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 datasets and 216 contours were analysed. A STAPLE contour was created and compared to each individual contour.

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 < 0.001), 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.

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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]. Dyspnea 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...
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 Gastrografin.

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 | Disease stage | Tumour location | Contrast group | Length (cm) | Scan type | Time* (mins) | Volume (cc) [SD] | Dice | HD95% (mm) | Kappa |
|---------|---------------|----------------|----------------|-------------|-----------|--------------|-----------------|------|------------|-------|
| 1       | T1aN0M0 (Stage I) | 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 I) | 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 | 0.861 |
|         |                |     |       |     | 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 III) | 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 II) | 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 [1.2] | 0.858 1.98 | 0.756 |
| 4       | T2aN0M0 (Stage I) | 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 I) | 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 I) | 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 II) | 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 III) | 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 | 31.4 [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.
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\cite{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

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**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) | 0.868 (0.032) | \(p = 0.252\)          |
| **Dice coefficient**|             |             |          |                        |
| [Median (IQR)]      | 0.893 (0.089) | p = 0.094   | 0.913 (0.035) | \(p = 0.042\)          |
| **Hausdorff distance** |             |             |          |                        |
| [Median (IQR)]      | 1.8 (2.6)   | 1.4 (0.5)   | 1.3 (1.3) | \(p = 0.041\)          |

Bold p-values = statistically significant.
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].

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

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.

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]. Jabour 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 minimizing 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 gastrooesophageal junction due to contrast accumulation in the stomach which we observed.

The presentation of diarrhea in two of the three patients in the Gastrografin 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.

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