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**Title:**

**Evaluation of a reproducible breath hold technique for the SABR treatment of lower lobe lung tumours**

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## **Abstract**

### **Aim**

Deep inspiration breath hold (DIBH) is a method of motion management used in stereotactic ablative body radiotherapy (SABR) for lung tumours. An external gating block marker can be used as a tumour motion surrogate, however, inter-fraction gross target volume (GTV) displacement within DIBH occurs. This study measured this displacement during a reproducible breath hold regime. Additionally, factors such as position of the gating block marker were analysed.

### **Methods and Materials**

121 cone beam computed tomography scans (CBCTs) from 22 patients who received DIBH SABR were retrospectively evaluated and the magnitude of inter-fraction GTV displacement was calculated for each fraction. This data was analysed to assess if any correlation existed between tumour displacement and variation in the gating block marker position on the patient, the amplitude of BH at CT, the amplitude of BH at treatment and the tumour location.

The measured tumour displacement was applied to the original planning CT to evaluate the dosimetric effect on surrounding organs at risk (OARs) using cumulative dose volume histograms (DVHs).

### **Results**

BH amplitude was reproducible within  $0.13 \text{ cm} \pm 0.1 \text{ cm}$  (mean  $\pm$  standard deviation). The magnitude of tumour displacement within BH ranged from 0 to 1.52 cm ( $0.41 \text{ cm} \pm 0.28 \text{ cm}$ ). Displacement in the superior-inferior (SI), anterior-posterior (AP) and left-right (LR) planes were  $0.31 \text{ cm} \pm 0.26 \text{ cm}$ ,  $0.16 \text{ cm} \pm 0.18 \text{ cm}$  and  $0.07 \text{ cm} \pm 0.12 \text{ cm}$  respectively. No statistically significant correlation was detected between tumour displacement within DIBH and the factors investigated. The range of variation in OAR dose was  $-7.0 \text{ Gy}$  to  $+3.6 \text{ Gy}$  with one statistically significant increase in OAR dose observed (oesophagus mean dose increasing by  $0.16 \text{ Gy}$ ).

### **Findings**

Reproducible BH was achievable across a range of patients. Inter-fraction GTV displacement measured  $0.41 \text{ cm} \pm 0.28 \text{ cm}$ . Due to this low level of motion, the correction of soft tissue moves did not adversely affect OAR dose.

## Introduction

The role of SABR in early stage lung cancer management has been established as the gold standard treatment where the patient is medically inoperable (1) (2) (3) with local control rates of up to 92% being reported (3). In addition SABR has benefit in the management of lung metastases with a local control rate of up to 80% at 1 year being reported (4) with minimal toxicity.

Motion management of lung tumours is essential in delivering SABR and one method of motion management is DIBH. DIBH delivered SABR has been shown to be dosimetrically desirable, over an internal target volume (ITV) technique where tumour motion over all respiratory phases is accounted for (5). It was reported that lung OAR dose, (all dose volume constraints), were reduced by 20% using a DIBH technique compared to a free breathing technique. Furthermore, with the addition of DIBH a reduction in planning target volume (PTV) margins was possible, which lead to a 40% reduction in dose to OARs (5) compared to a free breathing technique.

However, within DIBH inter-fraction variability of tumour position, relative to bony anatomy, occurs and this variation is observed on the daily-acquired CBCTs (6, 7). The magnitude of this positional variation has been reported by a number of studies and has been quantified as 3.3mm (6) (7)  $5.4 \text{ mm} \pm 2.5 \text{ mm}$ , (8) or even 6.7mm (9) with various methods being used to achieve a breath hold scan.

In order to account for this inter-fraction GTV displacement, image guided soft tissue tumour matches (away from the bony alignment) are necessary to ensure full dose coverage of the lesion.

Within this institution DIBH SABR is facilitated by the Varian Real-Time Position Management (RPM) system with audio-visual coaching. This has been shown to be a reliable and reproducible method of motion management (10) (11).

Patients are immobilised supine, arms up in a BodyFIX<sup>®</sup> system (Elekta, Sweden), with a full length evacuated cushion for the patient to lie in and immobilisation is further assisted by a coversheet suctioned around the patients contour.

The RPM system utilises an external gating block, which is placed at a stable point on the patient's chest (inside the suctioned cover sheet) and this is used to quantify the BH amplitude. This process is aided by providing the patients with video goggles showing live video feedback of the BH allowing the patient to monitor their own BH during treatment. This is reproduced for each treatment fraction and a CBCT is acquired to verify both bony and soft tissue anatomy.

SABR patients attend for a breathing assessment appointment, prior to CT simulation, to ensure they can consistently achieve a reproducible BH as visualised on the RPM system before acquiring a planning CT scan. This appointment consists of a number of steps. The immobilisation device is constructed and evaluated for both stability and comfort. The patient is assessed for any medical requirements prior to simulation, such as analgesia. The patient is then given an opportunity to practice DIBH as well as coached breathing techniques. They then return for CT simulation 48 hours later, having had experience of the process and practiced the technique.

This study aimed to quantify our institutions inter-fraction GTV displacement based on our process and evaluate if this displacement relates to minor changes in BH or the external gating block. A secondary aim was to evaluate the dosimetric impact of this tumour motion on the surrounding OARs.

## **Materials and Methods**

This study was approved by our institutional research committee. Data collection was in accordance with local protocol.

### *Data collection and evaluation methods*

Lung tumour patients treated with DIBH SABR in our institution were retrospectively reviewed. A convenience sampling strategy was utilised with the following criteria: Included were SABR lung patients treated with a BH technique from January 1<sup>st</sup> 2012 to April 30<sup>th</sup> 2013 and tumour location in the lower lobe. Excluded were SABR patients treated with a free breathing or coached breathing technique, breath hold delivered SABR to abdominal lesions, lesions in the upper or middle lobes of the lung and patients not treated as per standard departmental protocol. Within this institution, DIBH is indicated over alternative motion management techniques if the tumour motion is greater than 5mm.

This yielded a study population of 22 patients, 16 males and 6 females. Their ages ranged from 50-85 years old with an average age of 71.59 years. Of these patients 11 had primary lung tumours and 11 had metastases from a variety of primaries including melanoma, pancreatic cancer, caecal cancer, colon cancer, colorectal cancer and rectal cancer.

Patients were treated with between 3 and 10 fractions to a total dose ranging from 48Gy to 60Gy with the most common fractionation being 60Gy in 5 fractions.

12 had right lower lobe tumours and 10 had left lower lobe tumours.

A total of 121 fractions were delivered and a range of data (Table 1) was recorded from each patient who met the inclusion criteria.

A single investigator carried out all measurements. The intra-observer variability was quantified, where appropriate and was noted to be 0.2cm when measuring the daily BH amplitude.

### *Inter-fraction variation in tumour position*

At each fraction a CBCT was acquired by a full rotation of the gantry in a 90 second acquisition time. The patient achieved this using 3-4 breatholds depending on individual ability. The acquired CBCT dataset was first matched to the vertebral column and then to the soft tissue tumour GTV in the planning scan to quantify the inter-fraction GTV displacement. Soft tissue moves in AP, SI and LR planes and were recorded and applied to correct for this displacement.

Absolute values were generated and an overall magnitude of tumour displacement relative to bony anatomy was generated using the Euclidean distance formula for each fraction delivered.

A Pearson product-moment correlation coefficient ( $r$ ) was generated to investigate the relationship between the various factors and inter-fraction tumour displacement. The coefficient of determination was also generated.

### *Organs at Risk evaluation*

The relevant OARs were deemed to be lung, spinal cord, heart, oesophagus, and chest wall in accordance with local protocol.

All soft tissue moves recorded at treatment were retrospectively applied to the original planning scans in Eclipse™ Treatment Planning System, by moving the isocentre to the on-treatment position for each fraction delivered. The dose distribution was recalculated for each fraction, using the same monitor units. For each patient a cumulative plan was generated by the summation of all the delivered fractions. Cumulative DVHs were generated and then compared with the original approved DVH.

The GTV was not moved in tandem with the soft tissue moves. The significance of not moving the GTV was evaluated on Patient 1. As well as the standard replan, a second replan was carried out where the GTV contour was moved in conjunction with the treatment beams. The new GTV was assigned a Hounsfield unit (HU) value in line with the original lesion as measured on the planning scan. The original lesion, if outside the new GTV, was assigned a HU value in keeping with surrounding lung tissue. This was replicated for each fraction where soft tissue moves were applied. The new plans were

recalculated using the original monitor units and a composite plan generated. The relevant OARs were compared and only the ipsilateral lung maximum dose changed by 1.4Gy. All other OAR dose volume constraints were unchanged. It was therefore deemed acceptable not to move the GTV in tandem with the beams.

The mean, maximum and minimum dose to each OAR was reviewed as well as the bilateral lung volume receiving 20Gy (V20), the ipsilateral lung volume receiving 15Gy (V15) and the chest wall volume receiving 30Gy (V30). In addition, specific dose constraints used in the researchers institution were reviewed (Table 2).

The significance of the observed changes were evaluated using a two-tailed, Type 1 t-test to generate a p value, with a value of  $<0.05$  considered statistically significant.



## Results

### *Inter-fraction GTV displacement*

The overall magnitude of tumour displacement relative to the bony anatomy ranged from 0 to 1.52 cm, with a mean overall magnitude of motion of 0.41 cm with a standard deviation of  $\pm 0.28$  cm. See Figure 1 for summary of motion per patient. The largest displacement was observed in the SI plane with an average motion of  $0.31 \text{ cm} \pm 0.26 \text{ cm}$  compared with  $0.16 \text{ cm} \pm 0.18 \text{ cm}$  in the AP plane and  $0.07 \text{ cm} \pm 0.12 \text{ cm}$  in the LR direction.

The BH amplitude recorded at CT ranged from 1.2 cm to 2.8 cm with mean amplitude of 1.7 cm within the sample population.

The variation of BH amplitude at treatment measured on the RPM system retrospectively was found to range from 0 to 0.4 cm per fraction with a mean variation of  $0.13 \text{ cm} \pm 0.1$  cm. The magnitude of tumour displacement was found not to correlate significantly with the variation in BH amplitude giving a correlation coefficient ( $r$ ) of 0.069.

Variation in the daily placement of the external gating block was observed on a number of the CBCTs and this ranged from 0 cm to 3.8 cm, mean discrepancy of  $1.02 \text{ cm} \pm 0.85$  cm., no correlation was observed between this and GTV displacement. The influence of the block position on skin was also considered by evaluating if there was any correlation between tumour variability within BH and the distance the marker is placed from the xiphisternum. No significant relationship was observed. No correlation was observed between tumour location and inter-fraction displacement.

See Table 3 for correlation coefficient values for each factor investigated.

### *Organs at Risk Evaluation*

Review of the cumulative plans' DVHs revealed a range of OAR dose variation from -7.0Gy to +3.6Gy. Evaluating the maximum point dose, the minimum point dose and the mean dose to each OAR revealed that only the chest wall and the oesophagus maximum and mean doses were significantly affected (Table 4).

The remainder of changes observed were not statistically significant. A number of patients having lesions treated in both lungs did not have the ipsilateral lung minus PTV contoured and one patient did not have oesophagus contoured. Where ipsilateral lung minus PTV was not contoured the patients had bilateral lung minus PTV volumes to allow for a more complete view of the lung dose. In the case where the oesophagus was not contoured the GTV was located distal to the oesophagus and it was not deemed an OAR.

In addition the bilateral lung minus PTV V20 varied on average by  $-0.04\% \pm 0.30\%$  ( $p = 0.545$ ). The ipsilateral lung minus PTV V15 varied by  $-0.29\% \pm 0.75\%$  ( $p = 0.122$ ) and the chest wall V30 had a mean variation of  $-0.67\% \pm 0.89\%$  ( $p = 0.002$ ).

## Discussion

### *BH reproducibility and inter-fraction motion*

Patient ability to reproduce a stable BH amplitude on treatment was excellent. This data shows a mean variation of  $0.13 \text{ cm} \pm 0.1 \text{ cm}$  measured over 121 CBCTs and 22 patients.

This compliance shows that a stable breath hold is reproducible once coaching is utilised and the patient has sufficient time to adapt to the technique. In our experience the initial breathing assessment visit aids this process for the patients.

It should be noted that a single BH amplitude was selected to represent the amplitude for the entire CBCT, which is generally attained over 3 to 4 breaths. However, the data showed that compliance to BH amplitude was excellent with a mean variation of  $0.13 \text{ cm}$  recorded which reassures that a single BH is an adequate representation of amplitude over the scan acquisition.

Following on from this we also found that the range of inter-fraction displacement observed at this institution ( $0.41 \text{ cm} \pm 0.28 \text{ cm}$ ) using a DIBH technique was in keeping with the published literature across a range of breath hold techniques (8, 9).

The data has shown that the motion of lower lobe lung tumours can be comfortably controlled within 5mm. This facilitates margin reduction and significant lung sparing compared to an ITV technique, the dosimetric benefits to the lung have been well established (5, 12).

Patient 8 and Patient 21 were noted to have a larger range of motion despite no larger variation in the measured breath hold amplitude. Patient 8 required large moves in all directions for one fraction (0.9 cm AP, 1.0 cm SI and 0.7 cm LR), which accounted for the overall larger range of motion. Discounting this single fraction this patient's maximum magnitude of motion was 0.71 cm, which was similar to the remainder of the data. Patient 21 also had a slightly larger range of motion of 1.03 cm but again this was accounted for in a single fraction where a 0.9 cm SI shift was required.

### *Correlation with factors investigated*

It must also be acknowledged however, that the data also established that a level of inter-fraction displacement does occur within BH despite the reproducibility of the BH achieved.

This study has shown that the factors investigated show no statistically significant correlation with inter-fraction motion within DIBH. These factors included minor amplitude changes during daily treatment, positioning of the gating block relative to xiphisternum, minor discrepancies in the gating block positioning at daily treatment and tumour location within the lung. The mean variation in the daily positioning of the gating block was found to be 1.02cm relative to the planning CT. Clinically, this block is placed at a reference point on skin and a patient's the external contour may vary from day to day, as is the case with all skin marks. As such the variation observed here might well be a combination of block placement discrepancy and skin position discrepancy.

A recent study by Renming et al. (13), which was published since this research was carried out, also evaluated the inter-fraction variation produced with lung DIBH. They found a significant correlation between vertebral bone moves required and the inter-fractional soft tissue reproducibility, which wasn't examined in this research. This study had a large sample size but utilised an active breathing control system and a single breath hold CBCT so results may not be comparable.

This lack of correlation observed could be explained by the fact that in the main there was little variation observed in these factors and as such they had only a modest influence on the inter-fractional soft tissue moves required.

Some trends in the data were perceived but they did not reach a level of statistical significance. As expected there was a weak negative correlation between the motion observed and the distance from the diaphragm indicating less motion in tumours located more superiorly in the lower lobes.

This research has shown that there is no change in the stability or reproducibility of BH achieved in all areas of the lower lobe. This corresponds well with the data published by

Renming (13) who also reported no significant correlation between relative tumour position within the lung and inter-fractional soft tissue displacement.

### *Organs at Risk Evaluation*

Overall the application of soft tissue moves had little impact on the surrounding OAR doses.

Two OARs were affected significantly by applying soft tissue moves, with only one statistically significant increase in OAR dose observed which was not clinically significant (oesophagus mean dose increasing by 0.16Gy). The remainder of dose increases did not correlate significantly with soft tissue moves being applied. This verified that within the sample of 121 CBCTs reviewed, applying soft tissue moves (within the range observed of  $0.41 \text{ cm} \pm 0.28 \text{ cm}$ ) was safe and did not adversely affect OAR dose. However the limitation of assessing OAR dose on the initial planning scan is acknowledged as OARs may displace in tandem with the tumour displacement on a daily CBCT.

In the case of 4 patients the spinal cord maximum point dose was increased to above the prescribed tolerance of 18Gy. In Patients 6 and 14 this was a marginal increase from 18.4Gy to 18.5Gy and 18.1Gy to 19.3Gy respectively. Both tumours were located close to the spinal cord and the physician approved cord maximum point dose was also slightly above the tolerance level as these were point doses to a minimal volume. Patient 4 showed a 2.1Gy increase from 16.7Gy to 18.8Gy increasing the cord dose above the approved tolerance. Analysis of the OAR dose changes was limited to evaluation of the maximum, minimum and mean doses and three planning constraints. Review of dose points alone can be misleading without entire review of the DVH curve. ICRU 83 (14) recommends reporting of D2% as a more representative maximum dose.

Conversely to these results it has been reported (15) that OARs can be clinically affected with statistically significant variations of up to +10% being seen in OAR max points. However this study matched the soft tissue tumour without a threshold and the magnitude of variation from bone is not reported so it is difficult to assess if these results are comparable.

This study has highlighted areas for further research. As no variable investigated has been found to correlate with the soft tissue displacement observed, an area for further research could be to evaluate the role of the vacuum cover sheet in the patient set up as this was not considered in this study, as well as patient related factors such as pre-existing lung disease. Additionally the evaluation of the inter-fraction consistency of breath hold and soft tissue positioning would be of interest.

## **Conclusions**

This study has found that producing a reproducible BH is achievable across a range of patients. Our process has been shown to be a reliable and stable technique for inter-fraction motion management in lower lobe tumours.

It has shown that using this robust technique the magnitude of inter-fraction GTV displacement can easily be controlled in line with a range reported in the literature with a mean variation of  $0.41 \text{ cm} \pm 0.28 \text{ cm}$  being measured. As a result of this stringent motion management the application of the remainder of the soft tissue shifts has little effect on OAR dose.

No statistical correlation was found between tumour displacement and the variables investigated. From this data we can conclude that within this patient cohort, this small level of inter-fraction displacement may be somewhat inherent in BH and thus we cannot reduce it by adjusting any of the factors examined in this study. Soft tissue matching based on CBCT image guidance has been shown to be safe and can compensate for this motion ensuring adequate target coverage.

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**Conflicts of Interest**

None

**Ethical Standards.**

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees of the Beacon Hospital, Sandyford, Dublin 18.

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## Tables

<b>Data recorded per patient</b>	
<b>Pre-treatment data</b>	BH amplitude at CT
	RPM Gating block position on patient (relative to xiphisternum)
	Tumour position relative to spine, diaphragm and chest wall
<b>Treatment data</b>	Variation in BH amplitude at treatment (relative to amplitude at CT)
	RPM Gating block position variation on patient (relative to planning CT: this was visible on 48 of 121 CBCTs due to field of view limitations.
	Soft tissue moves in AP, SI, LR directions

Table 1. Data recorded per patient

<b>OAR</b>	<b>Maximum point dose</b>	<b>Volume constraint</b>
<b>Chest wall</b>	30Gy	If PTV overlaps 30Gy/30%
<b>Cord</b>	18Gy	N/a
<b>Heart</b>	30Gy	N/a
<b>Oesophagus</b>	27Gy	N/a
<b>Ipsilateral lung-PTV</b>	60	15Gy/30%
<b>Bilateral Lung-PTV</b>	60	20Gy/30%

Table 2. OAR Dose Constraints

<b>Factor Investigated</b>	<b>Correlation Coefficient (r)</b>	<b>Coefficient of Determination (R<sup>2</sup>)</b>
<b>Variation in amplitude of BH at treatment</b>	0.069	0.00483
<b>Variation in external marker position</b>	0.283	0.07997
<b>Depth of BH at planning CT</b>	0.349	0.1221
<b>Tumour location relevant to spine</b>	0.126	0.01582
<b>Tumour location relevant to posterior chest wall</b>	0.129	0.0165
<b>Tumour location relevant to lateral chest wall</b>	0.025	0.00061

Table 3. Correlation coefficient values

<b>OAR</b>	<b>Variation in min dose (Gy)</b>				<b>Variation in max dose (Gy)</b>				<b>Variation in mean dose (Gy)</b>			
	<i>Range</i>	<i>Mean</i>	<i>SD</i>	<i>P Value</i>	<i>Range</i>	<i>Mean</i>	<i>SD</i>	<i>P Value</i>	<i>Range</i>	<i>Mean</i>	<i>SD</i>	<i>P Value</i>
<b>Ipsilateral Lung</b>	-0.1 - 0.1	0	0.03	1	-6.8 - 1.3	-0.31	1.81	0.484	-0.6 - 0.3	-0.08	0.23	0.144
<b>Bilateral Lung</b>	0	0	0	n/a	-6.6 - 1.9	-0.38	1.66	0.294	-0.3 - 0.4	-0.01	0.15	0.776
<b>Chest Wall</b>	-0.3 - 0.2	-0.01	0.09	0.648	-7.0 - 1.1	-1.9	2.37	0.0012	-1.8 - 0.2	-0.3	0.46	0.006
<b>Heart</b>	-0.1 - 0.1	0	0.05	0.665	-2.5 - 2.7	-0.48	1.39	0.122	-0.6 - 1.1	-0.01	0.31	0.892
<b>Oesophagus</b>	-0.1 - 0.4	0.03	0.11	0.249	-2.2 - 0.7	-0.43	0.77	0.017	-1.0 - 0.1	0.16	0.3	0.028
<b>Spinal Cord</b>	-0.1 - 0	-0.01	0.03	0.162	-2.7 - 3.6	-0.07	1.3	0.795	-0.1 - 0.3	0	0.11	1

Table 4. OAR Evaluation



## Figures

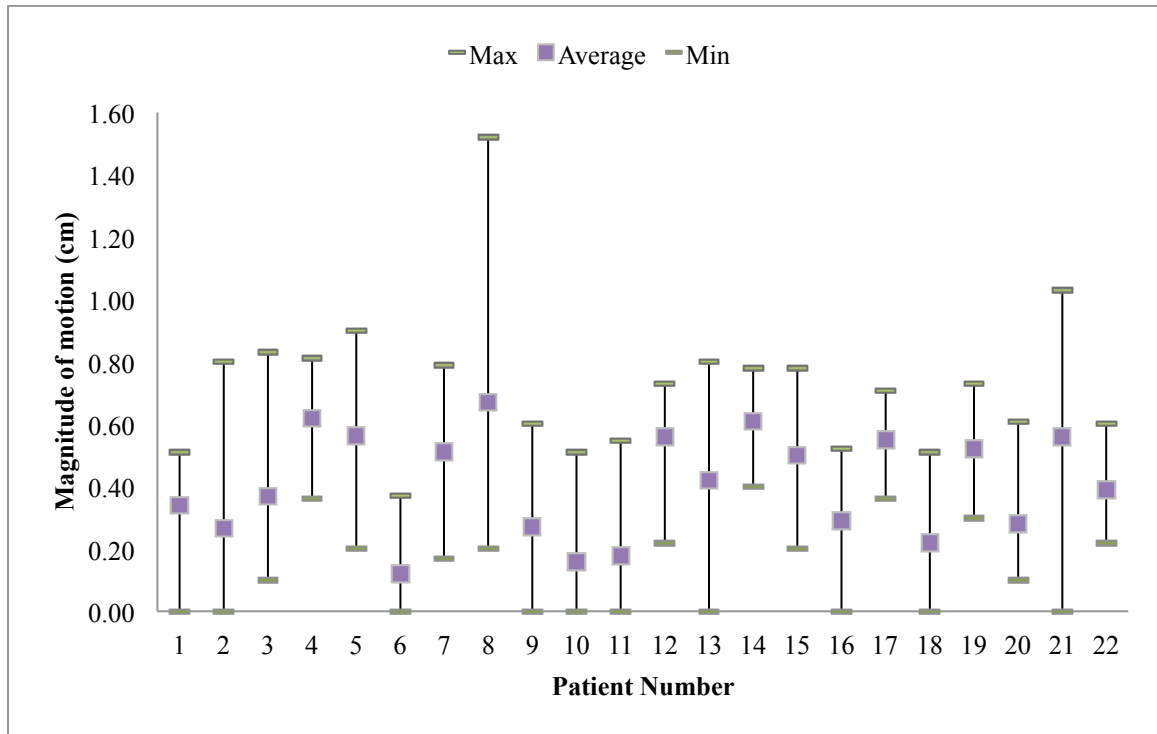


Figure 1. Summary of tumour motion per patient