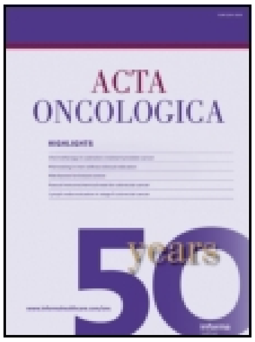

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Deep inspiration breath hold radiotherapy for locally advanced lung cancer: Comparison of different treatment techniques on target coverage, lung dose and treatment delivery time

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To the Editor,

Patients with locally advanced non-small cell lung cancer (NSCLC) treated with concomitant chemo-radiation have a poor survival of 10–15% after five years and a high risk of local progression [1]. After radiation therapy (RT) 30% of patients present with symptomatic radiation pneumonitis, associated with significant morbidity and 2% mortality [2]. Mean lung dose (MLD) and relative amount of lung volume receiving a radiation dose of 20 Gy or more (V20) are reported to correlate with radiation pneumonitis [2–5].

Increased lung volume in deep inspiration breath hold (DIBH) facilitates a potential for lung toxicity decrease [6,7]. DIBH RT has been successfully applied for a decade, primarily for breast cancer RT [8,9]. However, it is generally feared that lung cancer patients will have poorer lung function and a lower compliance. In our clinical routine all lung cancer

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patients are scanned in voluntary DIBH, to have an image set without image artefacts [10] and this single voluntary DIBH is well tolerated. A few centres reported on the use of spirometric devices for lung cancer DIBH [6,7,11,12], but to our knowledge, there are no studies on voluntary DIBH with visual guidance and optically monitored respiration.

Modern rotational intensity-modulated techniques can reduce the lung dose, but result in a low dose bath. Further, there is a question of interplay effect due to the tumour and the thoracic skeleton motion [13,14]. In DIBH interplay effects are eliminated due to absence of target motion. In recent years, novel linear accelerator technologies enabled use of flattening filter free beams (FFF), with a potential of faster treatment delivery [15].

The purpose of our study was to evaluate different treatment techniques delivered in DIBH to find the optimal combination of target coverage, toxicity risk and treatment delivery time.

Material and methods

Ten patients with locally advanced NSCLC referred for RT participated in a DIBH pilot study (approved by the local ethical committee, protocol no. H-2-2011-153). All patients were scanned according to our standard protocol for lung RT, with free breathing PET/CT, a four-dimensional computed tomography (4D-CT) and a DIBH CT scan.

Prior to their DIBH scan, the patients were coached to hold their breath in deep inspiration, to a level they felt comfortable with. Compliance was assessed as an ability to hold one DIBH of 20 s, an ability to perform repeated DIBHs throughout the treatment course and an increase in lung volume during DIBH.

Respiratory motion was monitored with the Real-time Position Management system (RPM^{TM}, Varian Medical Systems Inc.), which uses an infra red camera to track the respiratory signal from an optical marker placed on the patient's thorax. Visual feedback was provided to the patient via video goggles to insure a stable DIBH level.

All the patients were treated in free breathing (FB), their clinical 3D conformal treatment plans (3DC) were made by dosimetrists.

For each patient we calculated six plans in DIBH: a 3DC and five volumetric modulated arc therapy plans with Rapid Arc technique (RA). To minimise bias from different planners, all DIBH plans were calculated by the same medical physicist (MJ): 3DC plans were calculated with the same gantry angles as the corresponding FB clinical plans and in RA standard plan objectives were used. RA plans were calculated with 6 MV flattened beam (FF), 6 MV FFF and 10 MV FFF. The FF plans were calculated with two arcs, while the FFF plans were calculated with both one and two arcs. For all DIBH plans the applied clinical target volumes (CTV)-planning target volumes (PTV) margins corresponded to the margins in the clinical FB 3DC plan. Prescribed dose to the PTV was 66 Gy in 33 fractions. DIBH plans were compared with the clinical FB 3DC plans on target coverage and lung dose. The target coverage was evaluated as dose delivered to 95% of the PTV, 95% and 99% of the CTV and maximum dose ($D95_{PTV}$, $D95_{CTV}$, $D99_{CTV}$, Dmax, respectively). The lung dose was evaluated as relative lung volumes receiving at least 5 Gy, 20 Gy or 40 Gy (V5, V20, V40, respectively) and as mean lung dose (MLD).

The treatment planning was performed in Eclipse treatment planning system (Varian Medical Systems inc.) with an anisotropic analytical algorithm (AAA, version 10.0.28).

For the evaluation of the treatment delivery time, the number of DIBH (of 20 s duration) necessary to deliver the RT was noted. The statistical significance was tested with Student's t-test.

Results

All patients could comfortably perform a DIBH of at least 20 s during their planning session. Eight of 10 patients, that received 33 fractions of the RT, performed DIBH comfortably both at the beginning and towards the end of their treatment course.

In DIBH, the lung volume increased substantially for all patients, by a mean of 57% (range 35–85%; $p < 0.0001$; paired t-test). Patient 1 is shown in the Supplementary Figure 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2013.813644, the DIBH scan shows clear absence of motion artefacts around the diaphragm and a clearer tumour edge.

The amount of MU for different planning techniques as well as the number of DIBH of 20 s duration necessary to deliver the RT are presented in Supplementary Table I (to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2013.813644). Clinical 3DC plans consisted of three to five fields, requiring three to five DIBH for treatment delivery. Eight of 10 RA plans were feasible with two partial arcs (i.e. rotation of max 240°) and would require four DIBH of 20 s duration (see details in the Supplementary Table I, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2013.813644). Two of 10 RA plans required two full arcs (i.e. almost full gantry rotation of 358°) due to target size and/or complexity and hence would be delivered with six DIBH of 20 s. RA plans with FFF were also calculated with one arc only: 8/10 plans were made with one full arc and could be delivered within three DIBH. Two of 10

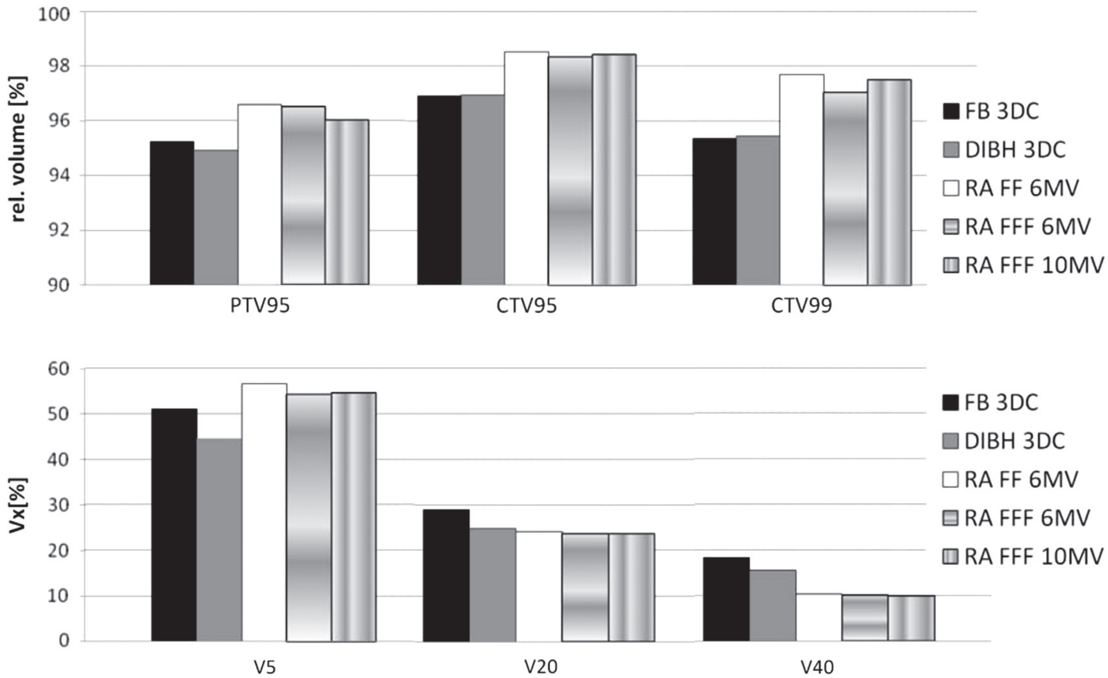

Figure 1. Presentation of target coverage and lung dose for different treatment techniques in FB and DIBH: Above: target coverage presented as the relative volume receiving at least 95% (PTV95 and CTV95) or 99% (CTV99) of the prescribed 66 Gy. Below: relative lung volume Vx, where x is 5, 20 and 40 Gy, respectively. Data for RA plans with one arc is not presented.

plans were feasible with one partial arc. These plans had smallest PTV (60 and 200 ml).

The DIBH 3DC plan did not affect target coverage but resulted in a small, but significant increase in Dmax (1.1% on average) compared to the clinical free breathing 3DC plan. In all DIBH RA plans, $D95_{CTV}$ and $D99_{CTV}$ increased significantly, while $D95_{PTV}$ had a trend towards an increase (Figure 1). Dmax trended towards a small decrease of 1–2% in RA plans with two arcs, making target dose distribution more homogeneous.

The DIBH 3DC plan reduced MLD by 15.7% ± 8.2% (mean ± SD, standard deviation). In all DIBH RA plans MLD was reduced by approximately 20%, the best reduction was achieved in the RA plan with two 6MV FFF arcs (21.8% ± 7.4%), while RA plans with one FFF arc achieved the smallest MLD reduction (18.5% ± 11.5%).

DIBH 3DC plan reduced lung V20 by 14.8% ± 9.2%.Best decrease in V20 was achieved with RA plans with two FFF arcs (by 20.5%), smallest decrease compared to the free breathing 3DC plan was with one arc FFF RA plans (by 11.8% for 6MV and by 9.8% for 10 MV).

DIBH also reduced the high dose volume in the lungs: V40 was reduced by almost 50% for all RA plans and 15% for the 3DC plan (Figure 1). As expected, the low dose bath increased in all DIBH RA plans (measured as lung V5), however, this increase was not significant for FFF energies, neither for plans with one nor two arcs.

There were no significant differences in the target coverage between the RA FFF plans with one arc and the RA FFF plans with two arcs. Absolute values on all lung parameters are presented in Table I.

Discussion

We investigated the benefit of voluntary DIBH RT for locally advanced NSCLC with comparison of dif-

Table I. MU and number of DIBH with different techniques.

	FB 3DC	DIBH 3DC	DIBH RA FF 6 MV	DIBH RA FFF 6 MV-2 arcs	DIBH RA FFF 6 MV-1 arc	DIBH RA FFF 10 MV-2 arcs	DIBH RA FFF 10-1 arc MV
MLD [Gy]	17.3 ± 6.6	14.7 ± 5.9*	14.0 ± 5.5*	13.6 ± 5.4*	14.3 ± 5.8*	13.9 ± 5.6*	14.3 ± 5.7*
V5 [%]	51.0 ± 23.6	44.6 ± 22.5*	56.6 ± 25.3*	54.3 ± 24.2	54.6 ± 24.8	54.7 ± 24.4	55.2 ± 24.4
V20 [%]	29.0 ± 12.2	24.9 ± 11.0*	24.2 ± 11.0*	23.6 ± 10.7*	26.4 ± 12.0	23.8 ± 11.5*	26.7 ± 11.8
V40 [%]	18.4 ± 6.8	15.6 ± 6.1*	10.3 ± 4.1*	10.1 ± 4.0*	9.7 ± 3.9*	10.0 ± 3.8*	9.5 ± 3.7*

*Indicates significant improvement compared to free breathing 3DC plan ($p < 0.05$), except for V5 for DIBH RA FF, where there is a significant decrease.

ferent planning techniques to the free breathing 3DC RT. FFF RA plans with two arcs performed best considering both target coverage and the risk of lung toxicity. All plans were deliverable with two to six DIBH, each lasting 20 s.

Lung inflation for NSCLC patients in our study was substantial, with an average lung volume increase of almost 60%. Studies using spirometry devices for an assisted DIBH reported much smaller lung volume increase: 36–42% [7,11,16]. The assisted DIBH is typically applied at 70–80% of the patient's maximum inspiration level [7,17], while we let the patient choose a maximum comfortable level of inspiration for the DIBH.

This is the first published study investigating DIBH RT for advanced stage NSCLC and FFF beams. FFF studies published on the lung SBRT targets [18] did not find any dosimetric differences between the FF and FFF RA plans, but the FFF plans required a higher amount of MU. We observed a ~20% increase in MU for both FFF energies compared to FF.

FFF beams' possibility of increasing the dose rate up to 2400 MU/min is not feasible when delivering 2 Gy per fraction with two arcs, since the maximum allowable gantry speed of one rotation/min limits the actual dose rate. However, when using one arc instead of two, the higher dose rate of FFF beams would result in reducing the number of DIBH necessary for the RT delivery to only two to three.

We observed an additional benefit of FFF, the low dose bath (evaluated as lung V5) caused by intensity modulation in RA FF was mitigated by FFF beams, regardless energy or number of arcs. Low V5 in FFF can be explained with lower energy and less scatter due to the absence of flattening filter [19].

RT in DIBH has a potential of decreasing the lung toxicity, since there is a larger part of the healthy lung outside the treatment field compared to a shallow breath hold or free breathing. We have shown a substantial decrease in MLD, lung V20 and V40. Especially MLD and lung V20 are widely used as predictors for radiation pneumonitis [2–5].

Giraud et al. showed a significant decrease in V20 and MLD in patients receiving RT in DIBH [7]: V20 decreased from 27% to 23%, and MLD decreased from 15.6 Gy to 12.8 Gy. Both MLD and V20 were lower than in our study, which can be explained by the authors reporting dose to the lung volume excluding the PTV, while we report doses to the whole lung volume, including the PTV. In a recent British study [11] V20 and MLD were reduced in DIBH, but less than in our study, which may be explained by the smaller lunge volume increase in their patient group (42% compared to our 57%).

In the above mentioned studies [7,11] the margins applied to the DIBH treatment plan were smaller than for the FB, while we kept the CTV-PTV margins unchanged. DIBH may have a potential of margin reduction, however inter-breath hold reproducibility of tumour position with visually guided voluntary DIBH needs to be evaluated. Inter-breath hold tumour position uncertainty was evaluated with spirometry systems (ABC) and found to be relatively small: 1.3–1.5 mm [11]. However, inter-fractional tumour position is still subject to a baseline shift, therefore daily imaged guidance in DIBH is important [11].

Limitation of our study is that plans were calculated with AAA, which is less accurate in low density lung tissue compared to Monte Carlo (MC) or newer treatment planning algorithms [20,21]. For 6MV, the AAA underestimates the dose in the low density lung tissue for 1–4% both outside and within the PTV [20,21], while it overestimates the mean dose in the soft tissue areas of the PTVs (typically the GTV).

Our work is primarily a treatment planning study; further investigation on robustness of intensity-modulated DIBH treatment plans on the anatomical changes occurring throughout the treatment course and the inter-breath hold variability is necessary and being carried out.

To conclude, DIBH resulted in considerable lung inflation (> 50%) and facilitated lung toxicity risk reduction. RA RT is deliverable with up to six DIBH of 20 s. RA with two arcs and FFF beam gave the optimal dosimetric profile. RA with one arc and FFF beam could be a solution for patients being able to demonstrate only a few reproducible DIBH.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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