Clinical and Translational Radiation Oncology 40 (2023) 100628

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Respiration-controlled radiotherapy in lung cancer: Systematic evaluation of the optimal application practice

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ARTICLE INFO

Keywords:
Respiration-controlled radiotherapy
Lung cancer
Inspiration
Optimal coverage
Advantages
Gating in prospective exhale

ABSTRACT

Background and purpose: Definitive radiochemotherapy (RCT) for non-small cell lung cancer (NSCLC) in UICC/TNM I–IVA (singular, oligometastatic) is one of the treatment methods with a potentially curative concept. However, tumour respiratory motion during RT requires exact pre-planning. There are various techniques of motion management like creating internal target volume (ITV), gating, inspiration breath–hold and tracking. The primary goal is to cover the PTV with the prescribed dose while at the same time maximizing dose reduction of surrounding normal tissues (organs at risk, OAR). In this study, two standardized online breath–controlled application techniques used alternately in our department are compared with respect to lung and heart dose.
Materials and methods: Twenty-four patients who were indicated for thoracic RT received planning CTs in voluntary deep inspiration breath-hold (DIBH) and in free shallow breathing, prospectively gated in expiration (FB-EH). A respiratory gating system by Varian (Real-time Position Management, RPM) was used for monitoring. OAR, GTV, CTV and PTV were contoured on both planning CTs. The PTV margin to the CTV was 5 mm in the axial and 6–8 mm in the cranio-caudal direction. The consistency of the contours was checked by elastic deformation (Varian Eclipse Version 15.5). RT plans were generated and compared in both breathing positions using the same technique, IMRT over fixed irradiation directions or VMAT. The patients were treated in a prospective registry study with the approval of the local ethics committee.
Results: The PTV in expiration (FB-EH) was on average significantly smaller than the PTV in inspiration (DIBH): for tumours in the lower lobe (LL) 431.5 vs. 477.6 ml (Wilcoxon test for connected samples; $p = 0.004$), in the upper lobe (UL) 659.5 vs. 686.8 ml ($p = 0.005$). The intra-patient comparison of plans in DIBH and FB-EH showed superiority of DIBH for UL-tumours and equality of DIBH and FB-EH for LL-tumours. The dose for OAR in UL-tumours was lower in DIBH than in FB-EH (mean lung dose $p = 0.011$; lungV20, $p = 0.002$; mean heart dose $p = 0.016$). The plans for LL-tumours in FB-EH showed no difference in OAR compared to DIBH (mean lung dose $p = 0.683$; V20Gy $p = 0.33$; mean heart dose $p = 0.929$). The RT setting was controlled online for each fraction and was robustly reproducible in FB-EH.
Conclusion: RT plans for treating lung tumours implemented depend on the reproducibility of the DIBH and advantages of the respiratory situation with respect to OAR. The primary tumour localization in UL correlates with advantages of RT in DIBH, compared to FB-EH. For LL-tumours there is no difference between RT in FB-EH and RT in DIBH with respect to heart or lung exposure and therefore, reproducibility is the dominant criterion. FB-EH is recommended as a very robust and efficient technique for LL-tumours.

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https://doi.org/10.1016/j.ctro.2023.100628
Received 15 September 2022; Received in revised form 5 April 2023; Accepted 15 April 2023
Available online 17 April 2023

Introduction

Within the framework of radiation protection and for normal organ sparing, it is necessary to optimize the applied dose. Accurate application of the radiation dose and the requirement of reproducibility are known imperative principles in radiotherapy [1]. Precise dose coverage of the tumour is required, while the dose to organs at risk must be limited. The movement of the organs during breathing varies, not only from patient to patient, but also during the breathing cycle within a patient. There are known inter- and intrafractional changes, which must be taken into account for radiotherapy [2–4]. Because of the movable clinical target volume (CTV), a control of the intrafractional motion is mandatory. Erroneous variation of setup during the course of radiotherapy (RT) can impair treatment, especially if steep dose gradients are planned to limit the dose to organs at risk [5]. Image-guided radiotherapy (IGRT) using markers can reduce setup errors, potentially improves treatment efficacy and decreases treatment related morbidity [6–8].

With modern techniques, the complex lung deformation can be mapped onto the patient thorax using surrogate markers, such as a real-time position management (RPM) marker block. The position of the RPM block represents an external surrogate marker that exactly follows the appearance of a certain breathing phase and state, and thus the tumour position that allows gating. Exhale gating is only applicable, when the respiratory cycle is serene and periodic. Difficulties arise when the breathing pattern changes, resulting in target dislocation [4,9,10].

The aim of this study was to determine the best respiratory mode depending on tumour localization in the upper, middle or lower lobe in order to optimally apply radiotherapy while at the same time protecting adjacent normal tissue.

Materials and methods

Study design and participants

The study has been set up as a prospective registry study with the approval of the ethics committee of the Medical Faculty of the University Duisburg-Essen, 22-106788-BO.

The study protocol is described in the flow chart (Fig. 1).

Patients with non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC) or another histology with extension to the lung, who were indicated for thoracic RT, were included. The majority of patients with lung cancer receive induction chemotherapy at the West German Cancer Centre.[11] The only exclusion criterion was inability to maintain a calm, reproducible and steady respiratory phase. All patients received planning CTs during defined breathing exercises, following professional guidance how to maintain a reproducible deep inspiratory breath-hold state or a regular, serene and reproducible breathing cycle:

1. A fast spiral CT during deep voluntary inspiration breath-hold (DIBH) in the venous phase after intravenous contrast, and
2. A prospectively gated sequential mode CT in expiration during shallow breathing (FB-EH), sequential mode acquires images without CT couch motion and image volume is defined by collimator width.

A SENSATION® open CT scanner was used (Siemens®, Erlangen Germany). In DIBH the HU *(Hounsfield unit)* values in the central vessels should not exceed 120 HU in order to be able to differentiate hilar structures. Prospective gating was used to minimize artifacts from irregular breathing that often can affect retrospective gated 4DCT scans. A retrospectively gated low dose 4D free breathing CT was only performed in patients with lower lobe tumours, to estimate the amplitude of tumour motion and from that the size of the PTV margin. Dose exposure for these two to three planning CT scans was within the range of values of a single full dose 4D-CT according (CT in FB-EH, mean $CTDI_{vol}$ 7.080 mGy; CT in DIBH, mean $CTDI_{vol}$ 8.131 mGy; $\sum$15.211 mGy; low dose 4D-CT mean $CTDI_{vol}$ 11.170 mGy, $\sum$15.211–26.381 mGy). Here the standard full dose CT dose index ($CTDI_{vol}$) for modern CT scanners amounts upto $\sum$10.3–28.9 mGy for adults for full dose 4D CT scans (CTDI for 4D CT for lung cancers of 19.6±9.3 mGy (N = 168, mean ± 1SD)). [12].

The Real- time Position Management system (RPM; Varian Medical Systems, Palo Alto) was used to record the entire respiratory cycle and mode by means of the breathing induced movements of an RPM block. The RPM block was placed on the patient's abdomen near the sternum to record the breathing curve and mode. The signal was available at the CT scanner for the acquisition of prospectively gated CT scans or for retrospectively reconstructing 4D-CT image sets. These planning CT's were used to select the individual best scenario to treat the PTV but spare the lung or heart optimally.

Definition of the target volume in both respiratory exercises DIBH and FB-EH

The gross tumour volume (GTV) and the clinical target volume (CTV) as well as the organs at risk (OAR) were delineated on the DIBH CT with intravenous contrast agent according to institutional guidelines, e.g. CTV comprising the pre-chemotherapy tumour involved tumour beds with a margin of at least 5 mm. The PET/CT before start of treatment was available for all patients. First, the initial tumour volume at diagnosis was defined on the PET/CT before start of induction chemotherapy. This was registered with the further planning CTs: GTV was delineated on the DIBH CT with contrast agent, and then the tumour volume was defined on the prospectively gated FB-EH CT. All CTs were registered along the timeline: 1. PET/CT at diagnosis, 2. planning CT in DIBH with contrast agent, 3. FB-EH CT, 4 if defined mandatory low dose 4DCT.

The tumour volume defined on the prospectively gated FB-EH CT, was defined by deforming it from the DIBH-CT using the Eclipse deformable image registration algorithm (Varian Eclipse Version 15.5). The consistency of the contours was always checked by elastic deformation (Varian Eclipse Version 15.5). The contours were propagated to the exhale phase and if available to the 4D-CT scans using elastic deformation.

All contours were controlled by two independent radiation oncologists, and if necessary they were manually adapted. The PTV margin to the CTV was 5 mm in the axial and 6–8 mm in the cranio-caudal direction, 8 mm for lower lobe tumours with a breathing defined amplitude.

Treatment planning and therapy

Radiotherapy treatment plans were generated and compared for both breathing modes DIBH and FB-EH using the same technique, IMRT or VMAT. The best plan was chosen by means of the standard criteria based on ICRU Report 83 and our previous radiation protocols regarding PTV, coverage and organs at risk (OAR) [13–15].

Clinical management was standardized with the use of the routine pathway for high quality assurance. For treatment delivery and online verification of the correct dose application the Varian Truebeam linear accelerator v2.5 was routinely used [16,17]. During the irradiation fraction, the image-guided radiation therapy (IGRT) software allows online generation of kV-images, using the orthogonal on-board imager (OBI). The image-guidance technique uses markers, indicating the position of the diaphragmatic copulas according to the planning CT. These markers were displayed online and off-line in the kV-images acquired during irradiation (regions of interest, ROI). It uses an algorithm to determine the location of the markers in each triggered image and verifies whether they are at a predetermined margin within the defined position (regions of interest, ROI). As marker, a lung – soft tissue contrast within a circle was used. Soft tissues adjacent to lung were the

Flow Chart

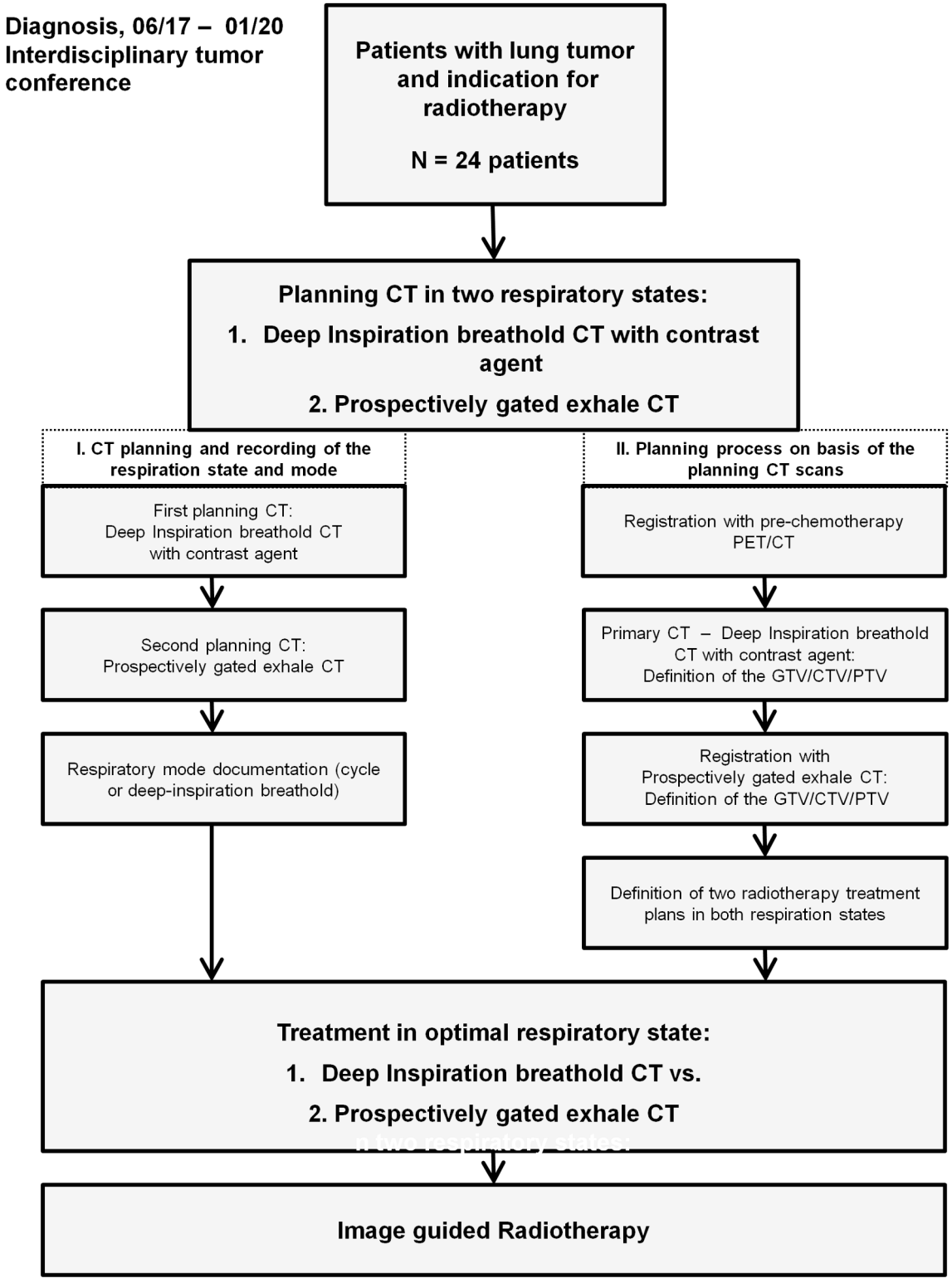

Fig. 1. Flow chart: The study protocol is described in the flow chart.

diaphragm at first, or the thoracic wall at second instance (Fig. 2a – d, Fig. S2a – d Supplement). The soft tissue contrast at the diaphragmatic cupolas here should be within 5 mm of the diaphragm markers.

The gating window is defined on the derived motion respiratory curve. Fig. 2a – d, Fig. 2a – e Supplement Fig. S2a – d show examples for defining the optimum gating windows for DI-BH and FB-EH.

The gating window is defined by the image guidance team during treatment application. At our department image guidance is performed and monitored on a continuous basis. The radiation oncologist defines and can adapt the necessary gating window.

Here, we defined the conventional gating window of ±2.0 mm – 7.0 mm for the optional set-up position of the internal markers. The first and every insecure session were guided by an experienced radiation oncologist. Each regularly performed radiation session was controlled by a radiation oncologist.

DI-BH states show a much higher variability than the FB-EH respiratory phase [18].

This is a very important issue for defining image-guidance and also in lower lobe tumours the PTV margin. In upper lobe tumours, or rigid tumours that invade e.g. the mediastinum or the thoracic wall, it was due to the radiation oncologist's guidance that a larger gating window was permitted without compromising the PTV position or coverage, or vice-versa a narrower gating window was applied in highly volatile locations like in lower lobe tumours.

The marker or region of interest (ROI) for the correct set-up control was set on the diaphragm on the kV image. The ROI is shown as a colored circle and the defined marker location as a crosshair in online image-guidance. The circles are shown in three colors online: green online, if the marker is within the tolerance limits; orange online, if the software could not find the marker; and red, if the marker is out of range online (>5 mm). This visualization allows the user to qualitatively verify any marker shifts during treatment application [16,17]. Total doses prescribed were 30–39 Gy at 3 Gy per fraction for M1 patients or 60–66 Gy at 2 Gy per fraction for M0 patients. For comparison, all mean organ doses were normalized to the prescribed total dose. In addition, the relative lung volumes, receiving at least 20 Gy (V20) or 30 Gy (V30) were determined from treatment plans normalized to a total dose of 50 Gy, as this was the most common total dose per treatment series. At 50 Gy, a re-planning was routinely performed for patients without distant metastases to ad attention to tumour shrinkage.

Clinical outcome measures and statistical analysis

The primary outcome measure was the verification of robustness, the measurement of the planned dose to organs at risk and the volume of PTV in different respiratory phases. Tumours were categorized in lower lobe or non-lower lobe tumours as the heart exposure differs by this criterion. A predefined analysis plan was calculated before the treatment plan was applied. The primary goal was to achieve a high probability of local tumour control (tumour control probability, TCP) with a low risk of complications in normal tissue (normal tissue complication probability, NTCP). Non-lower lobe tumours comprised tumours in the upper or middle lobes or centrally located tumours. Non-parameteric Wicoxon test for connected samples were used. All *p*-values were for 2-sided comparisons. SAS statistical software version = 0.4, SAS/STAT 15.1 was used (SAS Institute, Cary, NC).

Results

All patients' characteristics are summarized in Table 1. Twenty-four patients were enrolled from June 2017 to January 2020 (15 male, 9 female participants). The median age was 63 years (range, 34–77), the median lung volume in DIBH was 4880,8 ml (range 3109.3–8360.7 ml) and in FB-EH 3360,05 ml (range 1530.4–5947.0 ml). A total of 70.8 % patients had tumours in the tumour category cT3-cT4 (8th UICC/AJCC TNM edition). Tumour stages are indicated in Table 1. The tumour localization of eight patients was on the left side. One patient presented with a bilateral tumour manifestation.

The PTV in expiration (FB-EH) was on average significantly smaller than the PTV in inspiration (DIBH) for tumours in the lower lobe (LL) 431.5 vs. 477.6 ml (Wilcoxon test for connected samples; $p = 0.004$). The same relationship was valid for upper lobe tumours (UL). Here the PTV in FB-EH measured 659.5 ml and in DIBH 686.8 ml respectively ($p = 0.005$).

Furthermore, the ratio between $PTV_{Inspiration}$ and $lung\text{-}volume_{Inspiration}$ was smaller with 15.7% (range 0.25–50.2%) in DIBH compared to 21.3% (0.28–62.4%) in FB-EH for UL tumours. In the UL cohort the mean lung dose was 18.21% (4.2–29) in DIBH vs. 23.33% (4.7–42.3) in FB-EH ($p = 0.011$). Mean heart dose was 10.27% (0.7–20.7) in DIBH vs. 18.04% (0.7–37.2) in FB-EH ($p = 0.016$). The V20 (LungV20, lung volume receiving >20 Gy) values for lung exposure were more favorable in DIBH compared to FB-EH for UL tumours ($p = 0.002$) (s. Table 2). The same holds for LungV30 ($p < 0.001$, Wilcoxon test for connected samples). In addition, the mean lung dose ($p = 0.011$) and mean heart doses ($p = 0.016$) were lower in DIBH for UL-tumours in comparison to FB-EH (Fig. 3, Table 2). Therefore, intra-patient comparison of plans in DIBH and FB-EH showed superiority of DIBH for Non-LL-tumours and especially for UL tumours.

Fig. 4a shows the dependence of the difference between mean lung dose with DIBH and mean lung dose with FB-EH (delta mean lung dose)

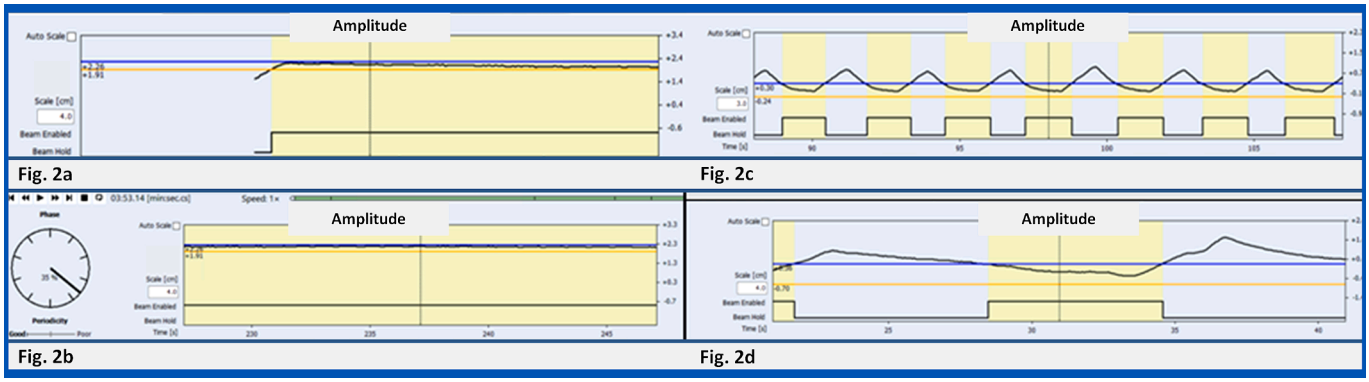

Fig. 2. a – d: demonstration of different gating windows (blue line: upper border, orange line: lower border) in various patients. 2a, 2b: respiratory gating in deep-inspiration breath-hold technique, 2c, 2d: respiratory gating in free-breathing exhale technique. Fig. S2a – d Supplement: Demonstration of different gating windows (blue line: upper border, orange line: lower border) in various patients. The conventional gating window of ±3 mm – 7 mm is usually used as the optional set-up position of the internal markers. 2a, 2b: Respiratory gating in deep-inspiration breath-hold technique, 2c, 2d: Respiratory gating in free-breathing exhale technique. Fig. S2e Supplement: Example for the definition of the gating window of the breathing curve in deep-inspiration breath-hold (DI-BH) technique in the treatment planning. The teaching lasted 17.48 s. Here the gating window was defined in DI-BH with 4.7 mm (±2.35 mm).

Table 1
Patient characteristics.

Patient characteristics	Number of Patients
Histology	
Non-small cell lung cancer	18
Small cell lung cancer	3
Other	3
cT-category	
ycT0	2
cT1	3
cT2	2
cT3	2
cT4	15
cN-category	
N0	5
N1	0
N2	9
N3	10
cM-category	
cM0	0
cM1a-c	9
cM1a (singular pulmonary metastasis)	2
UICC Version 8th TNM stage classification	
IIB	1
IIIA	5
IIIB	6
IIIC	3
IVA (singular pulmonary metastasis)	2
IVB	7
RT intent	
palliative	7
curative	17
Location: of the tumour	
Upper lobe (Non-lower lobe)	13
Lower lobe	8
Upper and lower lobe	3
Laterality of the primary tumour	
left-sided	8
right-side	15
bilateral	1
Gender	
Female	9
Male	15
Age	Median and Range
Median	62.54 years
Range	34.62–77.53 years

Note: All numbers represent patients' counts, except in the rows with patients' age.

on tumour location ($p = 0.0004$, F-test) and the lymph node status cN0-3 according to the UICC 8th ed. NSCLC classification ($p = 0.032$, F-test) as categorical variables using the linear model.

In addition, non-parametric cross-tabulation and analysis with the Friedman test shows a significant influence of tumour location (upper vs, lower lobe) on ranked delta mean lung dose (deltaMLD) controlled for cN0-3 status ($p = 0.0004$).

There was a correlation between mean lung dose (MLD) and mean heart dose (MHD) sparing by irradiation in DIBH vs FB-EH. Fig. 4b shows a significant dependence of the difference of mean heart dose in DIBH and during FB-EH (ΔMHD) on the difference of mean lung dose in DIBH and during FB-EH (ΔMLD) ($p = 0.0003$, F-test). The Spearman correlation coefficient was rs = 0.655 and was significantly different from rs = 0 ($p = 0.0005$).

For LL-tumours, the plans in FB-EH showed no difference in OAR in comparison to DIBH (mean lung dose $p = 0.683$; mean heart dose $p = 0.929$). All values are shown in Table 3.

The RT set-up margin was checked online for each fraction and was robustly reproducible, especially in FB-EH.

For FB-EH the standard set-up gating window was ±1.7 mm – 6.5 mm (mean value 4.3 mm), for DIBH the chosen set-up window was ±1.75 mm – 9.8 mm (mean value 7.3 mm) ($p = 0.003$).

The approved control value for image guidance of radiation for FB-EH was in acceptance range in 96.34 % of all cases (90.9 %– 100 %), for DIBH in 95.2 % (76.9 %- 100%) $p = 0.93$, (Cohran-Armitage trend test). On a per X-ray image basis acquired during irradiation, however, DIBH was associated with a larger likelihood of deviations of the diaphragmatic cupolas form the marker positions of >5 mm ($p < 0.001$, chi^2-Test).

Discussion

In this work we wanted to analyze the best respiratory phase or state in image guided radiotherapy of lung cancer dependent on individual tumour extent. The concept aims to improve the precision of radiation delivery in the treatment of respiratory changeable tumours. To date, there is no study that defines the optimal respiratory phase for an individualized treatment dependent on tumour localization. By compensating respiratory movement, an increased dose can be directly focused on the tumour, resulting in a higher tumour control rate with constant or reduced side effects and improved chances of cure.

The current gold standard for determining the planning target volume of the irradiated tumour is the contouring of several individual GTVs of the 4D-CT with the addition of a subsequent margin [8,19,20].

Modern techniques such as gating for more precise irradiation can now represent an essential procedure for more effective treatment of tumours that are in motion [21]. Panakis et al. [22] could demonstrate that active breathing control systems can effectively reduce up to 25% the PTV margins. [22].

The aim of such targeted radiation is the best possible protection of normal tissue.

Here an image-based, non-invasive technique was established that uses image processing methods to determine the exact position of the tumour during irradiation.

We used two breathing exercises, DIBH and FB-EH, associated largely different lung volumes. Both can consistently be reproduced, but the FB-EH is more robust due to the limited variations of expiration. The inspiration mode DIBH demonstrates a larger variability of lung extension [18 23]. The FB-EH shows a robust breathing phase for radiation application, also for patients with limited lung capacity. Our group [24]

Table 2
Non-lower lobe lung tumours, comparison expiration vs. inspiration; Mean organ doses are given as relative (rel.) doses, relative to the prescription dose.

	Rel. mean Lung dose Expir. [%]	Rel. mean Lung dose Insp. [%]	Rel. mean Heart dose Expir. [%]	Rel. mean Heart dose Insp. [%]	V20 Lunge Expir. [%]	V20 Lunge Insp. [%]	V30 Lunge Expir. [%]	V30 Lunge Insp. [%]
Average	23.33	18.21	18.04	10.27	22.99	15.83	15.79	9.91
Min	4.7	4.2	0.7	0.7	1.1	1.1	0.3	0
Max	42.3	29	37.2	20.7	40.7	27	32	19.1

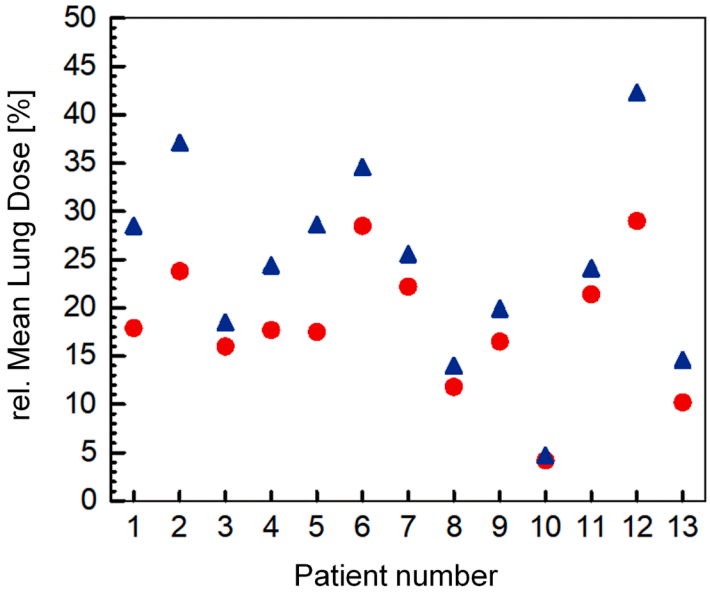

Fig. 3. Comparison of relative mean lung dose for upper lobe and non-lower lobe lung tumours in deep inspiration breath-hold radiation in comparison with prospective expiration radiation, triangles for expiration/FB-EH, and circles for inspiration/DIBH.

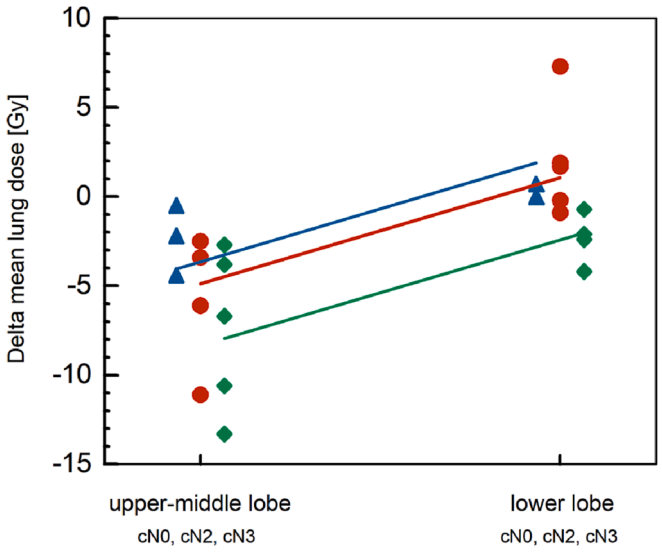

Fig. 4a. Dependence of the delta mean lung dose [Gy] on tumour location ($p = 0.0004$, F-test) and the lymph node status cN0-3 ($p = 0.032$, F-test). Sparing of mean lung dose by inspiration breath-hold in comparison to exhale gating (FB-EH) dependent on tumour location and lymph node status. Triangles, blue: cN0 patients Circles, red: cN2 patients Rhombi, green: cN3 patients.

already determined the inter-fraction stability of the delivered dose distribution by FB-EH radiotherapy in lung cancer. [24] Here, the delivered equivalent uniform dose of the accumulated dose distribution over all analyzed fractions remained above 95% of the prescribed dose for the clinical target volume for all patients. [24].

Here using over all patients an on-board imager, patients treated with FB-EH or DIBH both showed a high rate of precise diaphragm cupola locations within 5 mm from those in the planning CT, of >95% over all patients.

Each fraction was applied based on verification of the current position with a CBCT/one-to-one match registration with the planning CT, external markers of the thorax (RPM block) to mirror the respiratory cycle and monitoring of diaphragm position by online kV-imaging during radiation.

If the patient is able to maintain a reproducible, serene respiration mode, the movements of the tumour are positioned within all images and optimal conditions are achieved in the planning dataset.

Using several of the different breathing phases, the tumour positions represented in breathing phases were divided in DIBH and FB-EH and then specified using a registration algorithm.

If the tumour is located in the upper lobe and does not extent to the lower or middle lobe, it seems more advantageous to perform the radiation session in DIBH mode. Especially large cT4-tumours in the UL fixed at surrounding normal tissues are less movable during the breathing exercise. The selection of the breathing exercise during irradiation, DIBH or FB-EH, should depend on the reproducibility of the DIBH and the benefits of the respiratory situation in relation to the organs at risk. The primary tumour localization in the upper lobe correlates with advantages of radiotherapy in DIBH compared to FB-EH. The OAR dose is significantly lower for the heart as well as for the lungs. The variability of the extension of the lower lobe during respiration is less important here.

Otherwise, if the tumour is spread to the lower lobe, the variation of the lower lung must be taken into account, as the difference may extent up to several centimeters [21,23]. The PTV is significantly smaller than in DIBH, while the dose for OAR remains similar. For tumours in lower lobe, radiotherapy in FB-EH has no difference in heart or lung exposure compared to radiation in DIBH. If the tumour is located in the lower lobe, the compliance to the breathing exercise is even more crucial as tumour movement during free breathing is larger, and inter- and intra-fraction positional variability during DIBH may often be larger. Thus, for such tumours FB-EH is recommended not only as a very robust and efficient technique, but also as an application method that can easily be verified with intra-fractional imaging.

Conclusion

To summarize, we prefer DIBH for upper lobe tumours, while we prefer FB-EH for lower lobe tumours, as it seems to be the more suitable and robust respiratory phase.

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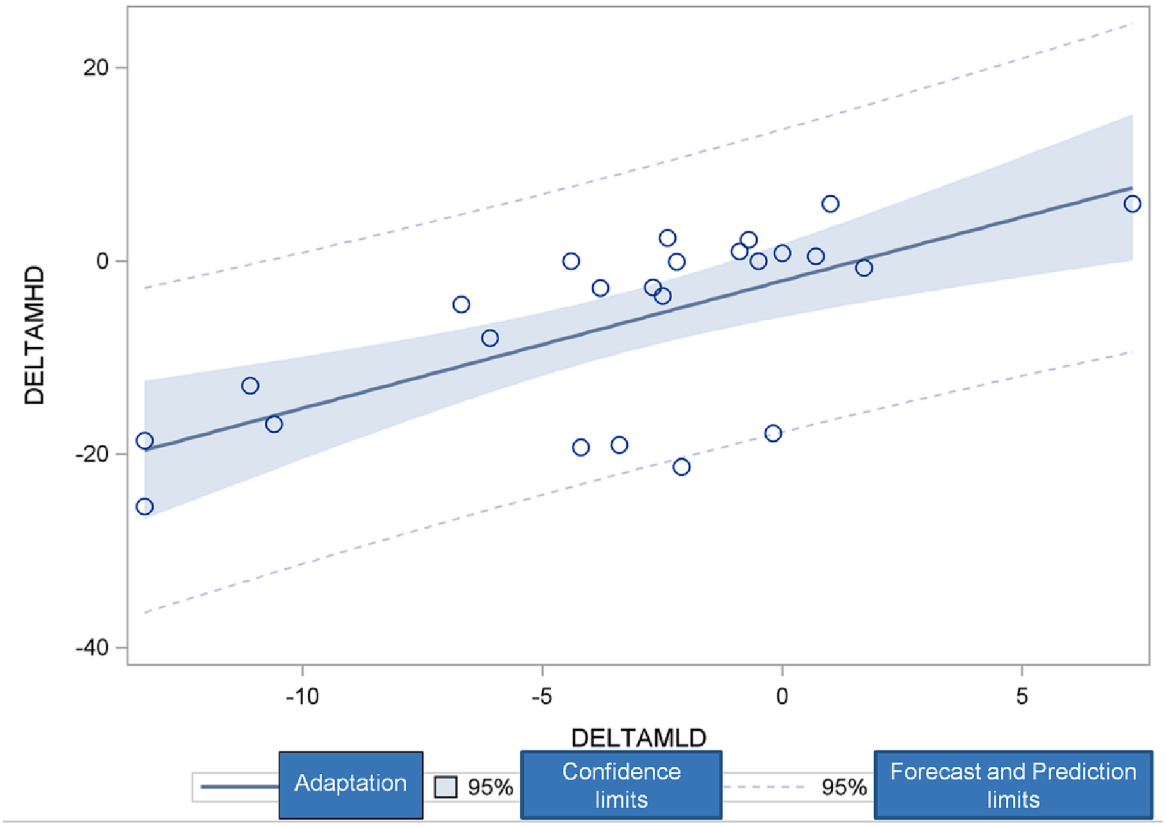

Fig. 4b. Comparison between deep-inspiration breath-hold and free breathing exhale radiation plans: The difference of mean heart dose (MHD) [Gy] in DIBH and MHD [Gy] during FB-EH (ΔMHD) is dependent on the difference of mean lung dose (MLD) [Gy] in DIBH and during FB-EH (ΔMLD), Spearman correlation non-parametric: rs = 0.655 and significantly different from rs = 0 (p = 0.0005). [Gy] = doses in Gray; Δ = DELTA, difference.

Table 3
Lower lobe lung tumour, comparison expiration vs. inspiration.

	Rel. mean Lung dose Expir. [%]	Rel. mean Lung dose Insp. [%]	Rel. mean Heart dose Expir. [%]	Rel. mean Heart dose Insp [%]	V20 Lunge Expir. [%]	V20 Lunge Insp. [%]	V30 Lunge Expir. [%]	V30 Lunge Insp. [%]
Average	23.45	23.46	23.12	19.45	24.65	23.35	14.53	13.05
Min	0.7	1.4	0.46	0.98	1.1	1.3	0.5	0.5
Max	37.7	35.7	41.1	43.5	45.7	40	31	22.3

The study has been set up as a prospective registry study with the approval of the ethics committee of the Medical Faculty of the University Duisburg-Essen, 22–106788-BO.

All procedures were performed according the Declaration of Helsinki.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2023.100628.

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