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Short Communication

Intrafraction motion analysis in online adaptive radiotherapy for esophageal cancer

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ABSTRACT

Intrafraction motion during magnetic resonance (MR)-guided dose delivery of esophageal cancer tumors was retrospectively analyzed. Deformable image registration of cine-MR series resulted in gross tumor volume motion profiles in all directions, which were subsequently filtered to isolate respiratory and drift motion. A large variability in intrafraction motion patterns was observed between patients. Median 95% peak-to-peak motion was 7.7 (3.7 – 18.3) mm, 2.1 (0.7 – 5.7) mm and 2.4 (0.5 – 5.6) mm in cranio-caudal, left–right and anterior-posterior directions, relatively. Furthermore, intrafraction drift was generally modest (<5mm). A patient specific approach could lead to very small margins (<3mm) for most patients.

1. Introduction

Radiation therapy has become an integral part in the neoadjuvant treatment of locally advanced esophageal cancer [1–2]. Optimal radiotherapy delivery accounts for day-to-day changes in target volumes. The introduction of magnetic resonance (MR) guided radiotherapy (MRgRT) has allowed for online plan adaptation of the treatment plan based on MRI visualization of the daily anatomy [3–5]. In a recent study we have demonstrated in a cohort of patients with esophageal cancer that MRgRT reduces the dose to organs at risk (OAR) when daily plan adaptation is applied in combination with the use of smaller treatment margins [5–6]. Daily plan adaptation compensates for set-up inaccuracies and interfraction tumor changes, leaving only intrafraction motion (e.g. breathing motion and tumor drifts) as residual errors. The aim of the current work was to retrospectively assess the intrafraction motion in this patient cohort.

2. Materials & methods

Nine esophageal cancer patients received neoadjuvant chemoradiotherapy treatment on a 1.5T MR-Linac (Elekta Unity, Elekta AB, Stockholm, Sweden) between July 2019 and March 2021, as previously reported by our group [5]. All patients consented to the MOMENTUM study (NCT04075305), which has been approved by the Medical Research Ethics Committee of the University Medical Centre Utrecht in the Netherlands [7]. In this cohort, the tumor location varied from the mid- (2) to distal-esophagus (5) and around the gastroesophageal junction (2). Clinical T and N stage were distributed as follows: cT2 (1), cT3 (7) and cT4b (1), N0 (6) and N1 (3).

All patients underwent a T2 weighted anatomical MR scan at the start of each treatment fraction, After registration to a reference scan, the gross tumor volume (GTV) and clinical target volume (CTV) contours were propagated and subsequently adapted by a radiation oncologist. An isotropic treatment margin of 6 mm was used to expand the CTV to create the planning target volume (PTV). Next, a treatment plan was created. In the meantime a second MR scan was acquired and treatment was started if the intrafraction motion between the scans was deemed appropriate (i.e. small) otherwise the plan was readapted. Cine-MR series were recorded for the full duration of dose delivery during each treatment on the MR-Linac. The series consisted of interleafed scans in the coronal and sagittal plane with an in-plane resolution of 1.2 $\times$ 1.2 mm^2 with a frequency of 3 Hz.

The delineated GTV was rigidly propagated to the reference frames of both the coronal and sagittal cine-MR series, which were chosen based on representation of the anatomy of the planning MRI. Cine images were registered to the reference frame with a Matlab (Mathworks Inc., Natick, MA, USA) GPU implementation of Evolution [8]. The motion fields following from registration of the cine slices were applied on a binary

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mask of the GTV and for every cine instance the motion trajectory of the center of mass of the GTV-mask was calculated. Analysis of the coronal slices resulted in the motion trajectory in cranio-caudal and left–right directions, while the anterior-posterior and again the cranio-caudal directions were obtained from analysis of the sagittal slices.

Two filters were used to separate the drifts from the periodic breathing motion. A high-pass filter of 0.05 Hz was used to extract the drift motion, while a low-pass average filter (50 frames, ±20 s) was used to isolate the respiratory motion. Furthermore, for each direction the difference between the maximum and minimum (peak-to-peak) value of the respiratory motion was calculated, excluding the top and bottom 5 percentiles to reduce sensitivity to outliers. Similarly, the minimum and maximum values of the filtered drift motion were determined to obtain the largest drift in each direction.

In order to calculate the impact of the intrafraction motion on the CTV-to-PTV margin, the motion trajectories were used to assess the standard deviation of the motion of the GTV throughout all fractions (σ_m). The difference between the blurred and non-blurred 95%-isodose level could then be estimated by:

$$M_{intrafraction} = 1.64\sqrt{\sigma_m^2 + \sigma_p^2} - 1.64\ \sigma P$$

where the parameter σ_p, describing the width of the penumbra modeled by a cumulative Gaussian which was set to 3 mm [9–11].

In total 183 fractions were successfully completed on the MR-Linac, yielding 183 sets of coronal and sagittal cine-MR series.

3. Results

The median (range) 95% peak-to-peak motion obtained from the coronal scans was 7.7 (3.7 – 18.3) mm in cranio-caudal direction and 2.1 (0.7 – 5.7) mm in left–right direction (Fig. 1A). Analysis of sagittal scans showed a median of 6.1 (2.3 – 15.5) and 2.4 (0.5 – 5.6) mm peak-to-peak motion in cranio-caudal and anterior-posterior directions, respectively. The largest peak-to-peak motion was observed in patients 1 and 3. For these patients a peak-to-peak respiratory amplitude of more than 1 cm in cranio-caudal direction was observed for all fractions.

The median (range) drift was largest in cranio-caudal direction, in particular as measured on the coronal scans: 2.7 (0.6 – 14.7) mm, while the cranio-caudal drift measured on the sagittal scans was 2.1 (0.5 – 9.9) mm. The median drift in AP and LR directions was 1.0 (0.1 – 5.2) mm and 1.0 (0.2 – 4.7) mm, respectively (Fig. 1B). The largest systematic cranio-caudal drift was 10 mm for two patients. However, when averaged over all fractions no systematic drifts greater than 1 mm were observed in any direction for any patient indicating that drifts could be systematic within a fraction, but were random over the entire treatment course.

In Table 1, the standard deviation of the motion of the GTV throughout all fractions (σ_m) for each patient is listed together with associated intra-fraction motion.

4. Discussion

This study provided an analysis of esophageal tumor motion during online MR-guided radiotherapy. A large variability in intrafraction motion patterns was observed between patients. Two patients displayed a systematic cranio-caudal drift of 10 mm, while three patients did not show an intrafraction cranio-caudal drift larger than 5 mm in any of their fractions. This indicated that small treatment margins (<5mm) would have been sufficient for these patients to ensure sufficient target coverage for each fraction. Furthermore, some patients displayed a large variability of breathing patterns during dose delivery, which was observed as changes in amplitude or periods of breath-hold.

The peak-to-peak motion caused by breathing was largest in cranio-caudal direction and typically 5–10 mm, while the motion in anterior-posterior and left–right directions was generally modest (<5 mm). In general, similar peak-to-peak distances were observed for each patient throughout all fractions, although small variations in breathing amplitude were observed between fractions.

We observed a difference of 0.1 – 3.5 mm in measured cranio-caudal motion between the coronal and sagittal cine scans. The largest cranio-caudal motion was measured on the coronal scans which is consistent with the findings of Lever *et al.* [12]. This difference could be explained by the difference in center of mass of the GTV-mask between the cine planes. Delineations projected on the coronal plane included a larger part of the stomach than those in the sagittal plane. This could result in a different location of the center of mass, which could be more subject to intrafraction changes of the stomach. Patient two displayed almost no difference between the scans for all fractions, while patient one, who had more tumor extension into the stomach, showed an average difference of 3.5 mm between cranio-caudal motion obtained from coronal and sagittal scans.

Previous studies on intrafraction motion patterns for esophageal cancer reported a similar spread of cranio-caudal respiratory motion between patients [11,13–18]. As all interfraction variations are inherently corrected in the online adaptive workflow, the CTV-to-PTV margins stem from the interfraction motion as listed in Table 1. Most margins were small (<2mm) and only patient 1 and 3 would have needed margins of 4 mm and 5 mm for the cranio-caudal direction. All margins were below the 6-mm CTV-to-PTV margin that were clinically applied in this study, but based on these results smaller margins could be safely applied in future studies, allowing a further dose reduction to the OARs. As the interfraction variation of the motion patterns within each patient were small, an adaptive strategy could be envisioned where the margin is adapted based in the observed motion patterns in the first fractions.

Also gating and tracking strategies could be employed for patients with breathing amplitudes of 12 mm or more [19–20]. The use of MRgRT allows for potential treatment intensification of the tumor (boost dose) [6]. In this scenario it is crucial that target movement is anticipated for to prevent increased toxicity to the surrounding OAR and to ensure that the dose is correctly administered to the target volume [21–22]. Sub-analysis of GTV coverage revealed that margins <5 mm would have been sufficient in this patient group to deliver at least 95% of the prescribed dose to the GTV in 90% of the fractions (Table 1). These relatively small margins might allow incorporation of dose escalation in the current workflow.

There were a few limitations in our study that need to be acknowledged. First, the relative small sample size of nine patients, with mostly distal tumors, could have influenced the results as distal tumors are more subject to large position variations [23]. Furthermore, a larger sample size might have concluded that it could be possible to adjust treatment margins based on intrafraction motion patterns after the first week(s) of treatment, as the interfraction variability of individual patients appeared to be low in this study, as no outliers were observed in Fig. 1A & 1B.

Secondly, the high-pass filter of 0.05 Hz was chosen to be low enough to contain all frequency components of the respiration motion, while allowing some variation in motion patterns. The breathing amplitude of patients who breathed at a very low rate could have been filtered out. This could have led to an underestimation of the respiratory amplitudes. We believe this would not have a large impact on our findings, as we had long recordings of multiple fractions for each patient.

Thirdly, the motion trajectories were determined from 2D cine-MR images, without adaptation of the GTV-mask. Deformations of the GTV-mask were not taken into account, which could have influenced the position of the center of mass. Furthermore, out-of-plane motion could have potentially resulted in inaccuracies in the determined motion patterns. Especially patients with a caudal tumor extension into the stomach might have been more vulnerable for out-of-plane motion. A solution could be to use deformable image registration to adapt the GTV contours to follow-up frames. However, this would have significantly

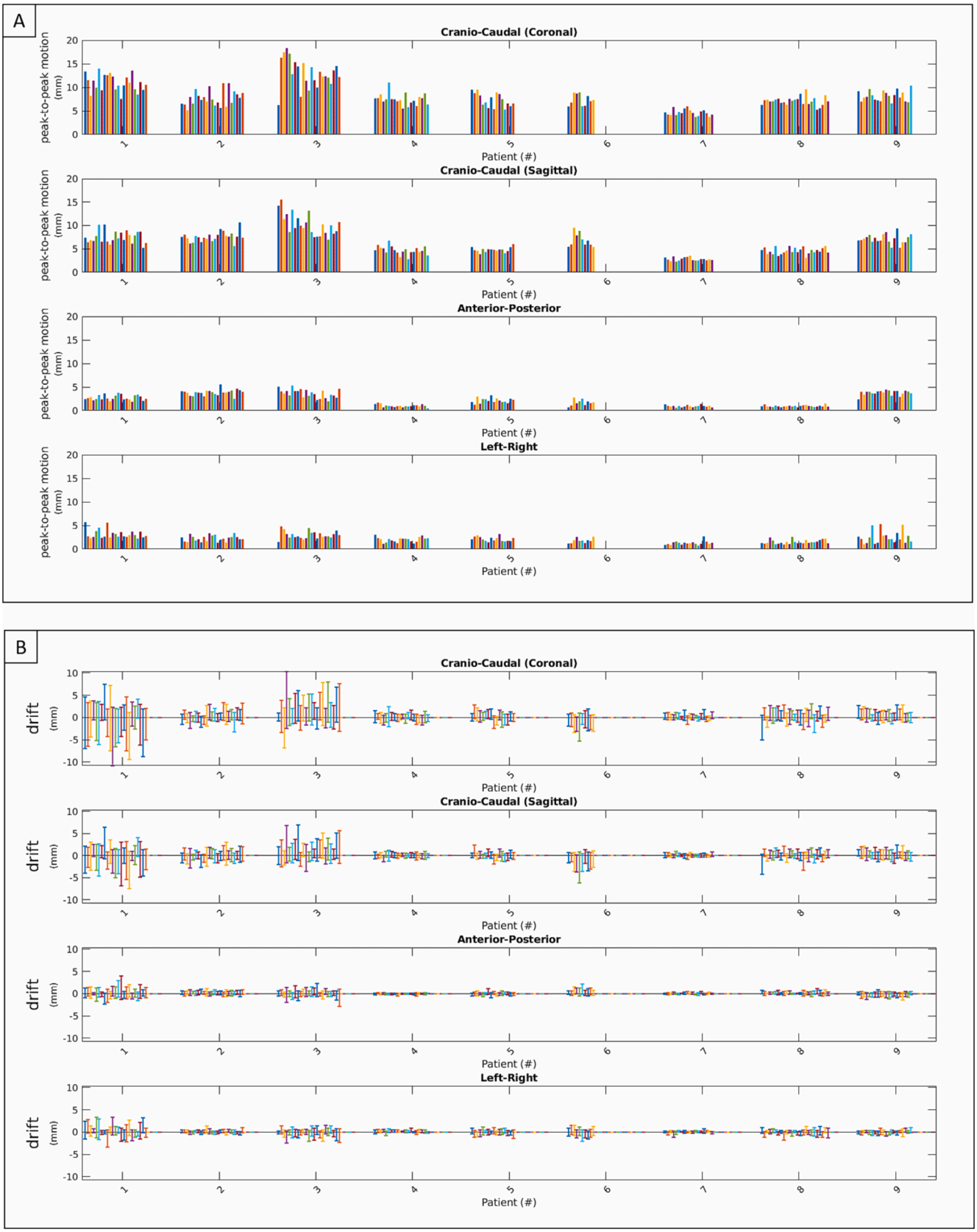

Fig. 1. A: 95% Peak-to-peak motion breathing for all patients. B: Min-max drift motion per fraction for each direction for all patients.

Table 1
Required margin $M_{intrafraction}$ in mm per patient to deliver at least 95% of the prescribed dose to the GTV in 90% of the beam-on time. Here, σ_m is the standard deviation of the motion of the GTV throughout all fractions.

	σ_m (mm)				$M_{intrafraction}$ (mm)			
Patient	CCc	CCs	AP	LR	CCc	CCs	AP	LR
1	4.7	3.2	1.2	1.5	4.2	2.3	0.4	0.6
2	2.7	2.6	1.3	0.8	1.7	1.6	0.4	0.2
3	4.9	3.6	1.3	1.2	4.6	2.8	0.4	0.4
4	2.5	1.6	0.4	0.6	1.5	0.6	0.0	0.1
5	2.6	1.7	0.7	0.8	1.5	0.7	0.1	0.2
6	2.7	2.6	0.8	0.9	1.7	1.6	0.2	0.2
7	1.6	0.9	0.3	0.5	0.6	0.2	0.0	0.1
8	2.6	1.7	0.4	0.7	1.6	0.7	0.0	0.1
9	2.8	2.4	1.3	0.9	1.8	1.4	0.4	0.2

increased the complexity and could have introduced an increase in sensitivity to registration errors, while the change in tumor shape was generally modest. Another possibility to capture out-of-plane motion could be to explore 3D cine imaging, which might decrease temporal resolution leading to an underestimation of the respiratory motion.

In conclusion, intrafraction drift was generally modest (<5mm), but showed a high interpatient variability. The calculated treatment margin indicated that a patient specific approach could lead to very small margins (<3mm) for most patients.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The Radiation Oncology Department of the University Medical Center Utrecht receives financial and technical support under research agreements as well sponsoring for travels and scientific symposia from: Elekta AB (Stockholm, Sweden), Philips NV (Best, The Netherlands).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2023.100432.

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