Supplementary material for Sibolt et al., Adaptation requirements due to anatomical changes in free-breathing and deep-inspiration breath-hold for standard and dose escalated radiotherapy of lung cancer patients, Acta Oncol, 2015; 54: 1453–1460.

Appendix

Material and Methods

The clinical protocol was approved by the Copenhagen Regional Committee on Health Research Ethics (protocol no. H-4-2012-066) and the Danish Data Protection Agency (ID. nr.: 2007-58-0015/HEH.750.24-61). Every patient gave informed consent to the work before inclusion. Patient characteristics are summarized in Supplementary table 1. Patients had varying number of primary tumors and lymph nodes involved as well as spread in the location of the primary tumor.

A marker-based optical breathing signal (RPM, Varian Medical Systems, CA, USA) was utilized both for phase sorting into 10 breathing phases during 4DCT and for visual patient guidance in DIBH 3DCT. During DIBH imaging, patients were audio-visually guided to hold their breath within a pre-defined amplitude level and a gating window of 2–3 mm width.

In FB, the primary GTV-T was delineated using the maximum intensity projection (MIP) method, resulting in a primary gross tumor volume including internal margins [10]. In DIBH, GTV-T was delineated directly on the 3DCT. CTV-T was rendered by adding a 5 mm isotropic margin to the GTV and shaping it to boundaries of non-involved tissue, such as bone and vessels. Furthermore, a PTV-T was created by adding 5mm isotropic margin to the CTV-T.

For treatment planning in FB, the untagged reconstruction of the 4DCT was utilized. Treatment planning was carried out for ST and DE treatment plans in FB and DIBH, using multiple half-arc volumetric modulated arc therapy (VMAT) (RapidArc, Varian Medical Systems, Palo Alto, CA, USA), resulting in a total of 64 original plans for the 16 patients. The ST plans were utilized for treatment in FB on Varian 2300 iX linear accelerators [16] in 33 fractions (fx), to a total dose of 66 Gy (2 Gy/fx, 5 fx/week). DE plans were achieved by increasing the $<D>_{GTV\text{-}T}$ to a maximum of 95 Gy (33 fx), while maintaining normal tissue doses similar to the ST plans (limited by dose to the lungs and to the spinal cord).

Results

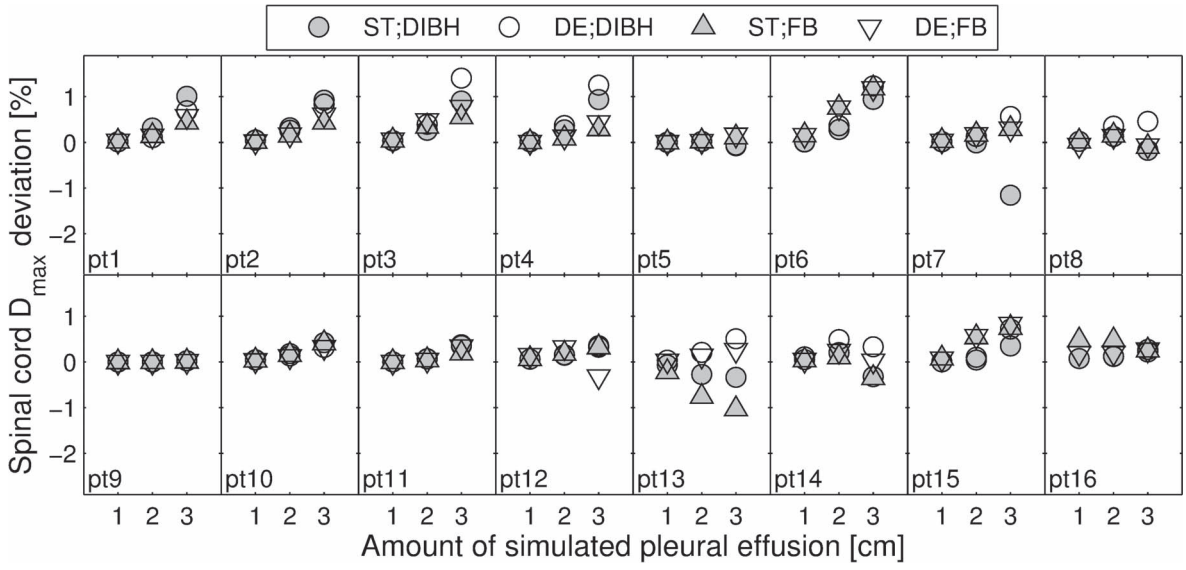
Pleural effusion

For phantom simulations, introduction of 1 cm or 2 cm pleural fluid had little effect on the spinal cord Dmax (Figure 2). However, introduction of 3 cm pleural fluid resulted in a decreased D_{max} of 4.9% for the centrally located tumor. An increase (0.9%) in the D_{max} was only observed for the anteriorly located tumor and 3 cm fluid.

Supplementary Table I. Summary of patient characteristics, including age, gender, TNM stage, tumor location, TMI and original GTV-T volume [cm^3] in DIBH and FB, respectively. Note, for patient 12, that the mentioning of two lung lobes indicates the single tumor extending through both lobes.

Patient	Age	Gender	TNM	Tumor location	TMI	DIBH GTV-T [cm^3]	FB GTV-T [cm^3]
1	77	M	T4N0M0	LUL	N	54	72
2	54	F	T4N2M0	LUL	Y	70	83
3	71	M	T4N0M0	LUL	Y	249	281
4	73	F	T4N0M0	LUL	Y	183	205
5	64	M	T2aN2M0	RUL	Y	38	46
6	67	M	T2aN2M0	RLL	N	33	54
7	74	M	T1aN2M0	LUL	N	2	4
8	65	M	T3N2M0	RUL	N	58	132
9	77	M	T2aN2M0	LUL	N	46	53
10	66	M	T3N2M0	LLL	Y	208	248
11	58	F	T3N2M0	RUL	N	114	143
12	58	F	T3N1M0	RUL_RML	Y	791	806
13	56	M	T4N1M0	LLL	N	383	437
14	59	M	T3N2M0	RLL	Y	91	140
15	70	M	T3N3M0	RUL	Y	151	170
16	64	F	T1bN3M0	LLL	Y	9	17

M, Male; F, Female; TNM, Tumor-Node-Metastasis staging; L/R-UL, Left/Right-Upper Lobe; L/R-LL, Left/Right-Lower Lobe; RML, Right Middle Lobe; TMI, Tumor Mediastinal Involvement; N, No; Y, Yes.



Supplementary Figure 1. Impact of pleural effusion on Dmax to the spinal cord for all 16 patients and combinations of scanning technique and fractionation.

Furthermore, only for a few patients (patient 1 for ST plan in DIBH, patients 3 and 4 for DE plans in DIBH, patient 6 for DE plans in DIBH and FB, patient 7 for ST plan in DIBH and patient 13 for ST plan in FB) gave the introduction of PE rise to changes in D_{max} to the spinal cord of $\geq 1\%$, with a maximum of 1.4% increase (patient 3 for 3 cm PE and DE plan in DIBH) (Supplementary Figure 1).

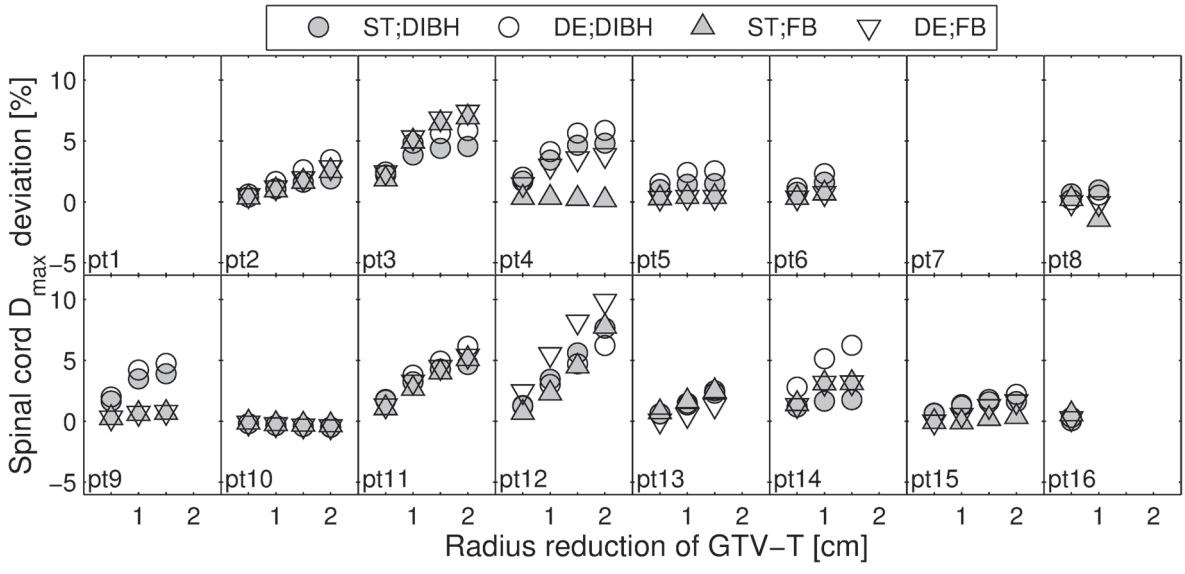
Tumor shrinkage

For phantom simulations, a 2 cm reduction of the tumor radius resulted in an increase in D_{max} to the spinal cord of 7.6% for the centrally located tumor (Figure 2). Even the smallest radius reduction of 0.5 cm resulted in an increase of $\geq 2\%$ for the Dmax of the spinal cord, regardless of tumor location.

For the patient population, TS had an impact on the Dmax to the spinal cord of $\geq 1\%$ increase at 1 cm radius reduction for the majority of the patients, and a maximum increase of 9.9% (DE plan in FB for patient 12) (Supplementary Figure 2). However, some patients (patient 10 and ST plans in FB for patient 4 and 8) had a small decrease in D_{max} of the spinal cord with decreasing tumor volume.

Atelectasis

For the spinal cord, atelectasis resulted in increments of 9.6% and 7.1% of the Dmax in DIBH for ST and DE plans, respectively. Corresponding numbers for FB were 9.2% and 11.1% for ST and DE plans, respectively.



Supplementary Figure 2. Impact of tumor shrinkage on Dmax to the spinal cord for all 16 patients and combinations of scanning technique and fractionation.