The use of the Active Breathing Coordinator throughout radical non-small cell lung cancer (NSCLC) radiotherapy

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Conflict of Interest Notification

The authors do not have any conflicts of interest to declare
Abstract

Purpose

To assess feasibility and reproducibility of an Active Breathing Co-ordinator used throughout radical radiotherapy for non-small cell lung cancer, and compare lung dosimetric parameters between free-breathing and ABC plans.

Methods and Materials

18 patients, recruited into an approved study, had free-breathing and ABC breath-hold treatment plans generated. Lung volume, $V_{20}$ and MLD were compared. Treatment (64 Gy in 32 fractions, 5 days/week) was delivered in breath-hold. Repeat breath-hold CT scans were used to assess change in GTV size and position. Set-up error was also measured and potential GTV-PTV margins calculated.

Results

17/18 patients completed RT using ABC daily. Intrafraction tumour position was consistent but interfraction variation had mean (standard deviation) values of 4.5 (5.2), 3.5 (2.9) and 3.4 (3.8) mm in the superior-inferior (SI), right-left (RL) and antero-posterior (AP) directions respectively. Tumour moved partially outside the PTV in 5 patients. Mean reduction in GTV volume from planning to end of treatment was 25 % ($p = 0.003$). Potentially required PTV margins were 17.5, 11.5 and 11.4 mm in SI, RL and AP directions. ABC reduced $V_{20}$ by 13 % ($p =
0.0001), $V_{13}$ by 12% ($p = 0.001$) and MLD by 13% ($p < 0.001$) compared to free-breathing; lung volume increased by 41% ($p < 0.001$).

**Conclusions**

Clinically significant movements of GTV were seen during RT for NSCLC using ABC. Image guidance and adaptive RT are recommended with ABC. However even without margin reduction ABC reduces the risk of lung toxicity and should allow dose escalation.

Keywords: lung; radiotherapy; ABC; interfraction variation; margins
**Introduction**

External beam radiotherapy (RT), with or without chemotherapy, is the treatment of choice for inoperable non-small cell lung cancer (NSCLC), although with standard techniques local disease control and survival are disappointing. There is evidence for a dose-response effect [1, 2] and for improved outcome with increased dose intensity [3]. However, dose escalation is limited by normal tissue toxicity, particularly of the lung. Attempts to increase dose above lung tolerance have been associated with increased radiation-induced pneumonitis [4, 5], while concomitant chemotherapy is associated with increased oesophagitis [6-11].

In current practice the size of the RT planning target volume (PTV) takes into account the movement of the tumour with respiration and consequent uncertainty of the tumour position, as well as uncertainties about patient position and other errors [12]. As a result a significant volume of normal lung tissue is included in the PTV.

The aim of modern RT is to reduce the dose and/or volume of normal tissue treated, particularly the lung, to allow for safe dose escalation to the tumour. One of the options is to control for tumour motion with respiration, and two main strategies to achieve this exist. Tumour motion can be unrestricted and monitored, with delivery of RT gated to a pre-defined phase of the respiratory cycle [13-15] or following the moving tumour [16]. Alternatively motion can be
minimized by planning and treating in passive [17-21] or active [22, 23] breath-hold.

We previously assessed the potential benefit of an active breath-hold technique using the Active Breathing Co-ordinator (Elekta Oncology systems Ltd Crawley, West Sussex, UK). Patients receiving radical radiotherapy were scanned in moderate deep inspiration breath-hold using ABC prior to, in the middle and in the final week of the treatment course. The use of ABC during the computed tomography (CT) scans was tolerated by 25 out of 30 (83%) patients. The random contribution of periodic tumour motion was reduced by 90% in the superior-inferior direction compared with free-breathing, and the reduction in PTV size with ABC resulted in an 18-25% relative reduction in physical lung parameters [24].

In this study the ABC device was used throughout a 6 week course of radical radiotherapy for NSCLC. We assessed feasibility and the effect on tumour position reproducibility between consecutive breath-holds and over the treatment course. We also assessed the potential benefit of ABC on lung dosimetric parameters and margins.

**Patients and methods**

The study protocol was approved by the local Committee for Clinical
Research (CCR) and Local Research Ethics Committee (REC). Eligible patients, due to receive radical RT for NSCLC, were consented in accordance with international and local guidelines.

Between April 2006 and August 2008 18 patients were entered in the study. All fulfilled the eligibility criteria of unresectable or inoperable locally advanced NSCLC, stage I – IIIB, WHO performance status 0 – 1, ability to give written informed consent and to comprehend instructions about the ABC procedure, and an ability to maintain breath-hold for at least 15 seconds with ABC.

The mean age of 18 assessable patients was 68 years (range 44 – 85) and the majority had stage IIIA or IIIB disease (Table 1).

**Equipment**

The use of the ABC device in our institution has been described previously [24]. Radiotherapy planning CT scans were acquired (Philips Brilliance CT Big Bore, Philips Medical Systems, UK) according to a standard protocol (2 mm slice thickness, collimation 16 x 1.5 mm, pitch 0.813, field of view 600 mm, rotation time 0.75 seconds, table speed 26 mm/second). Intravenous contrast was used in patients with adequate renal function. Images were transferred to the Pinnacle³ treatment planning system (Philips, Reigate, UK).

*Image acquisition*
With the patient in the treatment position, and following training with the ABC device, a free-breathing CT was performed with the patient instructed to breathe normally. The ABC mouthpiece and nose-clip were then attached and 3 CT scans with breath hold at approximately 70% of maximum inspiratory volume were acquired (ABCbase1, ABCbase2 and ABCbase3) in the same position. Tattoos to aid patient set-up were marked in free breathing.

Further CT scans in the treatment position and in breath-hold were performed in the middle (ABCmid) and at the end (ABCend) of the treatment course.

Target localization

Target localization was standardized with a set of guidelines aimed at minimizing intraobserver and interobserver variation. These included pre-set CT window/levels for use in contouring each region of interest, and specific instructions for fusing images.

On the free-breathing (FB) scan, visible tumour and involved lymph nodes (≥ 1 cm in diameter on CT and PET positive) were outlined and defined as the ‘free-breathing gross tumour volume’ (FBGTV). Spinal cord, normal lung (defined as both lungs as a single organ minus the GTV), heart and oesophagus were also outlined. The ‘free-breathing planning target volume’ (FBPTV) was generated by expanding the GTV by 1.5 cm in the superior-inferior direction and 1.0 cm axially. The co-ordinates for the FBGTV target centre (generated by the treatment
planning system using a spherical autoplacement function as the “centre of mass”, COM) and the volume of FBGTV, FBPTV and both lungs were recorded.

The same structures were outlined on the ABCbase1 scan (fused with the free-breathing images aligned using bony anatomy close to the tumour). ABC1PTV was generated using an identical margin (as above). The co-ordinates for the ABC1GTV centre of mass and the volumes of ABC1GTV, ABC1PTV and both lungs were recorded.

Similarly GTV and both lungs were outlined on ABC base2, ABCbase3, ABCmid and ABCend CT scans.

Planning

Conventional multiple field conformal RT was planned on the first ABC breath-hold scan (ABCbase1) using the Pinnacle\(^3\) treatment planning system and incorporating tissue inhomogeneity correction. A back-up treatment plan using the same beam arrangement was also prepared for the free-breathing scan in case of poor ABC tolerance and for comparison of dose volume parameters. After clinical acceptance of both plans the isocentre was verified using fluoroscopy.

Treatment
Treatment was delivered using multiple ABC breath-holds, given in 32 fractions of 2 Gy over $6\frac{1}{2}$ weeks (total 64Gy). Electronic portal imaging (EPI) was used to verify the patient set-up position.

**Data acquisition**

*Assessment of intrafraction tumour position*

Contours from ABCbase1 and ABCbase2 were imported into the ABCbase3 image dataset. Images were aligned using the bony anatomy of the spine in the region of the tumour, viewed in 3 planes. This was initially performed manually and subsequently using an automated function. The COM of the three ABCGTV contours were generated and their co-ordinates recorded. The standard deviation of displacement of COM of ABC2 and ABC3 relative to ABC1 provided a measure of the intrafraction variations of movement of the GTV. Non-overlapping volumes for ABC1GTV, ABC2GTV and ABC3GTV were also calculated.

*Assessment of interfraction tumour position*

ABCbase1, ABCmid and ABCend images were fused using bony anatomy as above. The standard deviation (SD) of the individual mean displacements of the COM of ABCmid and ABCend relative to ABC1 provided a measure of the systematic interfraction movement of the GTV of the patient group. The group random error was determined by calculating the mean of the individual SDs. The non-overlap regions comparing ABCmidGTV with ABC1GTV, and ABCendGTV
with ABC1GTV were calculated, as was any extent of the contours outside of the ABC1PTV.

For the purposes of this study CTV was equivalent to GTV. Potential intra-observer variation in tumour delineation was not taken into account.

We wished to test whether there was a relationship between change in the size of the lesion over the treatment course and shift in the GTV centre. GTV volumes in cm$^3$ were recorded from the ABC1 and ABCend CT scans and percentage changes calculated. A paired t-test was used to determine the significance of the change in GTV volume.

**CTV-PTV margin calculation**

A potential CTV-PTV margin using ABC was calculated. Errors were combined in quadrature, margin = $2.5 \Sigma + 0.7 \sigma$, where $\Sigma$ is total systematic errors and $\sigma$ total random errors of the CTV [25].

**Assessment of target and organ at risk dose-volume data**

The percentage volume of lung treated to a dose of $\geq 20$ Gy ($V_{20}$), mean lung dose (MLD), the percentage volume of the PTV receiving 90% of the prescription dose ($PTV_{90}$), $PTV_{95}$ and maximum spinal cord dose were recorded. Mean change in each parameter from the free-breathing to the ABC plans was calculated.
Results

17/18 patients completed the course of radiotherapy with ABC. One patient chose to transfer to treatment with free-breathing after 2 weeks of treatment although continued with subsequent ABC breath-hold CT scans and was included in the dosimetric analysis.

Assessment of intrafraction tumour position

Mean intrafraction variation in the GTV COM was 1.7 - 2.0 mm (SD 1.6 - 1.7 mm) in the 3 directions (Table 2). As the interim analysis after 12 patients showed reproducible intrafraction tumour position with ABC no further measurements were carried out.

Assessment of interfraction tumour position

Significant interfraction tumour position variation (≥ 10 mm) was seen in 5/18 patients. All movements occurred in either the superior inferior (SI) or anterior posterior (AP) directions which consequently had the largest systematic errors (Table 3). The largest recorded shift was 25 mm in the SI direction between ABCbase1 and ABCend for patient 1 (Figure 1). The absolute mean interfraction variation in breath-hold tumour position ranged from 3.4 to 4.5 mm (Table 2).

For the five patients there was partial movement of the GTV outside of the PTV with a mean (range) of 7 % (0.1 - 13 %) of the total GTV volume. This
unexpected result led to a modification of the study protocol after 12 patients had been treated, with ABC breath-hold CT scans performed at 1-2 weekly intervals throughout the course to allow for adaptation of the PTV if required. An adjustment of the PTV of > 5mm was required in 1 of the subsequent 6 patients.

There was a mean reduction in GTV volume from ABC1 to ABCend of 25 % (p = 0.003). For the 5 patients who showed interfraction tumour position variation, reduction in GTV volume was calculated as 59, 38, 2, 33 and 24 %.

**CTV-PTV margin**

Calculated margins were 17.5 mm, 11.5 mm and 11.4 mm in SI, RL and AP directions when using systematic and random set-up (Table 4) and tumour position errors (Table 3) using ABC.

If we assume that image guidance and adaptive radiotherapy would at least compensate for changes >1cm then remaining $\Sigma$ and $\sigma$ errors of tumour motion are 2.5 (2.1), 2.9 (2.5) and 2.7 (2.5) in the SI, RL and AP directions respectively. This would give possible CTV - PTV margins of 11.4, 11.6 and 9.9 mm in the SI, RL and AP directions.

**Assessment of target and organ at risk dose-volume data**

Mean reduction in $V_{20}$ in 18 patients for ABC plans when compared to free-breathing plans was 13% (p = 0.0001), reduction in $V_{13}$ 12 % (p = 0.001) and in
MLD 13% ($p < 0.001$). Mean increase in total lung volume with ABC was 41% ($p < 0.001$).

FB and ABC plans were compared in terms of target coverage and dose to other organs at risk. The FB plans had a higher $\text{PTV}_{90}$ ($p = 0.01$) and $\text{PTV}_{95}$ ($p < 0.001$). There was no significant difference in spinal cord maximum dose ($p = 0.5$) (Table 5).

**Discussion**

In this study we assessed the feasibility and reproducibility, particularly of tumour position, of using ABC during a radical course of radiotherapy. 17 out of 18 patients (94%) tolerated ABC throughout the full course of treatment with no patients finding the device very uncomfortable (unpublished data). The variation of intrafraction tumour position was less than the interfraction displacement, where 5/18 patients displayed COM movements of >1 cm. The mean (SD) variation in the position of GTV centre of the tumour in the 3 consecutive planning ABC breath-hold CT scans in 12 patients was 2.0 mm (1.7) in the SI direction and marginally less in the AP and LR directions. Mean (SD) displacements were greater than those reported by Koshani et al (0.2 (0.7), 0.3 (1.4) and 0.0 (1.5) mm in the RL, SI and AP directions), although the reported maximum displacements were 1.7, 3.1 and 4.2 mm in the respective directions [26].
Interfraction reproducibility of tumour position showed greater variation than intrafraction change. The absolute mean (SD) displacement of tumour centre at the end of treatment was 4.5 (5.2), 3.5 (2.9) and 3.4 (3.8) mm in the SI, RL and AP directions. The maximum displacements were 25, 9.7 and 11.7 mm (SI, RL and AP respectively) occurring in three different patients. The mean displacements are larger than reported displacements of -0.5 (3.8), 0.3 (1.6) and -1.3 (3.1) mm in the respective directions, with maximum displacements of 9.0, 3.8 and 6.8 mm [26]. The mean was calculated using the absolute values of the displacements to illustrate the maximum displacement. Maximum displacement occurred in the SI direction, followed by the AP and RL directions.

The 25 mm tumour shift recorded for patient 1 was apparently due to resolution of underlying lung collapse and consolidation through the treatment course. The displacements measured in other patients are not easily explained by observable structural lung changes. It is likely that breathing patterns change over time, so that the residual volume from which the ABC breath-hold starts, and therefore the actual breath-hold total lung volume, varies. A change in the size and shape of the lungs and physiological changes in lung tissue during a course of radiotherapy, which are difficult to assess by conventional imaging may also contribute to the observed alteration in tumour position. There is a suggestion from our results that greater reduction in GTV volume over the treatment course (i.e. response to treatment) is associated with greater position variation. A study assessing change in GTV size during RT using 4DCT or breath-hold CT scans...
found median reduction in GTV size of 25% after approximately 30 Gy and 44% after 50 Gy ($p = < 0.001$) but did not report significant shift of tumour outside the treated volume [27].

In looking further at possible reasons for tumour position variation we retrospectively assessed both breath-hold lung volume consistency and the relationship between diaphragm and tumour position for some of the cohort treated with ABC. As expected the lung volumes for the 3 consecutive ABC baseline scans were consistent (mean difference 2.5%), whereas there was greater discrepancy when comparing lung volumes over the treatment course (mean difference 7% for ABCmid and 4.6% for ABCend when compared with ABC1). However, GTV centre position variation and diaphragm position change were not significantly correlated. These results suggest that tumour position variation cannot be explained fully by varying breath-hold lung volume, and that the diaphragm should not be used as a surrogate for tumour position when using electronic portal imaging for treatment verification.

The study methodology, particularly intraobserver variation in contouring, may also contribute to the observed displacements [28] and this may be confounded by the absence of intravenous contrast in ABC scans hampering tumour outlining in or near the mediastinum. The use of rigid manual image registration in the first part of the study could also have introduced a small inaccuracy.
The calculated CTV-PTV margins using ABC and taking into account all errors were 17.5 mm in the SI direction, 11.5 mm in the RL direction and 11.4 mm AP. These are larger in all directions than our standard margins of 15 mm, 10 mm and 10mm in respective directions, due in part to patient set-up errors. While it is not possible to remove all systematic error from radiotherapy treatment, a potentially large benefit would be seen with better immobilization. When a theoretically reduced set-up error with a standard deviation of 1.5 mm was applied to a margin calculation using ABC, margins could be reduced to 7.6 mm SI, 5.4 mm AP and 4.7 mm RL from 10.2 mm SI, 10.7 mm AP and 8.8 mm RL, leading the authors to conclude that in the majority of cases better immobilization and tumour targeting were likely to have a greater impact on margin size than motion management [29]. Our results also suggest that standard margins may not be adequate in some patients.

The calculated margins in our previous work in a different patient cohort scanned but not treated with ABC during RT were 12 mm SI, 9.0 mm AP and 8.3 mm RL [24]. These margins were not applied in the current study because the reproducibility of ABC had not been determined throughout a course of radiotherapy. We have since recalculated margins based on this study and the previous data and clinically implemented ABC using margins of 1cm with an image guided and adaptive therapy protocol. However the clinical effects of the dosimetric consequences of margin reduction are not known. The slower dose build-up through lung tissue means it is often not possible to cover the PTV with
the 95% isodose. This is accepted as unavoidable, particularly as the margins used ensure that the 95% isodose adequately covers the GTV. If the margins are reduced due to improvements in tumour immobility, it must be ensured that this does not impinge on GTV coverage, potentially negating any benefits from dose escalation.

Mean reductions in $V_{20}$, $V_{13}$ and MLD of 13 %, 12 % and 13 % (all $p \leq 0.001$) respectively were achieved for ABC compared with free-breathing plans, despite no alteration in PTV margin to take reduced tumour motion into account. The benefit is likely to be due to the significant increase in total lung volume seen for ABC compared with free-breathing CT scans (mean increase 41 %, $p < 0.001$), reducing the relative volume of lung within the high dose volume. The use of ABC in radical RT of NSCLC should reduce the risk of severe lung toxicity without changing any other aspect of the treatment. Alternatively, dose may be escalated with ABC whilst maintaining the same risk of lung toxicity. These results have been used to model the potential increase in tumour control if ABC were used in conjunction with escalated dose [30] and to develop a clinical protocol to treat NSCLC using ABC with dose escalation.

The variation in the position of the tumour was assessed by CT scan over a course of treatment. The use of the CT scanner away from the treatment situation is a potential source of error. Since the introduction of cone beam CT, imaging has been carried out on the treatment couch in free-breathing, allowing
for regular adaptive adjustments. As the use of ABC has become part of standard practice, ideally image guidance in breath-hold should be performed prior to each treatment.

Conclusion

The ABC device can be used throughout radical radiotherapy for NSCLC with reproducible intrafraction tumour position. However, because of tumour position shift over time (interfraction variation), and patient set-up errors, a reduction in the size of the PTV margin is nevertheless not possible without image guidance and/or improved set-up.

Even with standard margins ABC leads to reduction in $V_{20}$, $V_{13}$ and MLD, most likely due to increased total lung volume and this allows for significant equitoxic dose escalation.

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References


Figure Legend

Figure 1. Example of a patient with significant volume and tumour position changes over the course of radiotherapy. Intrafraction tumour position at planning was consistent (left), but significant shrinkage and shift occurred from baseline to the end of radiotherapy (right). PTV, planning target volume; GTV, gross tumour volume; RT, radiotherapy.