Feasibility of the use of the Active Breathing Co ordinator™ (ABC) in patients receiving radical radiotherapy for Non Small Cell Lung Cancer (NSCLC)

Helen McNair, Juliet Brock, J Richard N Symonds-Taylor, Sue Ashley, Sally Eagle, Philip M Evans, Anthony Kavanagh, Niki Panakis, Michael Brada

Royal Marsden NHS Foundation Trust and Institute of Cancer Research

Corresponding author
Helen A McNair
Radiotherapy Department
Downs rd
Sutton
Surrey
SM2 5PT

Tel: +44 (0) 20 8915 6053
Fax: +44 (0) 20 8915 6793
Email: Helen.McNair@rmh.nhs.uk

Type of paper:	Full length original paper
Short Title:	"Feasibility of ABC"
Total number of pages:	13
Number of figures:	5
Number of tables:	1
Keywords:	Lung cancer Radiotherapy Active breathing control Tumour motion

Abstract

Introduction

One method to overcome the problem of lung tumour movement in patients treated with radiotherapy is to restrict tumour motion with an Active Breathing Control (ABC) device. This study evaluated the feasibility of using ABC in patients receiving radical radiotherapy for non small cell lung cancer.

Method

18 patients, median (range) age of 66 (44-82)years, were consented for the study. A training session was conducted to establish the patient's breath hold level and breath hold time. Three planning scans were acquired using the ABC device. Reproducibility of breath hold was assessed by comparing lung volumes measured from the planning scans and the volume recorded by ABC. Patients were treated with a 3-field coplanar beam arrangement and treatment time (patient on and off the bed) and number of breath holds recorded. The tolerability of the device was assessed by weekly questionnaire. Quality assurance was performed on the two ABC devices used.

Results

17/18 patients completed 32 fractions of radiotherapy using ABC. All patients tolerated a maximum breath hold time >15secs. The mean (SD) patient training time was 13.8 (4.8) min and no patient found the ABC very uncomfortable. 6-13 breath holds of 10-14 secs were required per session. The mean treatment time was 15.8 mins (5.8 mins). The breath hold volumes were reproducible during treatment and also between the two ABC devices.

Conclusion

The use of ABC in patients receiving radical radiotherapy for NSCLC is feasible. It was not possible to predict a patient's ability to breath hold. A minimum tolerated breath hold time of 15 seconds is recommended prior to commencing treatment.

Introduction

Lung tumour movement is one of the major challenges in radiotherapy. A patient's breathing pattern varies from day to day and can vary during an individual radiotherapy fraction. The range of motion has been found to be as much as 12mm +/- 6mm in lower lobe tumours [1]. As a consequence planning target volume (PTV) margins in the region of 1.5-2cm are used when treating patients with radical radiotherapy. There are varying technical approaches being investigated to compensate for tumour motion and hence reduce margins. These include tracking the tumour [2], gating the treatment delivery to part of the respiratory cycle [3,4] and using 4d CT to determine the tumour mean position and create an internal target volume [5]. An alternative approach is to reduce the motion by using either a voluntary breath hold [6] or an assisted breath hold with an active breathing control device (Active Breathing Coordinator™, ABC) [6,7]. The potential of using ABC to reduce motion has been explored by comparing CT scans with and without ABC [8,9,7]. ABC has been used for treatment of Hodgkin's disease [10] and breast cancer [11] and was well tolerated. It has been speculated that the use of ABC during radical radiotherapy for lung cancer would be too demanding for patients [12,13,14]. However we have found in a previous study that lung cancer patients can maintain an average breath hold time of 20 seconds [15]. Although there are studies that report the treatment of lung cancer patients with ABC, reproducibility rather than feasibility was the focus [16,17]. In this study we test the feasibility of treating NSCLC patients with radical radiotherapy using ABC. The tolerability of the ABC is assessed and the procedure for treatment and time taken is presented. A quality assurance procedure for the ABC is also described.

Methods

The study protocol was approved by the local Committee for Clinical Research (CCR) and Local Research Ethics Committee (REC). Eighteen patients referred for radical radiotherapy for non small cell lung cancer (NSCLC) were consented for treatment using ABC. The mean (SD) age of the 18 patients consented was 68(10) years. 17 patients were performance status (PS) 0 or 1 and one patient was PS 2. FEV1 (range 1.36-3.03) was available for 9 patients. Five tumours

were positioned in the lower lobe, 8 in the upper lobe and 5 in the middle lobe (Table1)... 13 patients had received neo adjuvant chemotherapy (2-4 cycles of platinum based doublet).

The ABC device enables patients to maintain a breath hold at a predetermined volume and length of time. It consists of a mouthpiece connected to a turbine-type flow meter and a balloon valve which is controlled via a signal from a laptop computer outside the treatment room. The patient also has the ability to release the valve by depressing a handheld switch.

Patient training

Patients were trained immediately prior to the planning CT scan. Initially they were shown how to correctly position the mouthpiece between their teeth and lips and the importance of maintaining a good seal around the mouthpiece with their lips was emphasised [18]. Subsequently they assumed the treatment position on a lung board developed in-house. They were asked to breathe freely through the mouthpiece and with the nose clip attached until they felt comfortable i.e when the breathing trace on the ABC screen was regular. They were then asked to perform repeated deep breaths with gentle breaths in between and the maximum inspiratory volume (MIV) was recorded. The breath hold volume for treatment (threshold level) was initially set at 70% of the MIV and a 5 second breath hold time was entered. Next they were asked to take a deep breath and assisted breath hold commenced when the breathing trace crossed the threshold volume level. The remaining breath hold time in seconds were counted down via the room microphone by the radiographer controlling the device whilst another radiographer remained with the patient to reassure and check comfort. The breath holds were increased by 5 second intervals only when the patient was comfortable. The maximum breath hold time and the threshold level were saved in the patient's file in the ABC programme and the time from entering the room to reaching the maximum breath hold time recorded.

CT planning

When maximum breath hold time was reached a contrast scan in free breathing (FB), without the ABC device, was acquired (Philips Brilliance CT Big Bore, Philips Medical Systems UK) using

2mm slice thickness. The tattoo positions were marked in free breathing for patient alignment prior to treatment and the scan completed in breath hold. To determine the breath hold time necessary for the scan a surview was acquired with ABC. An extra 5 seconds was added onto the scan time indicated from the scanner to determine the total breath hold time required for the scan to be captured in a single breath hold. If this was not possible then a split scan was performed. A fast protocol was used by decreasing the rotation time from 0.75 secs to 0.5 secs and increasing the pitch from 0.3 to 0.7. Although the increased pitch may reduce the resolution this was compensated by eliminating blurring effect due to breathing. Intrafraction reproducibility was assessed by immediately repeating the planning scan with 2 further breath holds.

A 3-field coplanar conformal plan treating patients to a dose of 64Gy in 32 fractions was produced for each scan using Pinnacle³ (Philips, Reigate, UK). GTV volumes ranged between 6.4cm³ – 96.3cm³ (Table 1).

The simulator was used to verify the isocentre in breath hold using digitally reconstructed radiographs (DRRs) imported into Omnipro (IBA, Schwarzenbruck, Germany). This also familiarised the patients with the ABC procedure before the start of treatment.

Treatment delivery and verification

Patients were treated on Elekta linear accelerators (Elekta Oncology Systems Ltd Crawley, West Sussex, England) with *iview* GT electronic portal imaging (EPI) system. The patient was aligned to the tattoos in free breathing. The isocentre from the ABC plan was set in the anterior-posterior (AP) direction using the couch height, correcting for couch sag. In the right-left (RL) and superior-inferior (SI) directions the isocentre was initially set to the anterior tattoo in breath hold. The couch position was noted and the required distance to the planned isocentre moved using the couch read out hence allowing the patient to breathe freely.

Audio instructions were given from outside the room. The patient was prompted at the peak of a breathing cycle to 'breathe gently and then when you are ready take a deep breath in'. The linac was switched on at the trough of the breath prior to the hold to compensate for the ~3-4 sec time delay from switch on to radiation 'on' (Fig 1). The maximum breath hold time was used and a

radiographer counted the seconds down using the audio system. The linac and ABC interface were not connected which meant if either the treatment beam or the breath hold had completed the duty cycle the other could be individually interrupted and manually restored.

Orthogonal EPI were taken to evaluate any treatment set-up displacement. A no action level (NAL) protocol was used; on the first three fractions EPI 's were averaged to calculate the systematic errors and this was corrected for on fraction four [19]. EPIs were repeated weekly and a tolerance of 6 mm used for bony anatomy displacement. The set up displacement, with and without correction applied was used to calculate the systematic error (Σ) of the group, the standard deviation (SD) of the distribution of the average set-up displacements per patient and the random error (σ) of the group, the SD of the patients' set-up displacements averaged over the patient group. During treatment the total treatment time (patient on and off the bed) and number and length of breath holds required were recorded. Patients were asked to fill in a questionnaire weekly and rate how uncomfortable they found the device, choosing from; Not at all, A little, Quite a bit, or Very much. There was also free text space for comments.

To assess interfraction reproducibility of tumour position during radiotherapy two further CT scans using the ABC device were acquired in the middle (ABCmid) and at the end of the treatment schedule (ABCend) for the first 13 patients.

Staff training

Training sessions were conducted with the staff prior to use. This included an overview of the system and practising activating the ABC device whilst giving audio prompts. Consistent audio instructions were recommended to avoid misinterpretation by the patient and aid communication between the ABC operator and linac operator.

Quality assurance of ABC

Two ABC devices were used, one for CT and one for treatment. It is essential that breath hold volumes for predetermined threshold levels are consistent within and compared to each device. A calibration system was devised using a 3 litre volumetric syringe (Hans Rudolph Model 5530)

and in house developed ABC volume curve analysis software. The ABC turbine and valve were coupled directly to the syringe and the laptop computer connected directly to the ABC control unit. Repeated syringed 'breath' holds using a threshold of 1 litre were performed and the volume of the syringe plunger position was measured using a scaled ruler with 0.01 litre increments. The software analyses volume curves to give statistical data for each breath and generates a chart for analysis. The breath statistics produced are: the indicated air volume (V_r), the peak flow and the average of the flow while the flow was greater than one – half of the maximum (F_{ahm}), and the start and stop times for each breath. For held breaths the additional statistics were: the threshold volume (V_t), the start and stop times of the hold and the flow averaged over the first 100 ms of the hold period (F_h). This software was also used to analyse the patients breath holds during planning and treatment sessions.

To quantify the effect of varying flow rates on actual lung volume at breath hold the volumes recorded by the ABC at the repeat planning scans were compared to the volumes measured by outlining the lungs on the CT scans in the first 13 patients.

We also compared the variation in tidal volume prior to commencement of breath holding with the variation in breath hold volumes. The tidal volume was assessed by measuring the difference between the ABC device recorded values at maximum inspiration and maximum exhalation. The volumes were only recorded in the time period between the first and second breath-holds. Within this period any volumes recorded close to the breath-holds were not included. The exclusion was due to visual inspections of the breathing traces revealing that many patients altered their breathing pattern to compensate for previous, or anticipate upcoming, breath-holds. It was a possibility that even a single breath-hold might significantly alter the tidal volumes. To guard against this possibility some patients had the tidal volumes before treatment assessed. These pre breath hold volumes were compared to those measured in-between the first and second breath hold. This was only possible in cases when the ABC device had been on for a significant time before treatment and the patient had been at rest.

This study aims to test the tolerability of the ABC in patients receiving radical radiotherapy for NSCLC. In order for ABC to be used routinely in clinical practice patients must be able to hold

their breath for at least 15 secs, about 7 times for each treatment. In our earlier study 80% of patients were able to achieve this. If the success rate is <50% then the device is unlikely to be introduced into clinical practice. In order to detect this level of success we aimed to recruit 18 patients into this study. If 13 or more patients were able to tolerate the ABC then we proposed to introduce this into clinical practice ($\alpha_{1\text{-sided}}=5\%$; power=80%)[20]

Results

Feasibility

17 patients completed 32 fractions of radiotherapy. 1 patient (patient 13) requested to be treated without the device after 2 weeks of treatment. The mean (SD) patient training time from entering the room to determining maximum breath hold time was 13.8(4.8) mins.

All patients tolerated a maximum breath hold time of >15 seconds; median 20 secs (range 15 - 25secs). There was no relationship with the maximum breath hold time and age, FEV1 or performance status (Figure 2).

The mean (SD) threshold level was 1.33(0.38) litres held at a mean (SD) of 69 (13)% of the MIV. The mean (SD) breath hold volumes per patient as recorded by ABC ranged between 1.10l and 2.6l (0.03-0.23l) (Figure 3). Since the beam wedge filter takes ~ 6secs to move into place the breath holds during treatment were often split to correspond with any wedged/unwedged changes in the field. This resulted in a mean (SD) breath hold time required per patient of between 10 -14 (2-7) secs with a mean of 6 -13 breath holds per treatment session. The maximum breath hold time was determined by the patient and was generally <25 secs.

CT planning

All planning scans were acquired in a single breath hold. Although the increased pitch reduced resolution, the breath hold increased resolution by eliminating blurring due to breathing and resulted in a good quality CT scan (Figure 4a and 4b).

Treatment

The mean (SD) treatment time (patient on – off the bed) was 15.8(5.8) mins.

Questionnaires of 15 patients were collected. No patient found the ABC very uncomfortable. 2 patients found the device 'Quite a bit uncomfortable' at CT planning but this decreased to 'A little' after week 1. The level of discomfort increased during treatment in only one patient and this was due to the patient having a cold. Patients recorded problems with the nose piece (2 patients), dry mouth (2 patients) and coughing (1 patient). 6 patients made positive comments regarding how staff encouraged and helped them relax.

Set-up accuracy

Using the NAL protocol the Σ was <2 mm in the right-left (RL) and the anterior-posterior (AP) direction (Table 1). A Σ of 2.4 mm remained in the superior-inferior direction which was also the direction where the largest random error was determined.

Quality Assurance

Calibration of devices showed the breath hold volume was related to speed of flow at threshold level (Figure 5). This is due to the reaction time of the ABC devices which was recorded as 124 msec and 106 msec of CT and treatment ABC respectively. Patients mean (SD) flow rates at breath hold ranged between 0.67 – 2.04 l/s (0.17-0.76).

To quantify the effect of varying flow rates on the lung volume at breath hold the lung volumes on the 10 patients who had 3 planning CT scans were outlined and compared to the volumes recorded by the ABC. The repeat CT scans during treatment were not used because the treatment may affect the lung volume. The mean (SD) ABC-held lung volume on CT scans ranged between 3953-7326cm³ (15-271cm³) per patient and the mean (SD) lung volumes recorded by the ABC were 1.18 - 2.57l (0.01 - 0.05l) per patient. The SD of individual patients ABC-held lung volume was <4 % in 16 patients and 6.1 % in 1 patient.

The pre breath hold values of tidal volume were found to be in agreement with the values recorded in-between the first and second breath holds in all of the cases measured. In 15/18 patients the SD of the tidal volume between the first and second breath hold was greater than the

SD of the breath holds. Values taken in-between subsequent breath-holds were found to increasingly deviate from the pre breath hold values.

Discussion

This is the first study focusing on the feasibility of the use of ABC during the complete course of radical radiotherapy for NSCLC. Seventeen out of 18 patients completed a 6 ½ week radical course of radiotherapy using ABC. The mean breath hold time of 20 secs determined here was comparable with our previous study [15] and studies where the feasibility of ABC was evaluated but not combined with treatment [9,7,21]. However it was not necessary to continually use the maximum breath hold time during treatment, mean breath hold time during treatment was 10 -14 secs. The acceptability rate with ABC is higher compared to studies using deep inspiration breath hold (dIBH). This may be because of differences in breath hold volumes. ABC uses 70%-80% of MIV whereas dIBH used 100% vital capacity which may cause fatigue when performing repeated breath holds [22]. We have since implemented ABC for all NSCLC patients receiving radiotherapy and recommend that the patient be able to hold their breath for a minimum of 15 seconds. The addition of concomitant chemotherapy may impact the feasibility. However 13/18 patients in this study received chemotherapy prior to radiotherapy and the patient who did not complete the study had not received chemotherapy. Exhale has been shown to hold the tumour in a more reproducible position than inhale [23]. The ABC uses exhale as its reference volume so the mid deep inspiration (mDIBH) breath hold is relative to the exhale volume. The additional advantage of treating during inhalation is that the V20 and the mean lung dose decreases with an increase in lung volume there is potential for dose escalation [24]. We have demonstrated that using ABC the dose could theoretically be escalated from 64Gy to a mean of 73.7 +/- 6.5Gy resulting in a statistically significant increase in tumour control probability from 0.15 +/- 0.01 to 0.29 +/- 0.11 [25].

In earlier reported studies it was not possible to complete the planning scan in one breath hold [8,26,27,9,7]. However modern multislice CT scanners enable a fast protocol to cover the entire

thorax. Although there is a risk of losing resolution, a fast scan enables a single breath hold ABC scan which reduces blurring caused by breathing.

Coaching for breath hold is essential for the success of the procedure. During gating a combination of audio and visual aids improve the reproducibility of breathing cycles; audio aid improves frequency and visual aid the amplitude of each breath [28]. With ABC we found that audio coaching was adequate. It has been suggested that patients need to be coached to breathe evenly and consistently to ensure a consistent held volume and avoid changes in the tumour position with each breath hold, particularly because the ABC resets expiration to zero [8]. However comfortable inspiration may be difficult to reproduce. When we compared the variation in tidal volume ('uncoached') with the variation in ABC-held volumes, 15/18 patients had more reproducible ABC-held volumes.

The delay between the ABC activation and the balloon valve closing causes a variation in held volume, depending on the flow rate when the threshold volume is reached (Figure 5). Any difference in volume held may result in a variation of tumour position. With a flow rate of 2 l/s there was a 300ml overshoot for 1.8l inspired volume but this was reduced for a rate of 1 l/s [29]. In our patients the mean flow rate at the threshold level was 0.67 - 2.04l/s and mean (SD) breath hold was 1.10 - 2.6l (0.03 - 0.23l). The important factor is whether the patient's flow rate and subsequent breath hold are consistent. To investigate the relevance of the variation in ABC recorded volumes we used the 3 repeat planning CT scans acquired in the first 12 patients. The overshoot of the threshold volume on the ABC was 80 – 400ml (Figure 3) but the SD of the lung volume measured on the CT was < 6% of the total lung volume. We also determined the intra fraction reproducibility of the tumour position during these breath holds to be < 2mm, [Brock J , unpublished] which corresponds with the intrafraction reproducibility of an earlier version of the ABC device in our previous study [15]. This suggests that although there is an overshoot beyond the threshold this is consistent for a given patient, and the variation in held lung volume of < 6% of the mean lung volume does not result in clinically significant changes in tumour position. However this is patient dependant and needs to be investigated further in a larger group of patients.

For example, patient number 8 had the largest SD (0.23l) of breath hold volumes and appeared to perform a large exhale before inhalation which may have contributed to the variation. However closer inspection revealed that the SD was explained by extremely variable initial breath holds in 3 fractions. This may have been due to the patient or equipment problems and was resolved before treatment commenced. When these initial breath holds were removed the SD was 0.08 l illustrating the consistency of the unusual breath hold pattern i.e performing large exhales prior to breath hold.

Reproducibility of breath hold and tumour position may also be related to lung volume and tumour location for example lower lobe tumours may be more sensitive to lung volume changes.

Staff training is important because confident staff will help the patient to relax. 6 patients made positive comments regarding the instructions given by the radiographers. The importance of clear communication has been emphasised in earlier studies where poor communication was cited as a reason for patients not tolerating ABC [14,30].

EPI images and bony anatomy were used to evaluate set up displacements and although the Σ and σ errors found here agreed with other published reports EPI has been shown to be less accurate than 3D, kilo-voltage imaging, cone beam CT (CBCT) due to the poor image quality of EPI in the thorax region [31]. Using the diaphragm as a surrogate of tumour position may seem logical, particularly since the patient is in breath hold. However this does not provide an accurate surrogate [32]. The 2 mins required to acquire a CBCT image is too long for a single breath hold and currently it is not possible to interrupt the CBCT acquisition. However we have since acquired CBCTs with the patient performing repeated breath holds with maximum breath hold time. The majority of the projections are therefore acquired with the patient in breath hold and the reconstructed scan has been suitable for matching to the planning CT scan.

Conclusions

The use of ABC in patients receiving radical radiotherapy for NSCLC is feasible. Patients ability to breath hold was not related to age, performance status or FEV1. A minimum tolerated breath hold time of 15 secs is recommended prior to commencing treatment. The breath hold volumes

were reproducible during treatment and also between two ABC devices. ABC allows the potential for dose escalation and possibly improved tumour control. The development of equipment and software to allow gating of the ABC with the linac and the acquisition of CBCT with breath hold would improve the treatment delivery and verification.

Conflict of interest Statement

There are no conflicts of interest

Acknowledgements

This work was undertaken in The Royal Marsden NHS Foundation Trust who received a proportion of its funding from the NHS Executive; the views expressed in this publication are those of the authors and not necessarily those of the NHS Executive. This work was supported by the Institute of Cancer Research, The Royal Marsden NHS Foundation Trust and Cancer Research UK Section of Radiotherapy [CRUK] grant number C46/A2131. We acknowledge NHS funding to the NIHR Biomedical Research Centre

Figure 1. Schematic diagram showing breathing cycle, when to prompt the patient to take a deep breath and the breath hold

Figure 2. Age, breath hold time and performance status (PS) of patients treated with ABC

Figure 3. Mean and standard deviation (SD) of breath hold volumes at treatment recorded by ABC compared to the predetermined threshold volume

Figure 4a. CT scan acquired with patient in Free Breathing (FB)

Figure 4b. CT scan acquired with patient using Active Breathing Co ordinator (ABC)

Figure 5. Flow at hold v volume held measured using 3l volumetric syringe

Figure 1

Figure 2.

Figure 3.

Figure 4a.

Figure 4b.

Figure 5.

Table 1 Patient and tumour characteristics

Age	PS	Stage	Tumour position	FEV1	Chemotherapy	GTV (cm ³)	Max breath hold time (secs)
65	1	IB	RMZ	-	Y	32.9	20
85	1	IIIB	RLL	1.36	Y	18.6	20
76	1	IIIB	LUL	1.67	Y	41	15
63	1	IIIB	RMZ	1.5	Y	21.5	25
74	1	IIIA	LLL	-	Y	89.6	25
62	0	111B	Central	-	Y	85.2	20
63	1	IIIB	Lt Hilar	-	Y	76.81	20
59	1	IIIB	LUL	2.8	Y	20	25
44	0	111B	RUL	3.03	Y	47.9	20
79	0	IB/IIA	RML	1.65	N	22.4	20
67	0	IIIA	LLL	-	Y	6.4	20
60	1	IIIB	LUL	1.82	Y	45.9	20
79	2	IB	LLL	-	N	24.3	15
59	1	IB	RUL	1.7	Y	35.9	15
76	0	IIB	RUL	-	N	43.3	15
77	0	IB	RLL	-	N	53.87	20
61	0	IIIA	RUL	1.88	N	55.28	20
79	1	III A	RUL	-	Y	96.28	25

Table2.Set-up errors calculated without (i.e aligning to skin marks only) and with the no action level protocol applied

	Set up protocol	Right-left (mm)	Superior-Inferior (mm)	Anterior-posterior (mm)
Σ	Skin marks	2.9	3.9	1.9
σ	Skin marks	3	4	2.2
Σ	No action level protocol	1.9	2.4	1.4
σ	No action level protocol	3	3.7	2.1

Σ - Systematic error
 σ - Random error

Reference

1. Seppenwoolde, Y, Shirato, H., Kitamura, K..et.al. Precise and real-time measurement of 3D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy. *Int. J Radiat. Oncol Biol. Phys.* 2002;53:822-834.
2. Shimizu, S, Shirato, H., Ogura, S..et.al. Detection of lung tumor movement in real-time tumor-tracking radiotherapy. *Int. J Radiat. Oncol Biol. Phys.* 2001;51:304-310.
3. Ford, E C, Mageras, G. S., Yorke, E., Rosenzweig, K. E., Wagman, R., and Ling, C. C. Evaluation of respiratory movement during gated radiotherapy using film and electronic portal imaging. *Int. J Radiat. Oncol Biol. Phys.* 2002;52:522-531.
4. Shirato, H, Shimizu, S., Kunieda, T..et.al. Physical aspects of a real-time tumor-tracking system for gated radiotherapy. *Int. J Radiat. Oncol Biol. Phys.* 2000;48:1187-1195.
5. Wolthaus, J W, Sonke, J. J., van, H. M., and Damen, E. M. Reconstruction of a time-averaged midposition CT scan for radiotherapy planning of lung cancer patients using deformable registration. *Med Phys.* 2008;35:3998-4011.
6. Rosenzweig, K E, Hanley, J., Mah, D..et.al. The deep inspiration breath-hold technique in the treatment of inoperable non-small-cell lung cancer. *Int. J Radiat. Oncol Biol. Phys.* 2000;48:81-87.
7. Wong, J W, Sharpe, M. B., Jaffray, D. A..et.al. The use of active breathing control (ABC) to reduce margin for breathing motion. *Int. J Radiat. Oncol Biol. Phys.* 1999;44:911-919.
8. Cheung, P C, Sixel, K. E., Tirona, R., and Ung, Y. C. Reproducibility of lung tumor position and reduction of lung mass within the planning target volume using active breathing control (ABC). *Int. J Radiat. Oncol Biol. Phys.* 2003;57:1437-1442.
9. Wilson, E M, Williams, F. J., Lyn, B. E., Wong, J. W., and Aird, E. G. Validation of active breathing control in patients with non-small-cell lung cancer to be treated with CHARTWEL. *Int. J Radiat. Oncol Biol. Phys.* 2003;57:864-874.
10. Claude, L, Malet, C., Pommier, P., Thiesse, P., Chabaud, S., and Carrie, C. Active breathing control for Hodgkin's disease in childhood and adolescence: feasibility, advantages, and limits. *Int. J Radiat. Oncol Biol. Phys.* 2007;67:1470-1475.
11. Remouchamps, V M, Letts, N., Yan, D..et.al. 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.* 2003;57:968-978.
12. Kashani, R, Balter, J. M., Hayman, J. A., Henning, G. T., and van, H. M. Short-term and long-term reproducibility of lung tumor position using active breathing control (ABC). *Int. J Radiat. Oncol Biol. Phys.* 2006; 65:1553-1559.
13. Kimura, T, Hirokawa, Y., Murakami, Y..et.al. Reproducibility of organ position using voluntary breath-hold method with spirometer for extracranial stereotactic radiotherapy. *Int J Radiat Oncol Biol Phys.* 2004;60:1307-1313.

14. Rosenzweig, K E, Hanley, J., Mah, D..et.al. The deep inspiration breath-hold technique in the treatment of inoperable non-small-cell lung cancer. *Int. J Radiat. Oncol Biol. Phys.* 2000;48:81-87.
15. Panakis, N, McNair, H. A., Christian, J. A..et.al. Defining the margins in the radical radiotherapy of non-small cell lung cancer (NSCLC) with active breathing control (ABC) and the effect on physical lung parameters. *Radiother. Oncol.* 2008;87:65-73.
16. Sarrut, D, Boldea, V., Ayadi, M..et.al. Nonrigid registration method to assess reproducibility of breath-holding with ABC in lung cancer. *Int J Radiat Oncol Biol Phys.* 2005;61:594-607.
17. Sarrut, D, Perol, D., Pommier, P., and Carrie, C. [Air breath control radiotherapy in severe insufficiency respiratory patients with NSCL: application for deformable registration method in thoracic radiotherapy]. *Cancer/Radiothérapie.* 2006;10:377-380.
18. McNair, H. Feasibility of active breathing coordinator (ABC). *Radiother and Oncol.* 2006;81:S183-S183.
19. de Boer, H C and Heijmen, B. J. A protocol for the reduction of systematic patient setup errors with minimal portal imaging workload. *Int. J. Radiat. Oncol. Biol. Phys.* 2001;50:1350-1365.
20. A'Hern, R P. Sample size tables for exact single-stage phase II designs. *Stats Med.* 2001;20:859-866.
21. Koshani, R, Balter, J. M., Hayman, J. A., Henning, G. T., and van Herk, M. Short-term and long-term reproducibility of lung tumor position using active breathing control (ABC). *Int J of Radiat Oncol Biol Phys.* 2006;65:1553-1559.
22. Rosenzweig, K E, Hanley, J., Mah, D..et.al. The deep inspiration breath-hold technique in the treatment of inoperable non-small-cell lung cancer. *Int. J Radiat. Oncol Biol. Phys.* 2000;48:81-87.
23. Koshani, R, Balter, J. M., Hayman, J. A., Henning, G. T., and van Herk, M. Short-term and long-term reproducibility of lung tumor position using active breathing control (ABC). *Int J Radiat Oncol Biol Phys.* 2006;65:1553-1559.
24. Hanley, J, Debois, M. M., Mah, D..et.al. Deep inspiration breath-hold technique for lung tumors: the potential value of target immobilization and reduced lung density in dose escalation. *Int J Radiat Oncol Biol Phys.* 1999;45:603-611.
25. Partridge, M, Tree, A., Brock, J..et.al. Improvement in tumour control probability with active breathing control and dose escalation: A modelling study. *Radiother and Oncol.* 2009;91:325-329.
26. Koshani, R, Balter, J. M., Hayman, J. A., Henning, G. T., and van Herk, M. Short-term and long-term reproducibility of lung tumor position using active breathing control (ABC). *Int J Radiat Oncol Biol Phys.* 2006;65:1553-1559.
27. Remouchamps, V M, Letts, N., Vicini, F. A..et.al. 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.* 2003;56:704-715.

28. George, R, Chung, T. D., Vedam, S. S..et.al. Audio-visual biofeedback for respiratory-gated radiotherapy: Impact of audio instruction and audio-visual biofeedback on respiratory-gated radiotherapy. *Int J Radiat Oncol Biol Phys.* 2006;65:924-933.
29. Remouchamps, V M, Letts, N., Yan, D..et.al. 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.* 2003;57:968-978.
30. Eccles, C, Brock, K. K., Bissonnette, J. P., Hawkins, M., and Dawson, L. A. Reproducibility of liver position using active breathing coordinator for liver cancer radiotherapy. *Int J Radiat Oncol Biol Phys.* 2006;64:751-759.
31. Borst, G R, Sonke, J. J., Betgen, A., Remeijer, P., van Herk, M., and Lebesque, J. V. Kilo-Voltage Cone-Beam Computed Tomography Setup Measurements for Lung Cancer Patients; First Clinical Results and Comparison With Electronic Portal-Imaging Device. *Int J Radiat Oncol Biol Phys.* 2007;68:555-561.
32. Brock, J, McNair, H., Panakis, N., Ashely S, and Brada, M. Correlation between Diaphragm position and intrafraction and interfraction tumour position using the Active Breathing Co-ordinator (ABC) throughout radiotherapy for non-small cell lung cancer (NSCLC). *Radiother and Oncol.* 2007;84:S152-