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research article

The spine and carina as a surrogate for target registration in cone-beam CT imaging verification in locally advanced lung cancer radiotherapy

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Background. The aim of the study was to evaluate the accuracy of volumetric lung image guidance using the spine or carina as a surrogate to target for image registration, as the best approach is not established.

Patients and methods. Cone beam computed tomography images from the 1st, 10th, 15th, and 20th fraction in 40 lung cancer patients treated with radical radiotherapy were retrospectively registered to planning CT, using three approaches. The spine and carina alignment set-up deviations from a reference (tumour/lymph nodes) registration in the lateral (LAT), longitudinal (LONG) and vertical (VRT) directions were analysed and compared. Tumour location and nodal stage influence on registration accuracy were explored.

Results. The spine and carina mean set-up deviation from reference were largest in the LONG, with the best match in the VRT and LAT, respectively. Both strategies were more accurate in central tumours, with the carina being more precise in 50% LAT and 66% LONG mean deviations. For all measurements in all patients a carina *vs*. spine registration comparison showed improved carina accuracy in LAT and LONG. In comparative subgroup analysis the carina was superior compared to spine in LAT and LONG in centrally located tumours, N2 and N3. Both strategies were comparable for peripheral tumours and N0.

Conclusions. Carina registration shows greater accuracy compared to spine in the LAT and LONG directions and is superior in central tumours, N2 and N3. The spine and carina surrogates are equally accurate for peripheral tumours and N0. We propose the carina as a surrogate to target for CBCT image registration in locally advanced lung cancer.

Key words: locally advanced lung cancer; volumetric image verification; tumour registration; carina registration; spine registration; adaptive radiotherapy.

Introduction

Recent advances in systemic and radiotherapy treatment have resulted in improved survival for patients with inoperable locally advanced lung cancer.[1] But still, nearly half of the patients will experience locoregional relapse.[2] The accuracy of different steps in radiotherapy treatment preparation and execution have a strong impact on local control.[3] With the introduction of computed tomography (CT), positron emission computed tomography (PET CT) and four-dimensional (4D) CT simulation, the target delineation accuracy increased.[4] Modern radiation techniques have enabled a more conformal dose delivery, the dose to normal tissue was reduced and the radical treatment of

more advanced N3 disease and/or dose escalation has become possible.[5] Because of the steeper dose gradient and smaller safety margins, the accuracy of treatment delivery became increasingly important. For daily treatment position verification, cone beam CT (CBCT) largely replaced electronic portal imaging because of better soft-tissue visibility. The alignment of the treatment image with the planning CT (pCT) is usually performed by radiation therapists (RTTs), who are not trained in target determination. The fast interpretation of CBCT is also challenging due to the lower quality of CBCT images (no i.v. contrast) and changes with or adjacent to the tumour during treatment.[6] Manual tumour matching is subjected to strong inter-observer variability even among radiation oncologists.[7] The optimal surrogate structure for image matching has not yet been established. Spine alignment is feasible and reproducible, but shows poor correlation with tumour position.[8] Recently, the carina surrogate alignment was explored and showed superior reproducibility compared to spine alignment.[7]

We performed a retrospective study to determine the accuracy of the carina *vs*. spine registration compared to target (primary tumour and lymph nodes) registration as a reference. To avoid interobserver variability, reference registration was performed by individual thoracic radiation oncologist. To consider tumour and normal structure variations during the course of treatment and their possible impact on image registration, the 1st, 10th, 15th, and 20th fraction CBCT were included in the registration analysis.

Materials and methods

Patient selection

We retrospectively included 40 consecutive lung cancer patients treated with on-line cone-beam computer tomography (CBCT) image guided radical radiotherapy from September 2018 to February 2019. All the patients had a visible tumour and/or lymph nodes on CT. They were treated with conventional, or hypofractionated volumetric modulated arc therapy on the Elekta Synergy linear accelerator (Elekta Synergy, Stockholm, Sweden). Clinical and treatment details were retrieved from medical records.

Simulation and planning

The planning CT scan was performed on the Big Bore CT simulator (Philips N.V., Eindhoven, NL), the Somatom Definition AS CT simulator (Siemens, Erlangen, D) and, in 6 patients, on Siemens Biograph mCT 40 (Siemens, Erlangen, D). The patients were immobilised on a Posirest-2 (Civco, Coralville, USA) with the arms abducted above the head (36 patients) or with a long thermoplastic mask (4 patients). The gross tumour volume (GTV) was delineated as the visible tumour and pathologic lymph nodes on free breathing pCT (with i.v. contrast). Additionally, 4D pCT was used for internal target volume (ITV) delineation in 10 tumours. Planning was performed on the Monaco treatment planning system using the Monte Carlo calculation algorithm. Conventional fractionation (1.8–2 Gy daily dose) was used in 37 patients, and hypofractionation in 3 (2.2, 2.2 and 2.75 Gy daily dose). The plan, pCT images and the delineated (target) contours were exported to the Elekta Synergy X-ray Volumetric Imaging (XVI) System.

Imaging

Kilovoltage gantry mounted CBCT systems were used for daily on-line CBCT treatment verification. According to physician instructions, localisation was based on automatic spine or carina matching between CBCT and pCT with additional manual translation correction by RTT. All set-up errors were corrected before treatment delivery.

Study procedure

Retrospective rigid image registration was done in the Elekta XVI System. We used the first treatment verification CBCT image from the 1st, 10th, 15th, and 20th fraction.

The CBCT image was retrospectively registered with pCT based on three different strategies: (a) bony registration on the spine, (b) soft tissue registration on the carina and (c) target (tumour/lymph node) matching on GTV/ITV. For 40 patients, we analysed 160 registration images and recorded 1440 corrections in the x (lateral – LAT), y (longitudinal – LONG) and z (vertical – VRT) directions.

First two retrospective registrations on the spine and carina were performed by RTT and were based on automatic registration using a clip box (Figure 1).

Residual translation errors were corrected manually, if necessary. Next, reference registration on target (tumour/lymph node) matching was performed by an experienced thoracic radiation oncologist. Following automatic bone registration, translational misalignments were manually

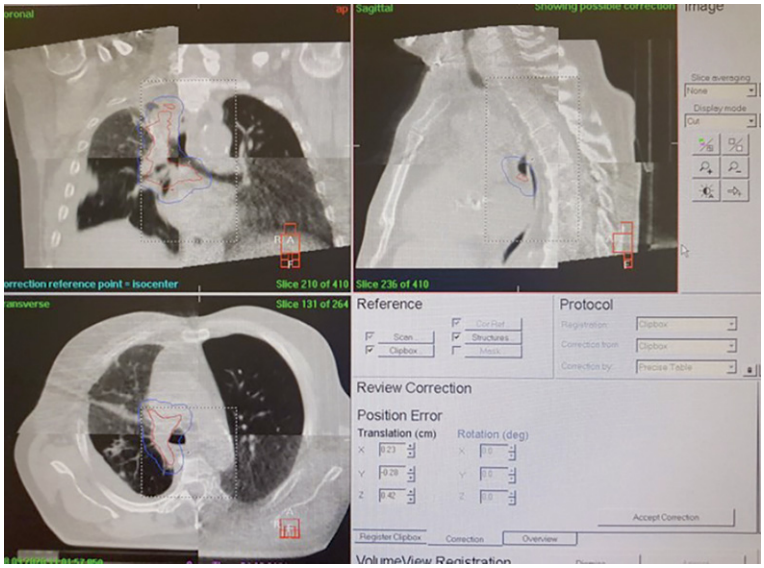


FIGURE 1. Automatic clip box carina registration with manual alignment check. Target contours (gross tumour volume [GTV] inner contour, planning target volume [PTV] outer contour) are imported for target registration.

corrected based on the visual adjustment of the GTV (ITV) contour on the CBCT image, to provide the best match for all known gross disease. If the lymph nodes were not visible, close anatomical surrogates were used. Translation corrections for target matching were recorded and used for the reference position. Spine and carina corrections were compared to the reference position and deviations in LAT, LONG and VRT measurements were analysed.

Statistics

Microsoft Excel 2010 and the Statistical Package for the Social Sciences, version 25.0 (SPSS Inc., Chicago, IL, USA) were used. General data were presented with descriptive statistics. Kolmogorov-Smirnov and Shapiro-Wilk tests rejected normal data distribution. The Nonparametric Mann Whitney U test (MW), Wilcoxon Signed Ranks test and nonparametric Kruskal-Wally's test (KW) were used for the analysis of the set-up deviation. The Wilcoxon Signed Ranks Test for dependent samples was used for comparison (pairwise). The KW and MW were used when we analysed the differences in a certain measurement according in two (MW) or into multiple groups (KW). A p value ≤ 0.05 was considered statistically significant.

Results

Patients, tumour and treatment characteristics

The patients, disease and treatment characteristics are summarised in Table 1. Radiation was the primary treatment of "de novo" lung cancer in 80% of patients. One patient was treated for local progression of epidermal growth factor receptor (EGFR)+ adenocarcinoma and one had postoperative regional recurrence. Five patients received reirradiation for local/regional recurrence. There were three plan adaptations after the 21st or 22nd fraction due to atelectasis (developing, resolution and worsening).

Spine to target registration set-up deviation analysis

The set-up deviation in the LAT, LONG and VRT directions for the spine according to target registration for the 1st, 10th, 15th, and 20th fractions were analysed (Figure 2A). The best registration match was in the VRT direction, with a mean set-up deviation between 1.2 and 1.68 mm. The biggest deviation was detected in the LONG direction (2.03–2.73 mm). Deviation differences from the 1st through 20th fractions were not statistically significant in any direction. There was no time trend detected. Comparison of deviations between directions on the 20th fraction showed a significant set-up difference in deviation between LAT *vs.* LONG ($p = 0.002$) and VRT *vs.* LONG ($p = 0.000$). The mean deviation for all set-up measurements was 1.39 mm in LAT (SD 0.9, range 0–4.0 mm), 2.44 mm in LONG (SD 1.6, range 0.5–8.0 mm) and 1.36 mm in VRT direction (SD 1.04, range 0–4.75 mm).

Carina to target registration set-up deviation analysis

Analysis of the set-up carina registration deviations from the target set-up measurements for the 1st, 10th, 15th, and 20th fractions were also analysed (Figure 2B). The smallest set-up difference was in the LAT direction (from 0.9 to 1.8 mm). The largest discrepancies were detected in the LONG direction (from 1.53 to 2.15). The difference in deviations for different fractions was not significant in any direction. There was no time trend in the deviations. Calculated from all the measurements, the mean deviation for the carina set-up deviations from the reference was 1.03 mm in LAT (SD 0.75,

range 0–3.75mm), 1.78 mm in LONG (SD 1.5, range 0–6.75mm) and 1.33 mm in the VRT direction (SD 1.25, range 0–5.25).

Comparison of spine to target and carina to target set-up deviation differences

The differences in the spine/target and carina/target mean set-up deviations were compared individually for the different fractions and the mean for all measurements in all directions (Table 2). The registration on carina was more accurate according to the reference in all measurements except in the vertical direction on the 1st and 20th fractions. The only significant difference was found on the 10th fraction VRT direction, with the smallest deviation for carina registration.

For all the measurements, registration on the carina was significantly closer to the reference registration in the LAT and LONG direction ($p = 0.003$ and $p = 0.002$, respectively). We found no difference in the set-up deviation in the VRT direction for all measurements.

The impact of tumour location (central/peripheral) and N stage on the spine/target and carina/target registration deviation

Analysis of the spine registration deviations from the reference showed a significantly better registration match for centrally located tumours in LAT on the 1st and 10th fractions, in LONG on the 1st fraction and in VRT on the 10th fraction (Table 3).

The carina/target registration comparison showed significantly smaller differences for central tumours in 50% LAT measurements (10th and 15th fraction), in 2/3 LONG measurements (10th –20th fraction), but not in the VRT direction (Table 4). We found no impact of the node stage on the spine/target registration deviations. When the carina was used for alignment, the differences were significantly smaller for N2 and N3 in the LAT 15th, LAT 20th, LONG 15th and VRT 20th fraction ($p = 0.034$, 0.028, 0.025 and 0.034, respectively) (Supplementary Tables S1–S2). Possible time trend for spine/target LAT deviation difference was detected for central tumours (Table 3).

TABLE 1. Patients, disease, and treatment characteristics

		N = 40
Gender	Female	16 (40 %)
	Male	24 (60 %)
Age (years)	Median (range)	67 (53–81)
Tumour location*	RUL	15 (37.5%)
	RML	3 (7.5%)
	RLL	7 (17.5%)
	LUL	8 (20%)
	LLL	8 (20%)
Central (C)/peripheral (P) tumour location**	C	17 (42.5%)
	P	22 (55%)
Histology	NSCLC	31 (77.5%)
	SCLC	9 (22.5%)
Disease treated	De novo lung cancer	32 (80%)
	Local progression	1 (2.5%)
	Local recurrence reirradiation	2 (5%)
	Regional recurrence	1 (2.5%)
	Locoregional recurrence reirradiation	4 (10%)
Systemic treatment	Concurrent chemotherapy	13 (32.5%)
	Sequential chemotherapy	16 (40%)
	Target therapy	1 (2.5%)
	None	10 (25%)
Tumour (T) stage	T0	1 (2.5%)
	T1	4 (10%)
	T2	14 (35%)
	T3	8 (20%)
	T4	13 (32.5%)
Lymph nodes (N) stage	N0	9 (22.5%)
	N1	1 (2.5%)
	N2	14 (35%)
	N3	16 (40%)
Fractionation	Conventional	37 (92.5%)
	Hypofractionation	3 (7.5%)
Radiation technique	VMAT	40 (100%)

* In one patient, two synchronous tumours were treated (RUL and LUL).
**In one patient, only the lymph nodes were treated (regional recurrence).

LLL = left lower lobe; LUL = left upper lobe; NSCLC = non-small cell cancer; RML = right middle lobe; RLL = right lower lobe; RUL = right upper lobe; SCLC = small cell lung cancer; VMAT = volumetric modulated arc therapy

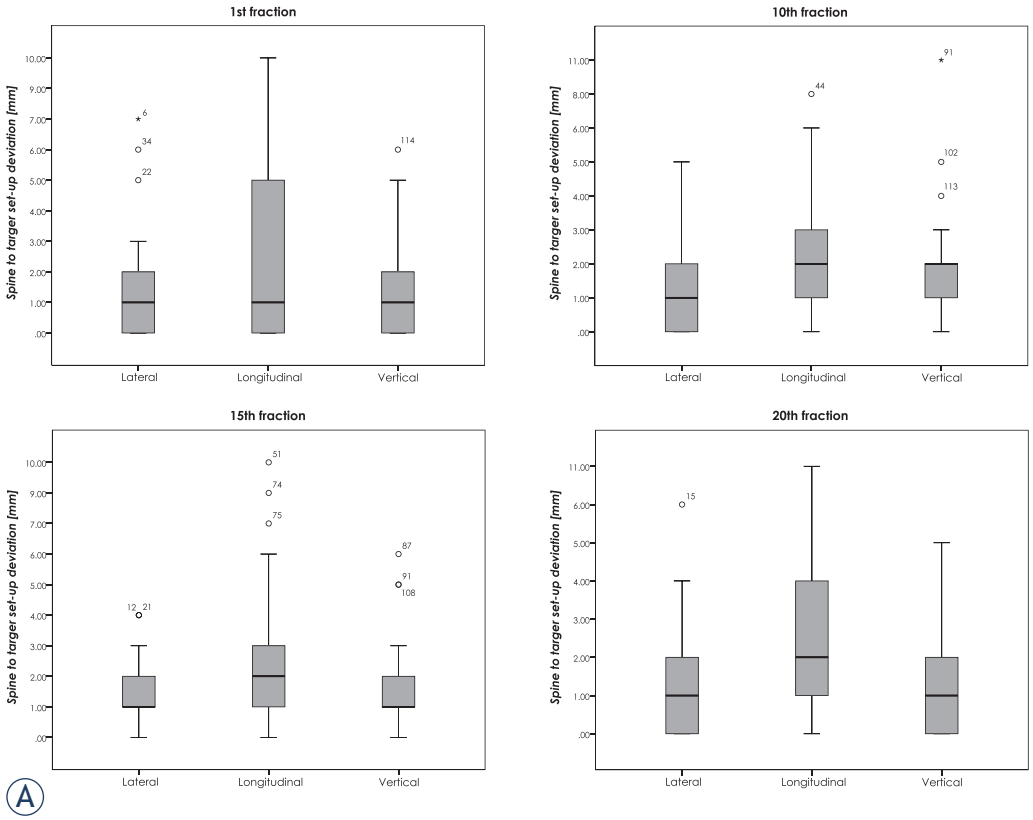


FIGURE 2. Spine to target **(A)** and carina to target **(B)** registration set-up deviation in the lateral (LAT), longitudinal (LONG) and vertical (VRT) directions.

TABLE 2. Mean set-up deviation difference (DD) comparison according to spine/target vs. carina/target registration

Fraction	LAT deviation mean (mm)			p value	LONG deviation mean (mm)			p value	VRT deviation mean (mm)			p value
	Spine/ target	Carina/ target	DD		Spine/ target	Carina/ target	DD		Spine/ target	Carina/ target	DD	
1st	1.28	0.90	0.38	NS	2.65	1.80	0.85	NS	1.20	1.43	-0.23	NS
10th	1.30	1.08	0.22	NS	2.03	1.53	0.50	NS	1.68	1.10	0.58	**0.04**
15th	1.48	1.08	0.4	NS	2.38	1.65	0.73	**0.05**	1.38	1.38	0	NS
20th	1.53	1.05	0.48	NS	2.73	2.15	0.58	NS	1.2	1.43	-0.23	NS
All measurements	1.39	1.03	0.37	**0.003**	2.44	1.78	0.66	**0.002**	1.36	1.33	0.03	NS

DD = deviation difference; LAT = lateral; LONG = longitudinal; NS = non-significant (p>0.05); target = primary tumour and lymph nodes; VRT = vertical

TABLE 3. Spine/target registration deviation according to tumour location

Fraction	LAT mean (mm)		p value	LONG mean (mm)		p value	VERT mean (mm)		p value
	Central	Peripheral		Central	Peripheral		Central	Peripheral	
1st	0.71	1.77	**0.048**	1.18	3.91	**0.002**	1.12	1.32	NS
10th	0.76	1.77	**0.008**	1.53	2.41	NS	1.41	1.86	**0.017**
15th	1.47	1.55	NS	2.59	2.32	NS	1.35	1.45	NS
20th	1.94	1.27	NS	2.29	3.14	NS	1.29	1.09	NS

LAT = lateral; LONG = longitudinal; NS = non significant (p>0.05); target = primary tumour and lymph nodes; VRT = vertical

TABLE 4. Carina/target registration deviation according to tumour location

Fraction	LAT mean (mm)		*p value*	LONG mean (mm)		*p value*	VERT mean (mm)		*p value*
	Central	Peripheral		Central	Peripheral		Central	Peripheral	
1st	0.65	1.14	NS	1.65	2.00	NS	1.06	1.77	NS
10th	0.53	1.55	**0.002**	1.18	1.86	**0.041**	0.82	1.32	NS
15th	0.71	1.41	**0.049**	1.00	2.23	**0.027**	0.88	1.77	NS
20th	1.00	1.14	NS	0.94	3.14	**0.019**	0.88	1.82	NS

LAT = lateral, LONG = longitudinal, NS = non significant (p>0.05); VRT = vertical; target = primary tumour and lymph nodes

The impact of tumour location (central/peripheral) and N stage on the spine/target vs. carina/target deviation differences

The deviation differences analysis between the spine/target and carina/target registration according to tumour location and N stage is shown in Supplementary tables S3–S5. For peripherally located tumours, the carina registration deviation was only smaller compared to the spine set-up deviation in the 1st fraction LONG with a deviation difference of 1.91mm (p = 0.034). In centrally located tumours, the registration on carina was found to be significantly more accurate on the 15th and 20th fractions LAT, (p = 0.012 and 0.048, respectively), the 15th and 20th fractions LONG (p = 0.010 and 0.011, respectively) and for all LAT and LONG measurements (p = 0.003). The deviation differences were 0.76, 0.94, 1.59, 1.35, 0.5 and 0.71mm, respectively. There was no difference in the set-up deviation in the VRT direction regardless of tumour location.

Comparison of the deviation differences according to the N stage showed a better correlation between the carina and target registration for N2 and N3 disease. We found deviation differences

of 0.63mm N2 and 1.17mm N3 in LONG, 0.48mm N3 in LAT for all measurements and 0.94mm N3 10th fraction LONG ($p = 0.013$, 0.015, 0.002 and 0.007, respectively). A small but significant 0.5mm difference in favour of the carina registration was found for N0 in all measurements LAT ($p = 0.034$). Because only 1 patient had the N1 stage, we excluded his measurements from this analysis (Supplementary Table S5).

Discussion

Since the introduction of CBCT into treatment verification, new insights to target position uncertainties have evolved[6], suggesting that image guidance could currently be the weakest link in the radiotherapy procedure.[3,9] Only a few studies have explored the carina as a surrogate in volumetric lung image guidance[7,10,11] and there is a lack of knowledge in this field. Here we present new data on the accuracy of the carina *vs*. spine surrogate compared to the target alignment as a reference in image registration.

A separate analysis of the spine and carina registration set-up differences compared to the reference (target) registration showed the smallest differences in the VRT and LAT directions, with the largest deviation in the LONG direction for both strategies (Fig. 2). The differences were not significantly different in time and no time trend was detected for the cohort, so we evaluated all the measurements together and again showed a good registration match in the VRT and LAT directions, but in LONG direction, the range of misalignment reached above 5 mm in both registration strategies. The greatest area of uncertainty in the LONG direction was also shown in the study by Ottosson *et al*. where they compared the spine and target registration in free-breathing and breath-hold CBCT in locally advanced lung cancer patients. The largest intra- and inter-fractional misalignments were found in the LONG direction, independent of the registration method.[12] Although we found a smaller mean LONG misalignment in the carina *vs*. spine registration (1.78 *vs*. 2.44 mm), uncertainties in image registration should be considered for both strategies, with the enlargement of the PTV in the craniocaudal (CC) direction.

To determine the best registration match compared to the reference, we compared differences in the set-up deviations for the spine and carina alignment. Both strategies were equally accurate in the VRT direction, but the carina was more accurate in the LONG and LAT directions in all measurements. The accuracy of the spine *vs*. carina registration was also tested in a study by a Canadian group, where four independent observers automatically and manually aligned the first fraction CBCT with the pCT in 30 lung cancer patients.[7] They used spine, carina and tumour registration strategies. Automatic spine and carina registrations provided similar tumour coverage, with the tumour inside the ITV in 60% of observations. The same group, in a second study, verified the tumour (T) and lymph node (LN) coverage following spine and carina registration for initial, middle, and final fraction CBCT. Both strategies improved the combined target coverage throughout the treatment course compared to tattoo alignment. Carina better improved the combined coverage and showed significantly superior nodal coverage compared to the spine, without compromising primary tumour coverage.[10] With a significantly better registration match in the LONG and LAT directions, our data supports the suggestion from the Canadian group that the carina may be superior to the spine in the image guidance of locally advanced lung cancer.

The second Canadian study showed similar primary tumour coverage, regardless of the registration strategy.[10] But in our study, the registration accuracy was influenced by tumour location. Both the spine and carina alignment showed smaller set-up differences for centrally located tumours with the difference being more significant in the carina registration LONG (66% fractions) and LAT (50% fractions). For peripheral tumours, we found no difference in the accuracy of spine *vs*. carina alignment, but for centrally located tumours, the carina was more accurate in the LAT and LONG directions. Our data suggests that the carina is a better surrogate for centrally located tumours. Importantly, we also showed that the carina is as accurate as the spine for registration in peripherally located tumours and can be proposed as a registration surrogate regardless of the tumour location.

According to our data, carina matching can also be used regardless of the nodal stage. We found no differences in the spine, but a better match for carina alignment in N2 and N3 disease. In advanced nodal disease, the carina showed superior registration *vs*. the spine in LAT and LONG. The finding is in concordance with the second Canadian study, where carina matching improved the node coverage compared to spine registration.[10] Importantly, we found no set-up difference for N0 disease suggesting that the carina and spine can equally be used as a surrogate in this stage. As there was

only a single case of early nodal disease, we cannot make any conclusions for N1. The reliability of spine matching for LN coverage was investigated in the study by Mohammed *et al*., where an equal geographical target miss was found for spine *vs*. combined target matching, but inferior LN coverage in the case of tumour matching, based on a weekly 4D CBCT registration.[9] Because the same geographical miss was shown for hilar and mediastinal lymph nodes, we can hypothesize that carina matching could safely be used in N1 as well.

Target alignment should be "the ground truth" and have an impact on the therapeutic ratio,[3,12] but is rather difficult to implement clinically. Due to the poor soft tissue contrast on CBCT and tumour changes during the course of treatment, only half of the tumours can clearly be contoured using CBCT.[13] For these reasons, we used contoured-based registration for reference. A similar approach was used for target coverage and geographical miss assessments studies[9,10] and target registration in the study by Ottosson *et al*.[12] Direct tumour registration is also impractical because it is time-consuming and unreliable due to high intra-observer variability.[7] In contrast, the carina is clearly visible on the CBCT and automatic carina alignment shows high reproducibility, superior even to spine alignment.[7] Although the carina shows some respiratory movement, especially in the CC direction, it is still an excellent surrogate for directly adjacent mediastinal lymph nodes. Preliminary data also suggests a good correlation between the carina and GTV motion.[7,11]

We acknowledge the limitations of our study, which was retrospective and relatively small. We also present a heterogeneous group of patients, though they represent real everyday radiotherapists' lung cancer patients. In our study, CBCT image changes were not systematically determined. Because the majority of changes appear in the first five weeks of radiotherapy,[14] we analysed CBCT images from the 1st, 10th, 15th and 20th fractions. Maybe the 25th and 30th fraction CBCT should have been included since we found cases for plan modification in the 6th week of treatment. Nevertheless, we detected no significant set-up differences in time. The rate of plan adaptation was low (7.5%), suggesting the need for a "traffic light" protocol implementation.[3]

In conclusion, carina registration was shown to be feasible, fast, and reproducible. Our data shows that, compared to target registration, carina is equally as accurate as spine registration, with superior accuracy in the LONG and LAT directions. The carina is a better surrogate than the spine for alignment in centrally located tumours, N2 and N3 disease. Although spine alignment can equally be used in N0 and peripheral tumours, for simplicity we propose that the carina should be the primary surrogate for the target in image guidance in locally advanced lung cancer. The next step should be to incorporate carina registration uncertainties into the PTV margin.

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