variations due to the reproducibility of the patient's breathing pattern. For each patient, the difference between the total predicted and measured dose was within 4%. However, the interfraction isocenter dose fluctuation in the breath hold technique was lower than 2% (2 SD), whereas with FB the observed fluctuations were about 5% (2 SD).

Discussion

Many authors have reported that breathing adaptation techniques could be a useful tool to reduce irradiation to organs at risk in adjuvant 3D-CRT for breast can-

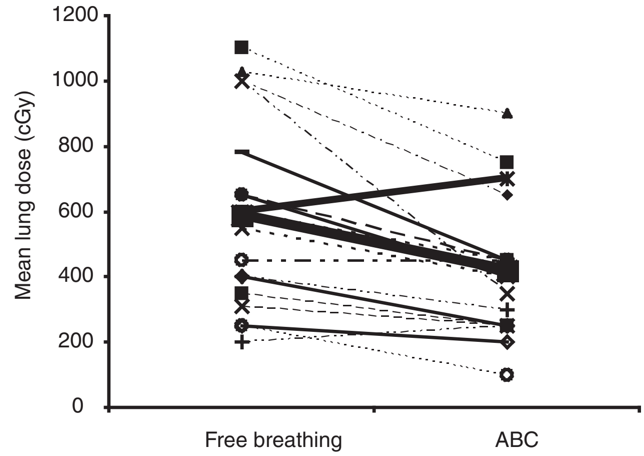

Figure 1 - Mean ipsilateral lung dose (cGy) in each patient in free-breathing condition and with the ABC system. The thickest line represents the mean value.

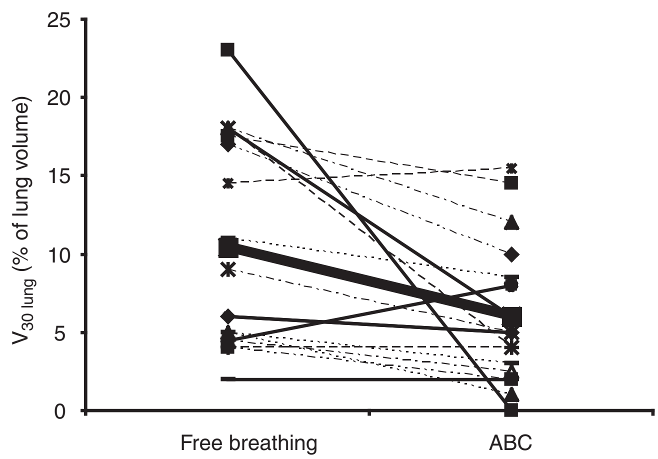

Figure 2 - V30 for the ipsilateral lung in each patient in free-breathing condition and with the ABC system. The thickest line represents the mean value.

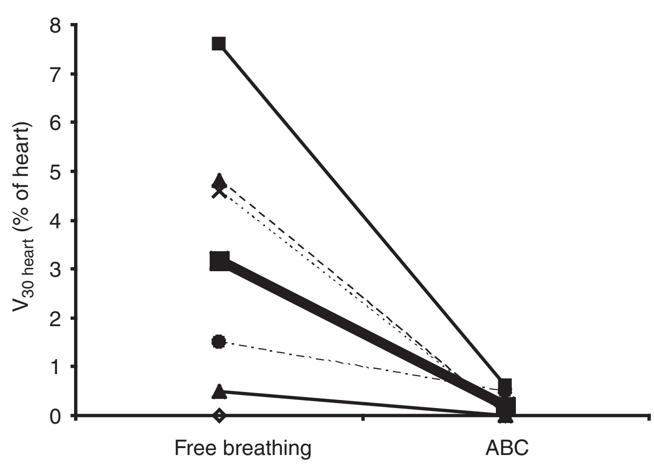

Figure 3 - V30 for the heart in each patient in free-breathing condition and with the ABC system. The thickest line represents the mean value.

cer[2-4,9,10,20-22]. However, to our knowledge, a perspective evaluation of feasibility of ABC-based radiotherapy planning in unselected patients is still lacking.

We carried out an investigation on the feasibility of ABC use for adjuvant radiotherapy in unselected patients with early breast cancer. In our experience, all but 2 of the enrolled patients (90%) completed the treatment planning in 1-5 sessions (median, 3). Given that for FB 3D-CRT treatment planning only one session was needed, a mean of 2 additional sessions was required to complete treatment with the ABC. Therefore, use of the ABC led to an increased workload for our radiotherapy department.

ABC use allowed for a better sparing of organs at risk than FB. A mean relative reduction of 25.3% for $MLD_{ipsilateral}$, 31.4% for $V30_{lung}$ and 91.0% for $V30_{heart}$ was recorded. Some interindividual variability was observed. Anatomical reasons, such as a different chest wall curvature and different size and shape of the breast, might have determined such variability. Our dosimetric results are in agreement with the literature.

Remouchamps *et al.*[10] in 2003 presented their initial clinical experience with the ABC for moderate deep inspiration breath hold during adjuvant whole breast radiotherapy in 5 left-sided breast cancer patients. After standard virtual simulation, patients with >2% of the heart receiving >30 Gy in free breathing were selected. A reduction in heart $V30_{heart}$ was achieved in patients with left-sided breast cancer[10]. A dosimetric planning study was performed by the same group in 15 patients with breast cancer (9 left and 6 right-sided). Patients underwent standard FB and ABC CT scans in the treatment position. Internal mammary and supraclavicular nodal regions were included in the target volume. Moderate deep inspiration breath hold significantly reduced the dose to the heart and the lung[4].

Sixel *et al.*[9] used ABC to quantify the potential benefit of radiation delivery during deep inspiration breath hold in 5 left-sided breast cancer patients. The internal mammary node region was always included in the target volume. The influence of the ABC on irradiated heart volumes varied considerably among the 5 patients. Three patients with substantial cardiac volume in the treatment field during normal respiration showed a significant dose-volume histogram improvement when deep inspiration was applied, with decreases in the heart volume receiving 25 Gy of more than 40 cc. Interestingly, the deep inspiration breath hold technique resulted in an increased heart volume irradiated in the other 2 patients[9].

One of the major drawbacks of the present study was the difference of PTV in FB and ABC plans. In fact, because of the almost negligible chest wall movement during breath hold when using ABC[14], we decided to eliminate the internal margin component from the PTV. This obviously led to a smaller PTV with ABC in almost all patients. Therefore, it is difficult to discern the advantages of ABC use deriving from a PTV reduction to the displacement of organs at risk relative to the radiation fields.

Three patients showed a slight worsening of dosimetric parameters for the lung (increase in both $MLD_{ipsilateral}$ and $V30_{lung}$ in one patient, increase in only $MLD_{ipsilateral}$ in another, and an increase in only $V30_{lung}$ in the last) with ABC, despite a relative reduction of PTV due to the abolition of the internal margin. All of them underwent ABC treatment planning in deep breath hold inspiration. In some patients, deep inspiration might produce a displacement of the contralateral breast relative to the target. Since beam angulation was adapted to prevent contralateral breast irradiation, in some cases a larger part of lung volume could have been irradiated.

Since treatment planning with the ABC leads to an increased workload compared to FB, selection criteria should be defined to rationalize its use. MLD was described as a reliable parameter in predicting the risk of radiation pneumonitis[23]. Lungs have been usually considered as a paired organ, and dosimetric parameters were computed based on dose distribution in both lungs[24, 25]. In the present study, we chose to consider the ipsilateral lung dose distribution, based on the consideration that, using a tangential technique, the dose to the contralateral lung is almost negligible. As a result, our values of MLD are probably “overestimated” compared to published values. Published data suggest that the risk of grade II radiation pneumonitis becomes noticeable if the MLD exceeds 10 Gy[23]. In our experience, MLD values were always below 10 Gy. In FB treatment planning, this could be due to the use of individualized internal margins[26] and forward intensity-modulated planning[16,27]. If these results are confirmed in a larger series and corroborated by clinical data, the risks of radiation pneumonitis could be so low as to not be further improved by irradiation during inspiration breath hold with the ABC.

Meta-analyses including older randomized trials –which employed outdated techniques with large target volumes, low energy photon beams and no CT simulation – suggested that the risk of ischemic heart death is increased in left-sided breast cancer patients 10 years after adjuvant radiation therapy[28,29]. More recent randomized trials and population-based case-control studies found only a small impact of left-sided breast irradiation on overall cardiac mortality and morbidity[30-32] with a mega-voltage tangential treatment technique. Data from National Cancer Institute’s Surveillance, Epidemiology and End Results data base on women treated between 1986 and 1993 showed a hazard ratio for left *versus* right-sided patients of 1.07 for ischemic heart disease and 1.05 for heart failure[33].

Although definitive conclusions about the impact of modern breast irradiation techniques on cardiac morbidity require more consistent data and a longer follow-up, the use of 3D-CRT together with CT simulation has undoubtedly played a major role in reducing cardiac mortality due to adjuvant radiation therapy for left-sided breast cancer over the years. In fact, a substantial reduction in volume of cardiac tissue encompassed within the radiation field can be achieved. However, as observed by Gyenes *et al.*[34], some patients with left-sided cancer may have an 'unfavorable anatomy' so that a substantial part of their heart is included in the tangential fields. For this subgroup of patients, long-term cardiac effects may not be negligible even with modern, standard treatment techniques.

Future investigations performing dosimetric comparison in selected patients could be of interest in order to rationalize use of the ABC. For example, dosimetric comparisons could be performed whenever conventional treatment planning without ABC results in unfavorable dose distribution in the lung or the heart. Unfortunately, dosimetric parameters and normal tissue complication probability models have a low accuracy in predicting late cardiac effects of radiotherapy, and criteria for defining "unfavorable cardiac anatomy" still remain little more than an arbitrary concept. Furthermore, it is still unclear whether or not there is a correlative effect between radiotherapy and several factors known to be independently associated with a high risk of cardiac morbidity (i.e., preexisting cardiac disease[35], hypertension, family history, diabetes[36], and administration of cardiotoxic systemic therapy with antracyclines[37] or trastuzumab[38]).

Conclusions

In unselected patients with early stage breast cancer, routine use of the ABC in postoperative 3D-CRT planning is feasible in clinical practice: 90% of patients completed the treatment planning with a mean of 3 sessions required to achieve a good level of collaboration. Our dosimetric results are encouraging and in agreement with the literature. However, in most patients, very low doses to critical normal structures, particularly to the lung, were observed during FB conditions and with the ABC. In such a low dose range, the potential clinical advantage of the ABC is of uncertain clinical significance. In our opinion, use of the ABC could be cautiously proposed in left-sided breast cancer patients, in order to reduce the risk of late cardiac morbidity, particularly in patients with an unfavorable dose distribution within the heart and/or with other cardiac risk factors.

References

1. Peto R: Worldwide meta-analysis of breast cancer treatment – EBCTCG 2005 – an update. Eur J Cancer Suppl, 3: 3, 2005.
2. Pedersen AN, Korreman S, Nyström H, Specht L: Breathing adapted radiotherapy of breast cancer: reduction of cardiac and pulmonary doses using voluntary inspiration breath-hold. Radiother Oncol, 72: 53-60, 2004.
3. Korreman SS, Pedersen AN, Aarup LR, Nøttrup TJ, Specht L, Nyström H: Reduction of cardiac and pulmonary complication probabilities after breathing adapted radiotherapy for breast cancer. Int J Radiat Oncol Biol Phys, 65: 1375-1380, 2006.
4. Remouchamps VM, Vicini FA, Sharpe MB, Kestin LL, Martinez AA, Wong JW: Significant reductions in heart and lung doses using deep inspiration breath hold with active breathing control and intensity-modulated radiation therapy for patients treated with locoregional breast irradiation. Int J Radiat Oncol Biol Phys, 55: 392-406, 2003.
5. Lu HM, Cash E, Chen MH, Chin L, Manning WJ, Harris J, Bornstein B: Reduction of cardiac volume in left-breast treatment fields by respiratory maneuvers: a CT study. Int J Radiat Oncol Biol Phys, 47: 895-904, 2000.
6. Remouchamps VM, Letts N, Yan D, Vicini FA, Moreau M, Zielinski JA, Liang J, Kestin LL, Martinez AA, Wong JW: Three-dimensional evaluation of intra- and interfraction immobilization of lung and chest wall using active breathing control: a reproducibility study with breast cancer patients. Int J Radiat Oncol Biol Phys, 57: 968-978, 2003.
7. Stranzl H, Zurl B: Postoperative irradiation of left-sided breast cancer patients and cardiac toxicity. Does deep inspiration breath-hold (DIBH) technique protect the heart? Strahlenther Onkol, 184: 354-358, 2008.
8. Wong JW, Sharpe MB, Jaffray DA, Kini VR: Robertson JM, Stromberg JS, Martinez AA. The use of active breathing control (ABC) to reduce margin for breathing motion. Int J Radiation Oncology Biol Phys, 44: 911-919, 1999.
9. Sixel KE, Aznar MC, Ung YC: Deep inspiration breath hold to reduce irradiated heart volume in breast cancer patients. Int J Radiat Oncol Biol Phys, 49: 199-204, 2001.
10. Remouchamps VM, Letts N, Vicini FA, Sharpe MB, Kestin LL, Chen PY, Martinez AA, Wong JW: Initial clinical experience with moderate deep-inspiration breath hold using an active breathing control device in the treatment of patients with left-sided breast cancer using external beam radiation therapy. Int J Radiat Oncol Biol Phys, 56: 704-715, 2003.
11. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP: Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol, 5: 649-655, 1982.
12. Hurkmans CW, Borger JH, Pieters BR, Russell NS, Jansen EP, Mijnheer BJ: Variability in target volume delineation on CT scans of the breast. Int J Radiat Oncol Biol Phys, 50: 1366-1372, 2001.
13. Deodato F, Picardi V, D'Angelo E, Morganti AG, Macchia G, Tambaro R, Cilla S, Sallustio G, Cacchione P, Papiccio G, Abiuso C, Piermattei A: Daily on-line portal imaging: is it feasible? Tumori, 7: S259, 2008.
14. Remouchamps VM, Letts N, Yan D, Vicini FA, Moreau M, Zielinski JA, Liang J, Kestin LL, Martinez AA, Wong JW: Three-dimensional evaluation of intra- and interfraction immobilization of lung and chest wall using active breathing control: a reproducibility study with breast cancer patients. Int J Radiat Oncol Biol Phys, 57: 968-978, 2003.
15. Herrick JS, Neill CJ, Rosser PF: A comprehensive clinical 3-dimensional dosimetric analysis of forward planned IMRT and conventional wedge planned techniques for intact breast radiotherapy. Med Dosim, 33: 62-70, 2008.
16. Borghero YO, Salehpour M, McNeese MD, Stovall M, Smith SA, Johnson J, Perkins GH, Strom EA, Oh JL, Kirsner SM, Woodward WA, Yu TK, Buchholz TA: Multileaf field-in-field forward-planned intensity-modulated dose compensation for whole-breast irradiation is associated with reduced contralateral breast dose: a phantom model comparison. Radiother Oncol, 82: 324-328, 2007.

17. Hong L, Hunt M, Chui C, Spirou S, Forster K, Lee H, Yahalom J, Kutcher GJ, McCormick B: Intensity-modulated tangential beam irradiation of the intact breast. Int J Radiat Oncol Biol Phys, 44: 1155-1164, 1999.
18. Piermattei A, Fidanzio A, Azario L, Grimaldi L, D'Onofrio G, Cilla S, Stimato G, Gaudino D, Ramella S, D'Angelillo R, Cellini F, Trodella L, Russo A, Iadanza L, Zucca S, Fusco V, Di Napoli N, Gambacorta MA, Balducci M, Cellini N, Deodato F, Macchia G, Morganti AG: Application of a practical method for the isocenter point in-vivo dosimetry by a transit signal. Phys Med Biol, 52: 5101-5117, 2007.
19. Grimaldi L, D'Onofrio G, Cilla S, Fidanzio A, Stimato G, Azario L, Deodato F, Macchia G, Morganti A, Piermattei A: Breast in-vivo dosimetry by a portal ionization chamber. Med Physics, 34: 1121-1127, 2007.
20. Jagsi R, Moran JM, Kessler ML, Marsh RB, Balter JM, Pierce LJ: Respiratory motion of the heart and positional reproducibility under active breathing control. Int J Radiat Oncol Biol Phys, 68: 253-258, 2007.
21. Korreman SS, Pedersen AN, Nøttrup TJ, Specht L, Nyström H: Breathing adapted radiotherapy for breast cancer: comparison of free breathing gating with the breath-hold technique. Radiother Oncol, 76: 311-318, 2005.
22. Krauss DJ, Kestin LL, Raff G, Yan D, Wong J, Gentry R, Letts N, Vargas CE, Martinez AA, Vicini FA: MRI-based volumetric assessment of cardiac anatomy and dose reduction via active breathing control during irradiation for left-sided breast cancer. Int J Radiat Oncol Biol Phys, 61: 1243-1250, 2005.
23. Kwa SL, Lebesque JV, Theuws JC, Marks LB, Munley MT, Bentel G, Oetzel D, Spahn U, Graham MV, Drzymala RE, Purdy JA, Lichter AS, Martel MK, Ten Haken RK: Radiation pneumonitis as a function of mean lung dose: an analysis of pooled data of 540 pts. Int J Radiat Oncol Biol Phys, 28: 575-581, 1998.
24. Seppenwoolde Y, Lebesque JV: Partial irradiation of the lung. Semin Radiat Oncol, 11: 247-258, 2001.
25. Seppenwoolde Y, Lebesque JV, de Jaeger K, Belderbos JS, Boersma LJ, Schilstra C, Henning GT, Hayman JA, Martel MK, Ten Haken RK: Comparing different NTCP models that predict the incidence of radiation pneumonitis. Int J Radiat Oncol Biol Phys, 55: 724-735, 2003.
26. Chopra S, Dinshaw KA, Kamble R, Sarin R: Breast movement during normal and deep breathing, respiratory training and set up errors: implications for external beam partial breast irradiation. Br J Radiol, 79: 766-773, 2006.
27. Morganti AG, Cilla S, Valentini V, Digesù C, Macchia G, Deodato F, Ferrandina G, Cece MG, Cirocco M, Garganese G, Lullo LD, Traficante D, Scarabeo F, Panunzi S, Gaetano AD, Sallustio G, Cellini N, Sofo L, Piermattei A, Scambia G: Phase I-II studies on accelerated IMRT in breast carcinoma: Technical comparison and acute toxicity in 332 patients. Radiother Oncol, 90: 86-92, 2009.
28. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, Godwin J, Gray R, Hicks C, James S, MacKinnon E, McGale P, McHugh T, Peto R, Taylor C, Wang Y; Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of randomised trials. Lancet, 366: 2087-2106, 2005.
29. Cuzick J, Stewart H, Rutqvist L, Houghton J, Edwards R, Redmond C, Peto R, Baum M, Fisher B, Host H: Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol, 12: 447-453, 1994.
30. Paszat LF, Mackillop WJ, Groome PA, Boyd C, Schulze K, Holowaty E: Mortality from myocardial infarction after adjuvant radiotherapy for breast cancer in the surveillance, epidemiology, and end-results cancer registries. J Clin Oncol, 16: 2625-2631, 1998.
31. Giordano SH, Kuo YF, Freeman JL, Buchholz TA, Hortobagyi GN, Goodwin JS: Risk of cardiac death after adjuvant radiotherapy for breast cancer. J Natl Cancer Inst, 97: 419-424, 2005.
32. Darby SC, McGale P, Taylor CW, Peto R: Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. Lancet Oncol, 6: 557-565, 2005.
33. Patt DA, Goodwin JS, Kuo YF, Freeman JL, Zhang DD, Buchholz TA, Hortobagyi GN, Giordano SH: Cardiac morbidity of adjuvant radiotherapy for breast cancer. J Clin Oncol, 23: 7475-7482, 2005.
34. Gyenes G, Gagliardi G, Lax I, Fornander T, Rutqvist LE: Evaluation of irradiated heart volumes in stage I breast cancer patients treated with postoperative adjuvant radiotherapy. J Clin Oncol, 15: 1348-1353, 1997.
35. Harris EE: Cardiac mortality and morbidity after breast cancer treatment. Cancer Control, 15: 120-129, 2008.
36. Harris EE, Correa C, Hwang WT, Liao J, Litt HI, Ferrari VA, Solin LJ: Late cardiac mortality and morbidity in early-stage breast cancer patients after breast-conservation treatment. J Clin Oncol, 24: 4100-4106, 2006.
37. Woodward WA, Strom EA, McNeese MD, Perkins GH, Outlaw EL, Hortobagyi GN, Buzdar AU, Buchholz TA: Cardiovascular death and second non-breast cancer malignancy after postmastectomy radiation and doxorubicin-based chemotherapy. Int J Radiat Oncol Biol Phys, 57: 327-335, 2003.
38. Tan-Chiu E, Yothers G, Romond E, Geyer CE Jr, Ewer M, Keefe D, Shannon RP, Swain SM, Brown A, Fehrenbacher L, Vogel VG, Seay TE, Rastogi P, Mamounas EP, Wolmark N, Bryant J: Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab, as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol, 23: 7811-7819, 2005.