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Evaluation of active breathing control-moderate deep inspiration breath-hold in definitive non-small cell lung cancer radiotherapy

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The purpose of this study is to evaluate the effect of Active Breathing Control-moderate deep inspiration breath-hold (ABC-mDIBH) on tumor motion and critical organ doses in non-small cell lung cancer (NSCLC) radiotherapy. 23 patients with locally advanced NSCLC were included in the study. All patients were scanned at free breathing and ABC-mDIBH for radiation treatment planning. 3 separate treatment plans were generated for each patient including one plan with ABC-mDIBH and uniform margins, one plan with free breathing and uniform margins, and one plan with free breathing and 3-dimensional non-uniform margins determined by Cone Beam Computed Tomography (CBCT) and XVI Motion View (X-ray Volume Imaging, Elekta, UK). Critical organ dose-volumes and physical lung parameters were comparatively evaluated on 3 separate dose-volume histograms of each patient acquired from planning software. Individual tumor motion of each patient with and without ABC-mDIBH was documented and compared. Use of ABC-mDIBH resulted in statistically significant improvement in physical lung parameters of V20 (lung volume receiving ≥ 20 Gy) and mean lung dose (MLD) which are predictors of radiation pneumonitis ($p<0.001$). Reduction in spinal cord dose and tumor motion with ABC-mDIBH was also statistically significant ($p<0.001$). ABC-mDIBH increases normal lung tissue sparing in definitive NSCLC radiotherapy by improving physical lung parameters along with spinal cord dose reduction through exact tumor immobilization. The incorporation of ABC-mDIBH into NSCLC radiotherapy may have implications for potential margin reduction and dose escalation to improve treatment outcomes.

Key words: active breathing control, moderate deep inspiration breath-hold, radiotherapy, non-small cell lung cancer

Radiotherapy plays an important role in the management of unresectable, locally advanced non-small cell lung cancer (NSCLC). Recent trials have shown improved local control rates through dose escalation[1-5], however, sparing normal tissues to avoid radiation-induced toxicity while escalating dose to the target requires precise target and organ-at-risk (OAR) localization which is not an easy task in an area prone to uncertainties due to respiratory movements.

Respiratory motion hampers the accuracy and precision of NSCLC radiotherapy through various limitations in image-acquisition, treatment planning, and radiation delivery thereby leading to potential errors between planned and delivered dose distributions[6]. Motion artefacts usually encountered in free breathing scans may be challenging for accurate structure delineation with the potential of compromised target and organ-at-risk localization[6, 7]. Using extensive margins to offset respiratory motion limits dose escalation due to increased risk of normal tissue toxicities.

Lung tumors have been shown to move in excess of 5 centimeters in some patients, mostly in the superior-inferior direction[8], and this high magnitude of motion significantly restricts precise radiation delivery. If the whole range of respiratory motion is to be accounted for, it is almost impossible to deliver curative doses to the target owing to the huge normal tissue volume included in the treatment field that may cause severe treatment-related toxicity. If the margin to offset respiratory motion is not taken into consideration without using any respiratory motion management strategy, normal tissue toxicity is also reduced but at the cost of probable "geographic miss" and compromised target coverage translating into treatment failure.

Several approaches have been suggested for the management of respiratory motion in radiotherapy including breath-hold techniques, respiratory gating techniques, forced shallow-breathing techniques, motion-encompassing methods and respiration-synchronized techniques[6]. Sophisticated technologies allowing higher doses to the target volume with

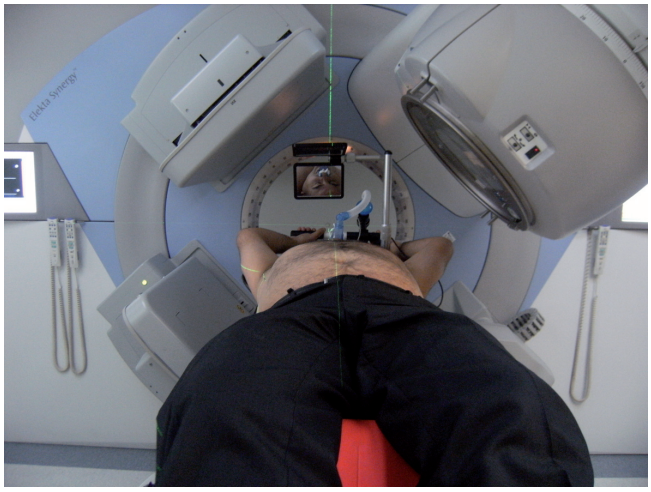

Figure 1. Set-up of a patient treated with ABC-mDIBH
ABC-mDIBH: Active Breathing Control-moderate deep inspiration breath-hold

normal tissue sparing capability have great potential to optimize treatment outcomes.

In this study, we evaluated the effect of ABC-mDIBH on tumor movement and critical organ doses in patients undergoing definitive radiotherapy for locally advanced NSCLC.

Patients and methods

Twenty-three patients with locally advanced NSCLC referred to our department for radical radiotherapy between January 2010 and July 2010 were prospectively studied. All patients had a training session with the ABC device (ABC, Elekta, UK) to get familiar with the system and to determine individual moderate deep inspiration breath-hold (mDIBH) levels set at 75% of maximum inspiratory capacity. Verbal instructions were given in order to motivate patients achieve a steady breathing pattern and patients were taught to practice breath-holds. Signaling for interruption of ABC process due to discomfort was also taught to the patients. Duration of breath-hold and threshold for mDIBH of every individual patient was documented during treatment. Patients with a comfortable breath-hold duration of ≥ 15 seconds were considered eligible to undergo treatment with ABC-mDIBH. Breathing trace of the patients were monitored with the ABC system through the patient mouthpiece connected to the device. Figure 1 shows the set-up of a patient treated with ABC-mDIBH.

After a 30-45 minute-long training session, patients were scanned at free breathing and mDIBH with 2.5 mm slice thickness at Computed Tomography (CT) simulator (GE Lightspeed RT, GE Healthcare, Chalfont St. Giles, UK) with arms above head, immobilized using a Wing-Board (CIVCO, Kalona, IA, USA). Nose clip was used to breathe through the mouth only, and the mirror enabled patients to see their breathing pattern on the monitor attached to the ABC system helping them achieve a steady breathing pattern necessary for simulation and treatment. Fifty cc contrast (iopromide) were routinely used in scanning. The acquired images were sent to the contouring workstation via network. Advantage Sim MD simulation and localization software (Advantage SimMD, GE, UK) was used for contouring treatment volumes and OARs on both free breathing and ABC-mDIBH scans at the same window level. Individual tumor motion in superior-inferior (SI), anterior-posterior (AP), and left-right (LR) directions was assessed for each patient using Cone Beam CT and XVI Motion View (X-ray Volume Imaging, Elekta, UK) data.

3 separate treatment plan groups generated for each patient were as follows:

First group: The structures were delineated on the ABC-mDIBH scans for the 1st group. Margins for Gross Tumor Volume (GTV) to Clinical Target Volume (CTV) were 6 mm and 8 mm for Squamous Cell Carcinoma (SCC) and adenocarcinoma/large-cell carcinoma, respectively. CTV was expanded by 10 mm uniformly in each direction to generate Planning Target Volume (PTV). All patients in the study were treated using ABC-mDIBH.

Second group: The structures were delineated on the free breathing scans for this group. Margins for GTV to CTV were 6 mm and 8 mm for SCC and adenocarcinoma/large-cell carcinoma, respectively. PTV was generated by expanding CTV by 10 mm uniformly in each direction in this group.

Third group: The structures were also delineated on the free breathing scans for this group with GTV to CTV margins of 6 mm and 8 mm for SCC and adenocarcinoma/large-cell carcinoma, respectively. However, in the generation of PTV, individual 3-dimensional tumor motion margins plus 5 mm set-up margin was added to the CTV instead of using the 10 mm uniform CTV-PTV margins.

Table 1. The details of the three treatment plan groups

Group	Breathing Phase Used For Planning	Margins For GTV to CTV		Margins For CTV to PTV
		SCC	AdenoCa and Large Cell Ca	
1st Group	ABC-mDIBH	6 mm uniform margin	8 mm uniform margin	10 mm uniform margin
2nd Group	Free Breathing	6 mm uniform margin	8 mm uniform margin	10 mm uniform margin
3rd Group	Free Breathing	6 mm uniform margin	8 mm uniform margin	individual 3-D margin for tumor motion + 5 mm

mDIBH: moderate deep inspiration breath-hold
GTV: Gross tumor volume
CTV: Clinical target volume
PTV: Planning target volume

Table 1 shows the details of the three treatment plan groups.

PrecisePLAN (Elekta, UK) Treatment Planning System was used in generating the 3 separate plans for every individual patient. Beam organizations, wedges, and the beam angles were identical in all 3 separate plans of each patient. Coverage of the CTV by the 95% isodose line was mandatory. PTV coverage with 95% isodose line wasn't achievable in some patients due to critical organ dose constraints. Physical lung parameters of V3, V5, V13, V20 and mean lung dose (MLD), spinal cord maximum dose, esophagus, and heart dose-volume parameters were calculated on every separate plan of each patient and parameters were compared with each other using Wilcoxon and Student's t test. Treatment duration of patients was documented. Definitive 6-week-long 60 Gy radiochemotherapy with weekly 40mg/m^2 cisplatin using ABC-mDIBH and image guided radiation therapy (IGRT) techniques was planned for every patient. XVI and Cone Beam Computerized Tomography were used for treatment verification. Response Evaluation Criteria In Solid Tumors (RECIST) [9] and National Cancer Institute of Canada (NCI-C) grading system v3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf) were used for assessment of treatment outcomes and toxicity. Follow-up visits were scheduled for every patient routinely at 3-month intervals. Informed consent was required to be included in the study along with ethics committee approval. Statistical Package for the Social Sciences, version 15.0 (SPSS, Inc., Chicago, IL) software was used for analysis and the level of significance was set at $p < 0.05$.

Results

Twenty-three (4 female, 19 male) patients with stage IIIB NSCLC were treated between January 2010 and July 2010 using ABC system. Median age was 57 (46-65) years. 11 patients had SCC, 11 patients had adenocarcinoma, and 1 patient had large-cell carcinoma. The tumor location was right upper lobe in 8 patients, right middle lobe in 6 patients, right lower lobe in 2 patients, left lower lobe in 6 patients, and left upper lobe in 1 patient. Median breath-hold duration was 23 (20-33) seconds. Median treatment duration was 8 (6-14) minutes. Median threshold for breath-holding was 1.5 (1.2-2.5) liters. Patient and tumor characteristics are shown in table 2.

Median lung volume was 5794 cc (3901-7437) in the 1st group with ABC-mDIBH and 4106 cc (2313-6934) in the

Table 2. Patient and tumor characteristics

Patient No	Gender	Age	Stage	Tumor Location	Histology	KPS	Threshold for mDIBH (lt)	Breath hold duration (seconds)	Treatment Duration (minutes)
1	Male	57	IIIB	RUL	AdenoCa	100	1.5	33	14
2	Male	56	IIIB	RUL	AdenoCa	90	2.1	30	11
3	Male	57	IIIB	LLL	SCC	90	1.4	21	12
4	Male	46	IIIB	RUL	AdenoCa	100	1.4	21	9
5	Male	48	IIIB	RUL	AdenoCa	100	2.6	30	11
6	Male	57	IIIB	LLL	AdenoCa	100	2.1	26	7
7	Male	58	IIIB	LLL	SCC	100	2.7	33	7
8	Male	58	IIIB	RUL	Large Cell Ca	100	2.2	31	8
9	Male	48	IIIB	RML	SCC	100	2.2	30	6
10	Male	65	IIIB	LUL	SCC	80	1.3	20	7
11	Male	61	IIIB	RML	SCC	100	2.1	24	6
12	Male	65	IIIB	RML	AdenoCa	90	1.8	22	7
13	Female	47	IIIB	RLL	AdenoCa	100	1.5	21	8
14	Male	62	IIIB	RUL	AdenoCa	100	2.2	28	6
15	Male	51	IIIB	RML	SCC	100	2.0	30	6
16	Female	56	IIIB	RML	SCC	100	1.5	23	8
17	Male	49	IIIB	RUL	AdenoCa	90	1.5	21	7
18	Male	54	IIIB	LLL	SCC	80	1.3	20	8
19	Male	64	IIIB	RUL	SCC	80	1.4	23	7
20	Female	50	IIIB	LLL	AdenoCa	100	1.5	22	8
21	Female	57	IIIB	LLL	AdenoCa	90	1.4	22	8
22	Male	47	IIIB	RLL	SCC	80	1.5	20	7
23	Male	65	IIIB	RML	SCC	100	2	27	6

RUL: Right Upper Lobe SCC: Squamous Cell Carcinoma
RML: Right Middle Lobe AdenoCa: Adenocarcinoma
RLL: Right Lower Lobe KPS: Karnofsky Performance Status
LUL: Left Upper Lobe mDIBH: moderate deep inspiration breath-hold
LLL: Left Lower Lobe

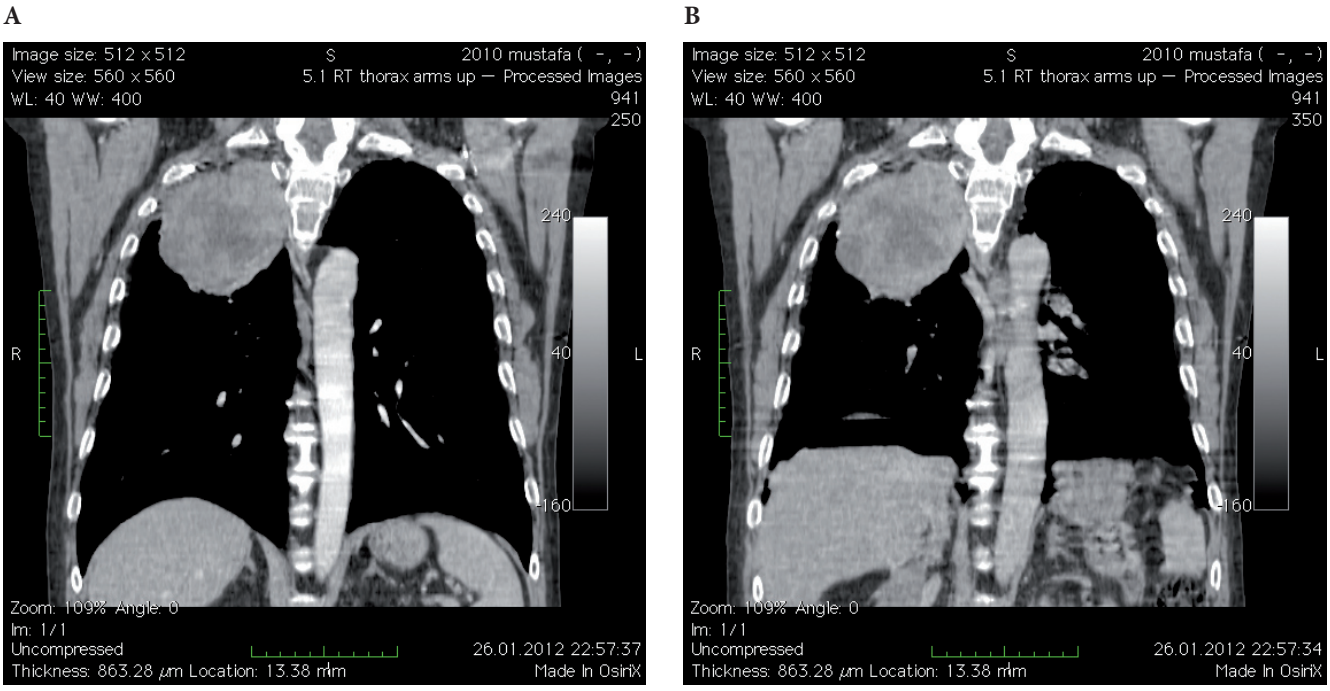

Figure 2. A. Lung volumes of a patient with ABC-mDIBH. B. Lung volumes of a patient with free breathing
ABC-mDIBH: Active Breathing Control-moderate deep inspiration breath-hold

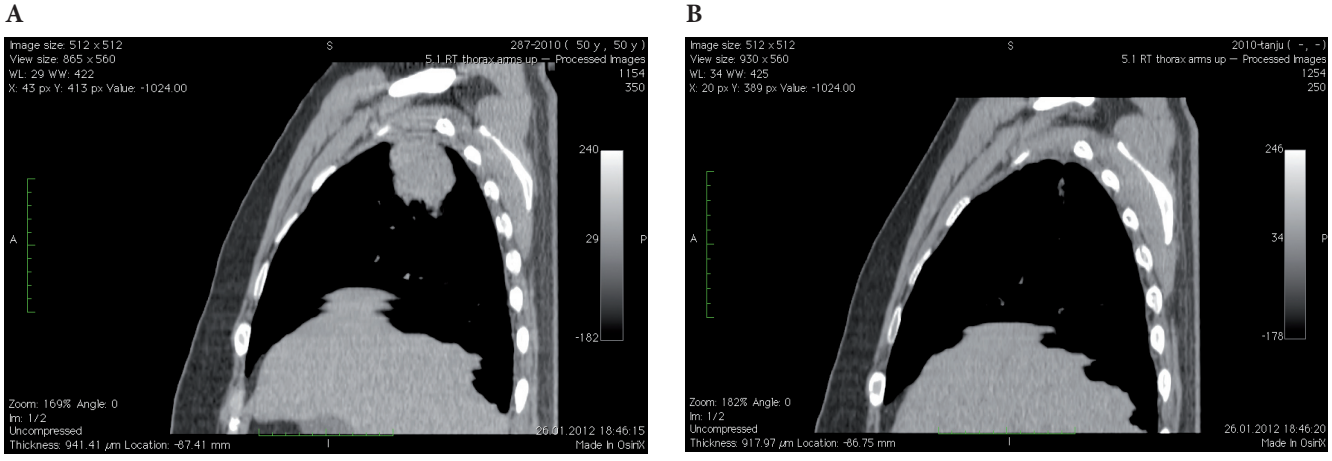

Figure 3. A. Pretreatment CT of a patient treated using ABC-mDIBH. B. Follow-up CT of the same patient at 3 months after completion of treatment using ABC-mDIBH
CT: Computed Tomography
ABC-mDIBH: Active Breathing Control-moderate deep inspiration breath-hold

2nd/3rd groups without ABC-mDIBH. Median increase in the whole lung volumes with ABC-mDIBH was 35% (6%-82%) ($p<0.001$). Figures 2a and 2b allowing a clear comparison show the lung volumes of both lungs of the same patient with ABC-mDIBH (Figure 2a) and with free breathing (Figure 2b).

Critical organ dose-volume parameters (median and minimum-maximum) of the 3 treatment plan groups are shown in table 3.

Median decrease in MLD in the 1st group compared to the 2nd group was 20% (1%-37%) while the median decrease in MLD in the 1st group compared to the 3rd group was 29% (10%-43%) ($p<0.001$).

Median decrease in V20 in the 1st group compared to the 2nd group was 21% (0%-37%), while the median decrease in V20 in the 1st group compared to the 3rd group was 30% (10%-44%) ($p<0.001$). Table 4 shows the median decrease in

Table 3. Critical organ dose-volume parameters (median and minimum-maximum)

	Lung						Spinal Cord	Esophagus		Heart			
	Vol. (cc)	MLD (cGy)	V20 (%)	V13 (%)	V5 (%)	V3 (%)	Maximum Dose (cGy)	1/3 vol. dose (cGy)	2/3 vol. dose (cGy)	3/3 vol. dose (cGy)	1/3 vol. dose (cGy)	2/3 vol. dose (cGy)	3/3 vol. dose (cGy)
1st Group	5794	1836 (695-2208)	29 (11-41)	37 (12-54)	49 (13-61)	55 (16-70)	3669 (1146-4993)	5014 (1174-6147)	247 (28-5124)	0 (0-77)	1316 (60-5938)	264 (0-4814)	80 (0-1189)
2nd Group	4106	2228 (878-3242)	37 (14-58)	46 (15-73)	58 (18-78)	63 (20-83)	5514 (1308-6823)	5448 (1147-6218)	231 (106-5611)	21 (0-160)	2117 (118-5998)	342 (44-4589)	83 (0-1515)
3rd Group		2399 (994-3304)	39 (16-60)	51 (17-73)	60 (19-79)	64 (24-83)	5703 (1992-6820)	5707 (1964-6257)	331 (119-5692)	51 (0-162)	3387 (121-6234)	662 (76-4618)	92 (0-2483)

MLD: Mean Lung Dose
V20: Volume of lung receiving ≥ 20 Gray (Gy)
Vol.: Volume

Table 4. Median decrease in MLD and V20 in the 1st group compared to the 2nd and 3rd groups

Median decrease in MLD in the 1st group compared to the 2nd group	Median decrease in V20 in the 1st group compared to the 2nd group	Median decrease in MLD in the 1st group compared to the 3rd group	Median decrease in V20 in the 1st group compared to the 3rd group	p
20%	21%	29%	30%	<0.001

MLD: Mean Lung Dose
V20: Volume of lung receiving ≥ 20 Gray (Gy)

MLD and V20 in the 1st group compared to the 2nd and 3rd groups.

Median decrease in V13 in the 1st group compared to the 2nd group was 19% (0%-34%), while the median decrease in V13 in the 1st group compared to the 3rd group was 26% (2%-41%) (p<0.001).

Median decrease in V5 in the 1st group compared to the 2nd group was 19% (0%-33%), while the median decrease in V5 in the 1st group compared to the 3rd group was 23% (2%-37%) (p<0.001).

Median decrease in V3 in the 1st group compared to the 2nd group was 17% (0%-29%), while the median decrease in V3 in the 1st group compared to the 3rd group was 27% (0%-50%) (p<0.001).

Median decrease in spinal cord maximum dose in the 1st group compared to the 2nd group was 29% (2%-78%), while the median decrease in spinal cord maximum dose in the 1st group compared to the 3rd group was 35% (10%-79%) (p<0.001).

The decrease in physical lung parameters associated with radiation pneumonitis, namely MLD, V20, V13, V5, V3, and the decrease in spinal cord maximum dose was statistically significant (p<0.001).

Median tumor motion in free breathing was 10 mm (6-14), 7 mm (5-12), and 7 mm (5-12) in SI, AP, and LR directions, respectively. Median tumor motion with ABC-mDIBH was 2 mm (1-3), 1 mm (0-2), and 1 mm (0-2) in SI, AP, and LR directions, respectively. The decrease in tumor motion in all directions with mDIBH was statistically significant (p<0.001).

Median GTV was 96.3 cc (28-472) in the 1st group, and 103.8 cc (26.5-427.5) in the 2nd and 3rd groups, without statistical significance (p=0.153).

Median follow-up time was 8.8 (5.2-13.8) months. All patients completed the full course of radical radiochemotherapy using ABC-mDIBH without ≥ grade III acute and late toxicity. Out of the total 23 patients, 4 patients (17.4%) experienced grade I esophageal toxicity and 2 patients (8.7%) experienced grade II esophageal toxicity during treatment which recovered after treatment completion. 2 patients (8.7%) experienced acute grade I pulmonary toxicity, and 1 patient (4.3%) experienced grade II late pulmonary toxicity. Follow-up assessments according to RECIST revealed partial response in 13 patients (56.5%), stable disease in 7 patients (30.5%), local progression in 2 patients (8.7%), and distant metastasis in 1 patient (4.3%). Pretreatment CT and follow-up CT of a patient treated using ABC-mDIBH are shown in figures 3a and 3b, respectively.

Discussion

Local control in locally advanced NSCLC is only about 30% and increasing local control and potential survival requires the delivery of higher curative doses to the target[1-5]. The increase in total dose usually translates into an increase in treatment-related toxicity limiting dose escalation. 3-Dimensional Conformal Radiation Therapy (3DCRT) and Intensity Modulated Radiation Therapy (IMRT) may allow dose escalation with tolerable toxicity[4, 5, 10-12], however,

management of breathing-induced tumor and organ motion is critical in precision radiotherapy to overcome uncertainties caused by patient breathing. Respiratory motion hampers both treatment planning and radiation delivery. Motion artefacts in free breathing scans are potential pitfalls leading to inaccuracies in defining treatment volumes and OARs. The use of extensive margins to account for respiratory motion increases the volume of normal tissues in the treatment field with the potential of increased toxicity. Thus, respiratory motion is an important concern in precise lung cancer radiotherapy requiring utmost consideration.

In the study by Hugo et al., cumulative lung dose for simulated motion management strategies of mid-ventilation aperture (MVA) approach, tracking, and breath-hold was assessed. Lung dose-volume metrics including V20 and MLD were lowest in the breath-hold plan in their study albeit with a slight difference, probably caused by larger lung volumes at end-inspiration[13]. Using a method to manage respiratory motion should be thoroughly considered for patients with lung cancer given the problems caused by breathing-induced motion in image acquisition, target and OAR localization, and treatment delivery. Clearly, further studies are warranted to determine the optimal respiratory motion management strategy for an individual patient with lung cancer to achive the best outcome. However, ABC-mDIBH is a viable method of respiratory motion management directly addressing the problem in lung cancer radiotherapy which may offer additional advantages over other approaches by increasing the lung volume resulting in reduction of the dose to the healthy lung tissue through decreasing the lung density. By moving the diaphragm inferiorly and the chest wall anteriorly, mDIBH may decrease the spinal cord dose by displacing the isocenter apart from the spinal cord. Margins to account for target motion may be reduced with the incorporation of ABC-mDIBH which may allow escalating the total dose delivered.

In the study by Giraud et al. evaluating respiratory gating techniques for optimization of lung cancer radiotherapy, the dosimetric benefits of deep inspiration breath-hold were found to be correlated clinically with a significant reduction of pulmonary acute toxicity, and the pulmonary, cardiac, and esophageal late toxicities[14]. However, beyond its advantages, ABC has drawbacks including the need for patient compliance and slightly increased treatment time common to all gated delivery techniques. Patients with lung cancer may have difficulty in breath-holding which hampers the implementation of the ABC procedure, however, patients in our study were able to achieve a minimum mDIBH duration of 20 seconds which is consistent with the literature [15, 16]. Here, we would like to draw attention to patient training. The rationale and potential benefits of ABC-mDIBH must clearly be explained to the patient with an attentive attitude and practicing breath-holds should be instructed to achieve a steady, reproducible breathing pattern. In this study, on-line set-up verification under image guidance with kilo-Voltage Cone Beam Computed Tomography (kV-CBCT) (X-ray Volumetric Imaging (XVI), Elekta, UK) mounted on the LINAC gantry was used to reduce the daily set-up variation and immobilization uncertainty.

In our study, median tumor motion at free breathing was 10 mm (6-14), 7 mm (5-12), and 7 mm (5-12) in SI, AP, and LR directions, respectively. SI motion was predominant in our study, which is consistent with the literature[17-20]. ABC-mDIBH significantly decreased tumor motion translating into improved OAR sparing, statistically significant in normal lung tissue and the spinal cord ($p<0.001$). American Association of Physicists in Medicine (AAPM) Task Group 76 report recommends using a respiratory motion management strategy when > 5 mm respiratory motion is present in any direction or when significant normal tissue sparing is achieved with the method used[6]. ABC, developed by Wong et al.[15], is an effective method for respiratory motion management. Modelling and feasibility studies reported the benefit of ABC in managing respiratory motion in NSCLC[21, 22].

In our study, ABC-mDIBH allowed statistically significant lung and spinal cord sparing, which may have great potential for dose escalation. The significant decrease in OAR doses in the 1st group compared with the 3rd group may be ascribed to the relatively larger CTV-PTV margins used in the 3rd group, which leads to more normal tissue irradiation. However, better OAR sparing should probably have a different explanation regarding the 1st and 2nd groups as the margins used were entirely the same. As lung volumes significantly increased with ABC-mDIBH ($p<0.001$), normal lung tissue exposure was minimized. In the study of Cheung et al.[23], decreased lung density by increasing the lung volume using ABC-mDIBH was shown to yield a statistically significant decrease in V20.

Radiation induced pulmonary toxicity has been reported to be correlated with MLD and V20 in many studies[24-28]. In a recent study, Marks et al. [25] suggested V20 ≤ 30%-35% and MLD ≤ 20-23 Gy for definitive lung radiotherapy to have a ≤ 20% risk of radiation pneumonitis. No ≥ grade III acute and late toxicity was observed in our study during the follow-up period. Follow-up assessments according to RECIST revealed partial response in 13 patients (56.5%), stable disease in 7 patients (30.5%), local progression in 2 patients (8.7%), and distant metastasis in 1 patient (4.3%). Our treatment results with ABC-mDIBH appears to provide significant respiratory functional benefit in our patients consistent with aforementioned studies. These encouraging results may have implications for modifications in our treatment strategy for locally advanced NSCLC in terms of potential margin reduction with ABC-mDIBH instead of using standard uniform margins to further improve our treatment outcomes. Moreover, individualized treatments with dose escalation may be considered if normal tissue sparing is adequately improved with ABC-mDIBH to allow dose modifications.

There are limitations of our study including the small number of patients and the lack of any other strategies to

compare with ABC. Our study primarily aimed at investigating the effect of ABC-mDIBH on tumor motion and critical organ dose-volume parameters in definitive NSCLC radiotherapy and revealed statistically significant reductions in spinal cord and lung dose-volume parameters through excellent tumor immobilization. Given the results of our study, improved normal tissue sparing with ABC-mDIBH may decrease treatment related toxicity and allow higher doses to be delivered to the target in definitive NSCLC radiotherapy with great potential to optimize treatment outcomes. Future studies comparing or compounding ABC-mDIBH with other techniques and documenting the clinical relevance of critical organ dose reductions along with studies investigating margin reduction and dose escalation with ABC-mDIBH are needed.

In conclusion, ABC-mDIBH increases normal lung tissue sparing in definitive NSCLC radiotherapy by improving physical lung parameters along with spinal cord dose reduction through excellent immobilization of tumor. The incorporation of ABC-mDIBH into NSCLC radiotherapy may have implications for potential margin reduction and dose escalation to improve treatment outcomes despite the need for further supporting evidence.

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