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Research article

Contrast enhanced oesophageal avoidance for stereotactic body radiotherapy: Barium vs. Gastrografin

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ABSTRACT

Introduction: SABR may facilitate treatment in a greater proportion of locally-advanced NSCLC patients, just as it has for early-stage disease. The oesophagus is one of the key dose-limiting organs and visualization during IGRT would better ensure toxicity is avoided. As the oesophagus is poorly seen on CBCT, we assessed the extent to which this is improved using two oral contrast agents.
Materials & methods: Six patients receiving radiotherapy for Stage I-III NSCLC were assigned to receive 50 mL Gastrografin or 50 mL barium sulphate prior to simulation and pre-treatment CBCTs. Three additional patients who did not receive contrast were included as a control group. Oesophageal visibility was determined by assessing concordance between six experienced observers in contouring the organ. 36 datasets and 216 contours were analysed. A STAPLE contour was created and compared to each individual contour. Descriptive statistics were used and a Kappa statistic, Dice Coefficient and Hausdorff distance were calculated and compared using a t-test. Contrast-induced artefact was assessed by observer scoring.
Results: Both contrast agents significantly improved the consistency of oesophagus localisation on CBCT across all comparison metrics compared to CBCTs without contrast. Barium performed significantly better than Gastrografin with improved kappa statistics ($p = 0.007$), dice coefficients ($p < 0.001$) and Hausdorff distances ($p = 0.002$), although at a cost of increased image artefact.
Discussion: Barium produced lower delineation uncertainties but more image artefact, compared to Gastrografin and no contrast. It is feasible to use oral contrast as a tool in IGRT to help guide clinicians and therapists with online matching and monitoring of the oesophageal position.

Introduction

A significant proportion of locally-advanced non-small cell lung cancer (NSCLC) patients are ineligible for standard of care radical treatment. Recommendations suggest 6–7 weeks of concurrent chemoradiotherapy [1,2], but due to competing comorbidities, logistic issues associated with daily attendance over many weeks and the toxic nature of treatment, almost half of patients do not receive curative treatment [3–5] and up to 21% receive no treatment whatsoever [6,7]. The situation was similar for early-stage NSCLC patients until the advent of stereotactic body radiotherapy (SBRT). SBRT shortened treatment courses to 1–2 weeks and provided high rates of local control with a low risk of toxicity [8,9]. As a result, there was a decrease in the proportion of patients going untreated and population-based survival estimates increased [10,11]. SBRT is a guideline recommended standard of care for peripheral tumours and is increasingly being shown to be safe for early stage central tumours [12,13]. SBRT may similarly provide an alternative treatment option for patients with locally-advanced disease whom are ineligible for chemoradiotherapy and now warrants further investigation. Westover et al. have shown 15 fractions of 3.3–4 Gray were well tolerated in 55 poor performance NSCLC patients (of which 32 had stage III disease) who were ineligible for surgery or concurrent chemoradiotherapy [14]. Dysponea and oesophagitis were the most frequent grade ≥3 toxicities observed. Furthermore, Tekatli et al. have demonstrated in 47 patients (18 with stage III disease) that 12 fractions of 5 Gray delivered over 3 weeks is a viable treatment option for unfit patients ineligible

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for long treatment courses and with tumours overlapping the trachea or main bronchi [15].

The safety of SBRT for locally-advanced lung cancer has yet to be established. As SBRT for central structures can be associated with significant toxicity [16], optimizing image guidance to avoid organs at risk is a prerequisite for Phase I testing. The oesophagus is a key example of this, with acute toxicities including odynophagia, dysphagia and weight loss and potential late oesophageal perforation, stenosis or tracheoesophageal fistula [17]. As oral contrast agents are frequently used in diagnostic radiology to enhance gastrointestinal visualization, we assessed the extent to which the oesophagus can be better localised on cone beam computed tomography (CBCT) and compared two oral contrast agents: barium and Gastrografin. Contrast agents are not routinely used at the onset of online image-guided radiotherapy (IGRT) and to the best of our knowledge we are the first to investigate their use in this setting. Both contrast agents have long been used in diagnostic radiography and radiotherapy simulation. Historically, barium has been regarded as superior for coating the mucosal surfaces of the gastrointestinal tract, however little quantitative data exists to support this, especially in the context of the oesophagus [18,19], hence the rationale for the initial phase of this study. We also determined whether the presence of oral contrast impacted visualization of tumours or organs at risk and how well the agents were tolerated by patients.

Materials & methods

Patients and contrast administration

Patients receiving radiotherapy with or without chemotherapy for Stage I-III NSCLC were prospectively enrolled into an institutional ethics approved study. Six patients were randomly assigned to either 50 mL Gastrografin® (iodine-based) or 50 mL barium sulphate (Liquibar 62.5%w/w, MCI Forrest) after providing written informed consent. Contrast was administered just prior to acquisition of the Planning CT (PlanCT) and each daily/weekly pre-treatment CBCT, depending on the patient's prescription schedule. Contrast was measured out into a cup and the patient was instructed to swallow the contrast whilst sitting on the treatment couch, just prior to lying down and undergoing positioning. The time was recorded at contrast consumption, therapists leaving the treatment room and CBCT acquisition. The therapists aimed to minimise the time between setup and CBCT as much as reasonably possible. Three previously treated patients with matched baseline characteristics, who did not receive contrast, were included as a control group. As these patients were historic controls, patient consent was not required.

Dosimetry considerations

Contrast was contoured and assigned a Hounsfield Unit of 0 for radiotherapy planning, as the institution's treatment-planning algorithm (Analytical Anisotropic Algorithm, Eclipse, v13.6, Varian Medical Systems, Palo Alto, CA) poorly accounts for very high-density material. The expected variation in dose was estimated to be insignificant, due to the small size of the oesophagus compared to the field sizes and the multi-field, intensity modulated nature of the treatment plans [20].

Image acquisition

All nine analysed patients were simulated and treated supine, with their arms immobilised above their head in a personalised, vacuum-shaped device. The PlanCT consisted of a 4DCT scan acquired in free breathing in axial mode with 1.25 mm slice thickness (GE Discovery CT590 RT; 120 kVp). CBCTs were acquired in free breathing using thorax-specific protocols either in full-fan (25 cm field-of -view) or half-fan mode (45 cm field-of-view) and reconstructed to 2.5 mm slice thickness (Varian TrueBeam; 110kVp).

Study outcome

The ability to visualise the oesophagus was determined by assessing how similarly six observers (four radiation oncologists and two SBRT trained-dosimetrists) were able to contour the organ. The PlanCT and three CBCTs per patient were used, resulting in 36 datasets and 216 contours for analysis. Three CBCTs per patient were chosen, as this was the maximum number some patients had and a consistent number of datasets per group was desired. For those with more than three CBCTs, the first three were used for analysis. Observers were asked to contour the oesophagus, including the lumen and extending out to the muscularis externa, on all axial slices from 1 cm above to 1 cm below the planning target volume (PTV). Window levelling was left up to the discretion of each observer. Each observer was blinded to the contours from other observers and to the presence or type of contrast agent. All contouring was performed in the Aria Contouring Workspace (v13.6, Varian Medical Systems, Palo Alto, CA) with a high resolution (0.1 cm).

Contour analysis

As the true position of the oesophagus on each dataset is unknown, a consensus contour was generated and used as a ground truth for contour comparison. A consensus contour was generated for each scan based off the six observer contours using the simultaneous truth and performance level estimation (STAPLE) method [21] in the Computational Environment for Radiotherapy Research (CERR) software program [22]. CERR also calculates a kappa statistic. The kappa statistic is a measure of agreement beyond chance and falls between −1 and +1. The general interpretation is such that ≤0 indicates no agreement, 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial and 0.81–1.00 as almost perfect agreement [23]. The consensus and individual contours were then analysed in the SlicerRT Extension of 3D Slicer [24] where dice coefficients and Hausdorff distances were calculated. The dice coefficient is a measure of similarity and based on spatial overlap of the contours [25]. The value of the dice coefficient can be between 0 indicating no overlap and 1, indicating complete overlap. The Hausdorff distance quantifies the magnitude of gross deviation between contours (i.e. larger distances = greater variation between contours) [26]. In order to reduce the effect of large outliers, the largest distance that falls within the 95% confidence level was used (HD95%).

Artefact assessment

In order to assess the impact of any contrast-induced artefact on the CBCT images, a qualitative assessment was conducted whereby each observer had to score the impact of any artefact on their ability to visualise regions of interest. The question asked was: *"Did the contrast or artefact hamper your ability to visualise the…"* with a score applied for each of the gross tumour volume (GTV), trachea, main bronchi and central vessels. Answers were scored as, 1 = No, 2 = Yes, but still able to identify sufficiently for IGRT purposes, 3 = Yes, unable to identify sufficiently for IGRT purposes.

Patient compliance

Patient compliance was assessed by the percentage of intended CBCTs given with contrast and on any reported side effects deemed contrast-related by the treating oncologist.

Statistical analysis

The mean volumes of the oesophagus contour on the PlanCT versus CBCT were compared per agent with a paired t-test. Mean kappa statistics were compared for each agent using a student's t-test, whilst the dice coefficient and Hausdorff distance were compared with a Mann-Whitney U test. Correlation between the timing of contrast consumption and CBCT acquisition with each of the metrics was analysed by calculation of a Pearson's correlation coefficient (r). Artefact assessment was carried out by comparing mean observer scores for each contrast group. Statistical analysis was carried out in SPSS Statistics (IBM Corp. v24.0. Armonk, NY). Significance for all tests was deemed as $p < 0.05$.

Based on the assumption of a kappa mean of 0.670 and a standard deviation of 0.065 [27], we needed 3 patients in each group to detect a difference of 0.2 in the kappa statistic at 0.05 confidence and 80% power.

Results

Patient characteristics and mean contour comparison metrics can be found in Table 1. The median contoured oesophagus length and volume (as calculated on the PlanCT) was 7.9 cm (4.6–16.9 cm) and 11.1 cc (6.5–62.7 cc) respectively. Patients swallowed the contrast in less than a minute and the mean time between consumption and the therapists leaving the treatment room was 2 minutes (1–5 min). The mean time from contrast administration to CBCT acquisition was 6 minutes (1–12 min). Fig. 1 shows the PlanCT, CBCT with contrast and a CBCT without contrast for a patient in the Gastrografin group.

The mean volume of the oesophagus contour on the CBCTs compared to the PlanCT was not significantly different with Gastrografin (13.5 cc vs 14 cc, $p = 0.19$) or barium (25.9 cc vs 26 cc, $p = 0.96$), but was significantly larger when no contrast was present (15.4 cc vs 17.3 cc, $p < 0.001$).

Contour analysis

The presence of either contrast agent on the PlanCT scans improved the consistency of oesophagus localisation across all comparison metrics (Table 2). Barium significantly improved the kappa statistic and dice coefficient and approached significance considering the Hausdorff Distance. When compared against one another, there was minimal difference between the two agents, with only the dice coefficient showing a significant improvement for barium over Gastrograffin.

The presence of contrast significantly improved the consistency of oesophagus localisation on CBCT across all comparison metrics (Table 3). CBCT scans with Gastrografin or barium had significantly better kappa statistics and dice coefficients than CBCT scans without contrast. When compared against one another, barium

Table 1
Patient characteristics and mean oesophagus contour comparison metrics per dataset.

Patient	Disease stage	Tumour location	Contrast group	Length (cm)	Scan type	Time* (mins)	Volume (cc) [SD]	Dice	HD95% (mm)	Kappa
1	T1aN0M0 (Stage IA)	RUL	Barium	5.1	PlanCT		6.5 [0.76]	0.938	1.26	0.877
					CBCT1	7	7.4 [0.63]	0.936	1.08	0.867
					CBCT2	2	6.6 [0.73]	0.930	0.84	0.864
					CBCT3	5	6.7 [0.63]	0.936	0.76	0.881
3	T1aN0M0 (Stage IA)	RUL	Barium	4.6	PlanCT		8.7 [0.46]	0.950	1.27	0.895
					CBCT1	10	5.7 [1.25]	0.866	1.96	0.750
					CBCT2	3	6.2 [1.1]	0.870	1.84	0.751
					CBCT3	7	5.5 [0.84]	0.900	1.44	0.807
6	T2aN2M0 (Stage IIIA)	RLL	Barium	15.6	PlanCT		62.7 [5.9]	0.911	4.46	0.833
					CBCT1	12	75.9 [14.2]	0.904	3.28	0.826
					CBCT2	7	60.9 [7.9]	0.910	3.92	0.846
					CBCT3	6	59.3 [8.4]	0.914	3.07	0.836
2	T2N1M0 (Stage IIA)	LLL	GG	10.1	PlanCT		11.1 [1.1]	0.924	1.27	0.864
					CBCT1	12	11.1 [2.1]	0.881	1.63	0.801
					CBCT2	6	14.2 [2.4]	0.789	3.37	0.629
					CBCT3	5	13.9 [3.2]	0.858	1.98	0.756
4	T2aN0M0 (Stage IB)	LUL	GG	7.9	PlanCT		11.4 [2.1]	0.901	1.63	0.817
					CBCT1	6	12.4 [2.6]	0.876	1.91	0.786
					CBCT2	5	11.0 [2.0]	0.883	1.91	0.782
					CBCT3	4	11.8 [3.1]	0.850	2.63	0.731
5	T1bN0M0 (Stage IA)	LLL	GG	7.8	PlanCT		18.2 [2.1]	0.907	1.75	0.832
					CBCT1	6	17.7 [3.1]	0.841	3.25	0.723
					CBCT2	3	18.1 [3.4]	0.863	2.50	0.762
					CBCT3	1	16.3 [2.4]	0.886	2.26	0.795
7	T1aN0M0 (Stage IA)	LLL	No Contrast	5.8	PlanCT		9.8 [1.3]	0.893	2.25	0.784
					CBCT1		11.0 [3.4]	0.765	4.62	0.555
					CBCT2		11.8 [2.1]	0.866	2.60	0.734
					CBCT3		11.2 [2.9]	0.794	3.69	0.619
8	T2bN0M0 (Stage IIA)	RLL	No Contrast	7.9	PlanCT		8.0 [1.3]	0.896	1.56	0.808
					CBCT1		11.3 [5.0]	0.747	4.25	0.551
					CBCT2		9.6 [2.3]	0.830	2.52	0.681
					CBCT3		9.5 [3.0]	0.779	3.84	0.579
9	T1N2M0 (Stage IIIA)	RUL	No Contrast	16.9	PlanCT		28.5 [6.0]	0.833	5.57	0.713
					CBCT1		28.4 [3.4]	0.761	4.92	0.615
					CBCT2		31.1 [4.5]	0.764	6.82	0.613
					CBCT3		32.0 [4.3]	0.753	6.69	0.603

LUL = left upper lobe, LLL = left lower lobe, RUL = right upper lobe, RML = right middle lobe, RLL = right lower lobe, GG = Gastografin, Time = time from contrast consumption to CBCT acquisition.

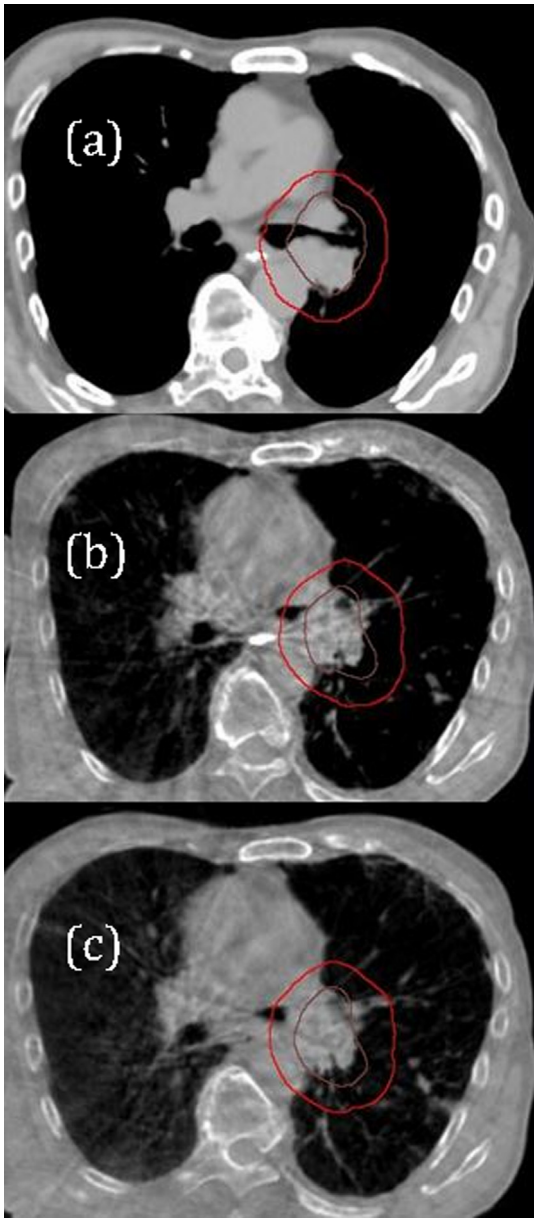

Fig. 1. Axial images of one patient's (a) planning CT with Gastrografin, (b) CBCT with Gastrografin and (c) CBCT without contrast. Planning target volume in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

performed significantly better than Gastrografin. The average kappa statistic and its corresponding interpretation for the contours were 0.617–substantial agreement (no contrast), 0.752–substantial agreement (Gastrografin) and 0.825–almost perfect agreement (Barium). The median dice coefficient improved from 0.812 in CBCTs without contrast, to 0.871 with Gastrografin and 0.916 with barium. The median Hausdorff Distance was 3.2 mm on CBCTs without contrast, 2.3 mm with Gastrografin and 1.6 mm with barium. Fig. 2 shows the improved contour consistency when contrast is present.

Timing assessment

The time between contrast consumption and CBCT acquisition was longest on each patient's first CBCT. On the subsequent CBCTs, the time shortened. This is likely due to the fact that it generally takes longer to position the patient on day 1 and quality assurance and equipment clearance checks must be carried out. No correlation was found between time and each of the comparison metrics. (Kappa, $r = 0.06$ ($p = 0.822$), Dice, $r = 0.03$ ($p = 0.916$), Hausdorff distance, $r = 0.17$ ($p = 0.505$)).

Artefact assessment

The observers scored contrast-induced artefact on CBCT to be worse with barium compared to Gastrografin for all four regions of interest. The mean score for the GTV, trachea, main bronchi and central vessels with barium were 1.5, 1.6, 1.8 and 2.1 respectively, compared to 1.2, 1.2, 1.4 and 1.6 for Gastrografin. Of 432 scores, 37 (8.6%) had contrast preventing assessors from identifying regions of interest sufficiently for IGRT purposes. 22 of these scores were assigned to central vessels, 6 to the bronchi, 2 to the trachea and 7 to the GTV. The 7 for the GTV were all related to 1 patient only (Barium) and in this case, the patient's oesophagus was significantly dilated along the entire length of the organ (Fig. 3).

Patient compliance

Patient compliance, as determined by the percentage of intended CBCTs given with contrast, was higher with the barium than with the Gastrografin (92% vs 52%), largely due to the occurrence of diarrhoea in 2 of the 3 Gastrografin patients, a known side effect of this agent.

Discussion

We assessed whether two oral contrast agents can improve the visualization of the oesophagus on CBCT images. Both agents enabled observers to more precisely identify the oesophagus compared to no contrast, and barium was superior to Gastrografin for this. As high radiation doses to the oesophagus can result in oesophageal ulceration, perforation and even death [28–31], improved visualization is a prerequisite for SBRT-like doses to be utilised safely.

Although oesophageal motion caused by peristalsis and swallowing, and motion due to respiration and the cardiac cycle can, in part, be assessed during 4D simulation, this does not account

Table 2
Metrics for contour comparisons on PlanCT scans with p-value comparing contrast to no contrast.

	No Contrast	Gastrografin	Barium	Gastrografin vs Barium
Kappa statistic [Mean (±SD)]	0.769 (0.049)	0.838 (0.024) p = 0.094	0.868 (0.032) **p = 0.042**	p = 0.252
Dice coefficient [Median (IQR)]	0.893 (0.089)	0.913 (0.035) p = 0.094	0.936 (0.039) **p = 0.002**	**p = 0.021**
Hausdorff distance [Median (IQR)]	1.8 (2.6)	1.4 (0.5) **p = 0.041**	1.3 (1.3) p = 0.091	p = 0.631

Bold p-values = statistically significant.

Table 3
Metrics for contour comparisons on CBCT scans with p-value comparing contrast to no contrast.

	No Contrast	Gastrografin	Barium	Gastrografin vs Barium
Kappa statistic [Mean (±SD)]	0.617 (±0.059)	0.752 (±0.053) **p < 0.001**	0.825 (±0.048) **p < 0.001**	**p = 0.007**
Dice coefficient [Median (IQR)]	0.812 (0.187)	0.871 (0.055) **p < 0.001**	0.916 (0.058) **p < 0.001**	**p < 0.001**
Hausdorff distance [Median (IQR)]	3.2 mm (3.0)	2.3 mm (0.9) **p < 0.001**	1.6 mm(1.4) **p < 0.001**	**p = 0.002**

Bold p-values = statistically significant.

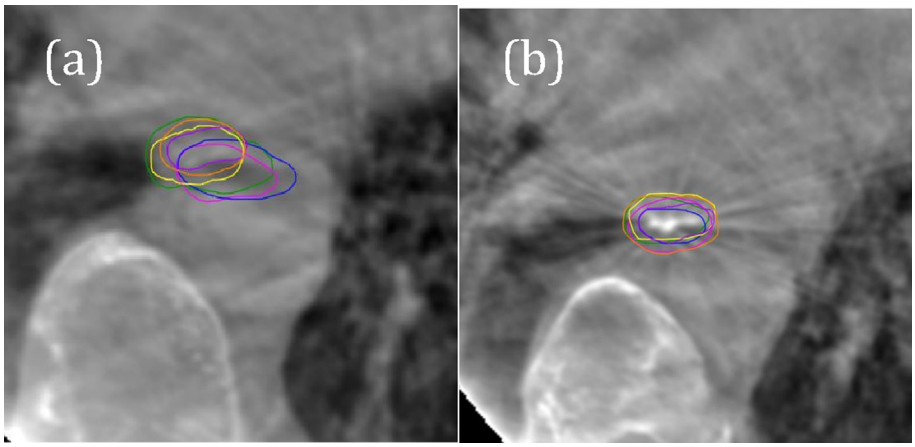

Fig. 2. Axial images of one patient after Gastrografin administration on different days showing inconsistent coating of the oesophagus – (a) poor coating and subsequently greater variation between observer contours compared to (b) improved coating, leading to less variation between contours.

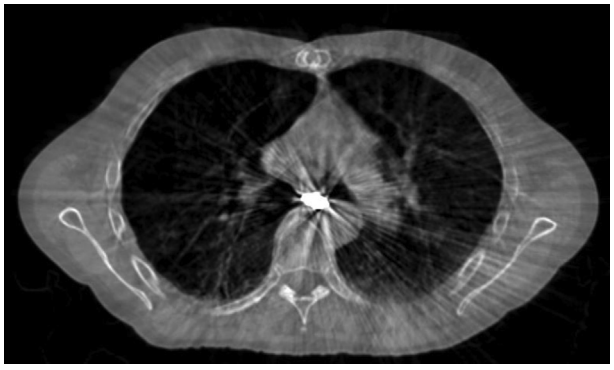

Fig. 3. Axial CBCT image showing artefact caused by barium in a dilated oesophagus.

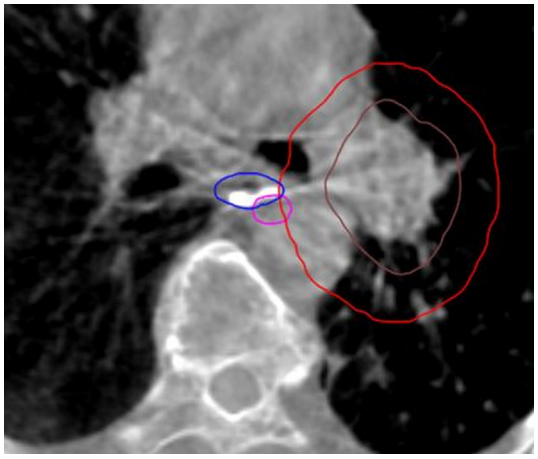

Fig. 4. Axial image of a pre-treatment contrast-enhanced CBCT on a patient where the contrast agent highlights the altered oesophagus position (blue) compared to the planned position (pink). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

for the day-to-day differences that can occur during treatment or between PlanCT and treatment as has been demonstrated for lung tumours [32]. Fig. 4 shows a patient in our study where the oral contrast highlighted a significant difference in the position of the oesophagus on a CBCT (blue) during treatment compared to the planning CT (pink). As such differences can be almost 1 cm [33,34] and exacerbated by tumour responses to treatment [35,36], it is unfeasible to account for this variation with treatment planning [37]. With accurate image guidance it may be feasible to utilise a strategy where central lung tumours are treated with SBRT only on days when the oesophagus has not moved into the high dose region or to employ adaptive re-planning. Both strategies clearly rely on optimal visualization of the oesophagus.

Previous studies have assessed the ability to visualise the oesophagus on tomographic imaging and have highlighted the difficulties [38–42]. McCall et al. tested the contouring variability of 13 medical dosimetrists using three thoracic CT datasets [39]. Compared to the lungs, heart and spinal cord, the oesophagus scored worst, with a mean Dice coefficient of 0.74. Similar results were found by Breunig et al who reported a Dice coefficient of 0.75 [40]. Tsang et al found a Dice coefficient of 0.64 when 36 clinicians contoured the oesophagus on a single dataset [42]. Jabbour et al investigated contouring variability of gastrointestinal organs amongst 12 radiation oncologists and found a kappa statistic of 0.62 for the oesophagus, despite using a breath hold scan with intravenous contrast [41]. These results are comparable to those we found on CBCT without contrast. To the best of our knowledge, we are the first to report results from CBCT images using oral contrast.

Whilst barium and Gastrografin, which is iodine-based, have similar physical characteristics (atomic number, densities, k-shell binding energy), barium is more resistant to dilution. This viscosity allows better attachment to mucosal surfaces for longer which is likely the biologic rationale for why we found better visualization using barium. Although barium did not always completely coat the oesophagus throughout its length it did cause potentially clinically significant artefact and was more likely to do so than Gastrografin. Finding the ideal balance between optimal visualization and minimising artefact is the rationale for our continuing research into finding the optimal dose of barium that should be administered before treatment. This will likely limit the accumulation of artefact at the gastroesophageal junction due to contrast accumulation in the stomach which we observed.

The presentation of diarrhoea in two of the three patients in the Gastrograffn group was also a significant finding of this study. Gastrografin is known to have a laxative effect and has been demonstrated in doses over 35 mL and when administered over multiple days [43]. This further supports our decision to proceed with barium moving forward.

We acknowledge limitations to our study. As the true position of the oesophagus on each dataset is unknown, we, like researchers before us, have assessed precision rather than accuracy. The consensus contour we created as a reference is based on the delineations of the observers and thus limited by their expertise. We used a combination of Radiation Oncologists and SBRT-trained Radiation Therapists in this study who are collectively responsible for daily image guidance. Another limitation of this study is the heterogeneity of the tumour locations and volumes between patients creating variability in the length and portion of the oesophagus analysed. For the subsequent phase of this study we aim to limit our analysis to patients with locally-advanced disease as ultimately the purpose of this research is to optimally utilise SBRT for central disease.

Barium allows more precise visualization of the oesophagus on CBCT than Gastrografin and using no contrast. As using 50 ml of barium results in potentially clinically significant artefact, research into finding the optimal dose of barium is required. This represents a step towards using SBRT for locally-advanced NSCLC.

Declaration of Competing Interest

The author declare that there is no conflict of interest.

References

[1] Robinson LA, Ruckdeschel JC, Wagner Jr H, Stevens CW. Treatment of non-small cell lung cancer-stage IIIA: ACCP evidence-based clinical practice guidelines. Chest 2007;132(3 Suppl):243s–65s.

[2] Auperin A, Le Pechoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010;28(13):2181–90.

[3] Coate LE, Massey C, Hope A, Sacher A, Barrett K, Pierre A, et al. Treatment of the elderly when cure is the goal: the influence of age on treatment selection and efficacy for stage III non-small cell lung cancer. Journal of Thoracic Oncology. 2011;6(3):537–44.

[4] Robinson AG, Young K, Balchin K, Owen T, Ashworth A. Reasons for palliative treatments in stage III non-small-cell lung cancer: what contribution is made by time-dependent changes in tumour or patient status? Current oncology (Toronto, Ont). 2015;22(6):399–404.

[5] Driessen EJM, Bootsma GP, Hendriks LEL, van den Berkmortel FWPJ, Bogaarts BAHA, van Loon JGM, et al. Stage III non-small cell lung cancer in the elderly: patient characteristics predictive for tolerance and survival of chemoradiation in daily clinical practice. Radiother Oncol 2016;121(1):26–31.

[6] Hancock J, Rosen J, Moreno A, Kim AW, Detterbeck FC, Boffa DJ. Management of clinical stage IIIA primary lung cancers in the national cancer database. Ann Thoracic Surg 2014;98(2):424–32.

[7] David EA, Daly ME, Li C-S, Chiu C-L, Cooke DT, Brown LM, et al. Increasing rates of no treatment in advanced-stage non-small cell lung cancer patients: a propensity-matched analysis. J Thoracic Oncol 2017;12(3):437–45.

[8] Nyman J, Hallqvist A, Lund J-Å, Brustugun O-T, Bergman B, Bergström P, et al. SPACE – a randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. Radiother Oncol 2016;121(1):1–8.

[9] Lagerwaard FJ, Haasbeek CJA, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;70(3):685–92.

[10] Haasbeek CJ, Palma D, Visser O, Lagerwaard FJ, Slotman B, Senan S. Early-stage lung cancer in elderly patients: a population-based study of changes in treatment patterns and survival in the Netherlands. Ann Oncol 2012;23 (10):2743–7.

[11] Dalwadi SM, Szeja SS, Bernicker EH, Butler EB, Teh BS, Farach AM. Practice patterns and outcomes in elderly Stage I non-small-cell lung cancer: a 2004 to 2012 SEER analysis. Clin Lung Can 2018;19(2):e269–76.

[12] Bezjak A, Paulus R, Gaspar LE, Timmerman RD, Straube WL, Ryan WF, et al. Efficacy and toxicity analysis of NRG Oncology/RTOG 0813 trial of stereotactic body radiation therapy (SBRT) for centrally located non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 2016;96(2):S8.

[13] Senthi S, Haasbeek CJ, Slotman BJ, Senan S. Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. Radiother Oncol 2013;106(3):276–82.

[14] Westover KD, Loo Jr BW, Gerber DE, Iyengar P, Choy H, Diehn M, et al. Precision hypofractionated radiation therapy in poor performing patients with non-small cell lung cancer: phase 1 dose escalation trial. Int J Radiat Oncol Biol Phys 2015;93(1):72–81.

[15] Tekatli H, Haasbeek N, Dahele M, De Haan P, Verbakel W, Bongers E, et al. Outcomes of hypofractionated high-dose radiotherapy in poor-risk patients with "Ultracentral" non-small cell lung cancer. J Thoracic Oncol 2016;11 (7):1081–9.

[16] Timmerman R, McGarry R, Yiannoutsos C, Papiez L, Tudor K, DeLuca J, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24(30):4833–9.

[17] Werner-Wasik M. Treatment-related esophagitis. Semin Oncol 2005;32(2 Suppl 3):S60–6.

[18] Carr DH, Banks LM. Comparison of barium and diatrizoate bowel labelling agents in computed tomography. Brit J Radiol 1985;58(689):393–4.

[19] Garrett PR, Meshkov SL, Perlmutter GS. Oral contrast agents in CT of the abdomen. Radiology 1984;153(2):545–6.

[20] Robinson D. Inhomogeneity correction and the analytic anisotropic algorithm. J Appl Clin Med Phys 2008;9(2):2786-.

[21] Warfield SK, Zou KH, Wells WM. Simultaneous truth and performance level estimation (STAPLE): an algorithm for the validation of image segmentation. IEEE Trans Med Imaging 2004;23(7):903–21.

[22] Deasy JO, Blanco AI, Clark VH. CERR: a computational environment for radiotherapy research. Med Phys 2003;30(5):979–85.

[23] McHugh ML. Interrater reliability: the kappa statistic. Biochemia Medica 2012;22(3):276–82.

[24] Pinter C, Lasso A, Wang A, Jaffray D, Fichtinger G. SlicerRT – radiation therapy research toolkit for 3D Slicer. Med Phys 2012;39(10):6332–8.

[25] Dice LR. Measures of the amount of ecologic association between species. Ecology 1945;26(3):297–302.

[26] Gardner SJ, Wen N, Kim J, Liu C, Pradhan D, Aref I, et al. Contouring variability of human- and deformable-generated contours in radiotherapy for prostate cancer. Phys Med Biol 2015;60(11):4429–47.

[27] Wu AJ, Bosch WR, Chang DT, Hong TS, Jabbour SK, Kleinberg LR, et al. Expert consensus contouring guidelines for IMRT in esophageal and gastroesophageal junction cancer. Int J Radiat Oncol Biol Phys 2015;92(4):911–20.

[28] Abelson JA, Murphy JD, Loo Jr BW, Chang DT, Daly ME, Wiegner EA, et al. Esophageal tolerance to high-dose stereotactic ablative radiotherapy. Dis Esophagus 2012;25(7):623–9.

[29] Sainathan S, Wu LD, Andaz S. Delayed esophageal perforation from stereotactic body radiation therapy for locally recurrent central nonsmall cell lung cancer. Lung India: Off Organ Ind Chest Soc 2014;31(2):158–60.

[30] Yoshimura S, Mori K, Kawasaki K, Tanabe A, Aikou S, Yagi K, et al. A surgical case of radiotherapy induced esophageal perforation accompanying pyogenic spondylodiscitis: a case report. Surg Case Rep 2017;3:98.

[31] Onimaru R, Shirato H, Shimizu S, Kitamura K, Xu B, Fukumoto S, et al. Tolerance of organs at risk in small-volume, hypofractionated, image-guided radiotherapy for primary and metastatic lung cancers. Int J Radiat Oncol Biol Phys 2003;56(1):126–35.

[32] Ruben JD, Seeley A, Panettieri V, Ackerly T. Variation in lung tumour breathing motion between planning four-dimensional computed tomography and stereotactic ablative radiotherapy delivery and its dosimetric implications: any role for four-dimensional set-up verification? Clin Oncol (Royal College of Radiologists (Great Britain)) 2016;28(1):21–7.

[33] Dieleman EMT, Senan S, Vincent A, Lagerwaard FJ, Slotman BJ, van Sörnsen de Koste JR. Four-dimensional computed tomographic analysis of esophageal mobility during normal respiration. Int J Radiat Oncol Biol Phys 2007;67 (3):775–80.

[34] Yamashita H, Haga A, Hayakawa Y, Okuma K, Yoda K, Okano Y, et al. Patient setup error and day-to day esophageal motion error analyzed by cone-beam computed tomography in radiation therapy. Acta Oncol 2010;49:485–90.

[35] Kwint M, Conijn S, Schaake E, Knegjens J, Rossi M, Remeijer P, et al. Intra thoracic anatomical changes in lung cancer patients during the course of radiotherapy. Radiother Oncol 2014;113(3):392–7.
[36] Knap MM, Hoffmann L, Nordsmark M, Vestergaard A. Daily cone-beam computed tomography used to determine tumour shrinkage and localisation in lung cancer patients. Acta Oncol 2010;49(7):1077–84.
[37] Woodford K, Panettieri V, Tran Le T, Senthi S. Feasibility of stereotactic body radiotherapy for locally-advanced non-small cell lung cancer. Clin Transl Radiat Oncol 2017;6:21–4.
[38] Collier DC, Burnett SSC, Amin M, Bilton S, Brooks C, Ryan A, et al. Assessment of consistency in contouring of normal-tissue anatomic structures. J Appl Clin Med Phys 2003;4(1):17–24.
[39] McCall R, MacLennan G, Taylor M, Lenards N, Nelms BE, Koshy M, et al. Anatomical contouring variability in thoracic organs at risk. Med Dosim 2016;41(4):344–50.
[40] Breunig J, Hernandez S, Lin J, Alsager S, Dumstorf C, Price J, et al. A system for continual quality improvement of normal tissue delineation for radiation therapy treatment planning. Int J Radiat Oncol Biol Phys 2012;83(5):e703–8.
[41] Jabbour SK, Hashem SA, Bosch W, Kim TK, Finkelstein SE, Anderson BM, et al. Upper abdominal normal organ contouring guidelines and atlas: a radiation therapy oncology group consensus. Pract Radiat Oncol 2014;4(2):82–9.
[42] Tsang Y, Hoskin P, Spezi E, Landau D, Lester J, Miles E, et al. Assessment of contour variability in target volumes and organs at risk in lung cancer radiotherapy. Tech Innovat Pat Support Radiat Oncol 2019;10:8–12.
[43] Slater A, Betts M, D'Costa H. Laxative-free CT colonography. Brit J Radiol 2012;85(1016):e410–5.