Physics Contribution

Quantification of Esophageal Tumor Motion on Cine-Magnetic Resonance Imaging

Frederiek M. Lever, MD, Irene M. Lips, MD, PhD, Sjoerd P.M. Crijns, PhD, Onne Reerink, MD, PhD, Astrid L.H. M.W. van Lier, PhD, Marinus A. Moerland, PhD, Marco van Vulpen, MD, PhD, and Gert J. Meijer, PhD

Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, The Netherlands

Summary

To our knowledge, this study is the first to quantify intrafraction motion of esophageal tumors on cine-magnetic resonance imaging (MRI). We successfully measured tumor movement in a large group of patients (n = 36), using a fast noninvasive semiautomatic method to quantify motion in 3 directions. Tumor mobility was highly variable between patients. Cine-MRI is a useful modality to analyze individual motion patterns. These patterns are useful for the development of individual treatment strategies.

Purpose: To quantify the movement of esophageal tumors noninvasively on cine-magnetic resonance imaging (MRI) by use of a semiautomatic method to visualize tumor movement directly throughout multiple breathing cycles.

Methods and Materials: Thirty-six patients with esophageal tumors underwent MRI. Tumors were located in the upper (8), middle (7), and lower (21) esophagus. Cine-MR images were collected in the coronal and sagittal plane during 60 seconds at a rate of 2 Hz. An adaptive correlation filter was used to automatically track a previously marked reference point. Tumor movement was measured in the craniocaudal (CC), left-right (LR), and anteroposterior (AP) directions and its relationship along the longitudinal axis of the esophagus was investigated.

Results: Tumor registration within the individual images was typically done at a millisecond time scale. The mean (SD) peak-to-peak displacements in the CC, AP, and LR directions were 13.3 (5.2) mm, 4.9 (2.5) mm, and 2.7 (1.2) mm, respectively. The bandwidth to cover 95% of excursions from the mean position (c95) was also calculated to exclude outliers caused by sporadic movements. The mean (SD) c95 values were 10.1 (3.8) mm, 3.7 (1.9) mm, and 2.0 (0.9) mm in the CC, AP, and LR dimensions. The end-exhale phase provided a stable position in the respiratory cycle, compared with more variety in the end-inhale phase. Furthermore, lower tumors showed more movement than did higher tumors in the CC and AP directions.

Conclusions: Intrafraction tumor movement was highly variable between patients. Tumor position proved the most stable during the respiratory cycle in the end-exhale phase. A better understanding of tumor motion makes it possible to individualize radiation delivery strategies accordingly. Cine-MRI is a successful noninvasive modality to analyze motion for this purpose in the future. © 2014 Elsevier Inc.
**Introduction**

Radiation therapy is an integral part of the treatment of esophageal tumors in all stages of the disease. Administered preoperatively with concurrent chemotherapy, radiation therapy significantly improves overall survival rates in potentially curable patients (1). If surgery is not an option because of age, morbidity, or extent of disease, definitive (chemo)radiotherapy is the primary treatment (2).

A dose–response relationship has been established for esophageal tumors (3, 4), suggesting that dose escalation could lead to a higher complete pathologic response rate in patients treated neoadjuvantly, and fewer local recurrences in the definitive chemoradiation group. However, dose escalation to the primary tumor is a delicate matter because the esophagus is both target and organ at risk. To prevent a higher toxicity, cautious administration of the boost dose is required without spilling of dose to the healthy surroundings.

Given that esophageal tumors are subject to respiratory and cardiac movement, margins are applied to ensure that sufficient dose is delivered to the tumor. In the future, motion management strategies may improve targeting the dose by reducing margins. As such, a better understanding of tumor movement is essential to explore the potential of safe dose escalation in combination with motion management strategies.

Previous studies have quantified esophageal motion on 4-dimensional computed tomography (4D-CT) (5-9). However, the use of 4D-CT for this purpose frequently includes the need for fiducial markers because of poor contrast features, provides additional radiation exposure, and visualizes the tumor position indirectly in time, owing to binning of data according to respiration phase. MRI, with its superior soft-tissue contrast, is an effective modality for noninvasive visualization of the tumor. Cine-MRI acquires subsequent images with a high temporal resolution and has already been of value in the quantification of intrafraction motion. Cine-MRI acquires subsequent images with a high temporal resolution and has already been of value in the quantification of intrafraction motion in other tumors (10-12). This study is the first to use cine-MRI for the quantification of esophageal tumor motion providing data on a large group of patients. The aim was to quantify 3-dimensional movement of esophageal tumors noninvasively by using a semiautomated method to characterize tumor movement directly throughout multiple breathing cycles. This motion characterization may aid the development of motion management strategies in preparation for future dose escalation strategies.

**Methods and Materials**

**Patients**

Thirty-six patients with pathologically verified tumors of the esophagus were included in this study between May 2011 and February 2013. Patients underwent MRI approximately 1 week before the start of treatment.

**Image acquisition and registration**

The MR imaging was performed on a 1.5-T scanner (1.5T Achieva, Philips, Best, The Netherlands) using a 16-channel phased array coil for reception (Torso XL, Philips). Patients were scanned in supine position with arms placed alongside the body. Before cine-MR imaging, T2-weighted turbo spin-echo images were obtained in the axial, coronal, and sagittal planes. These images were then used to plan the 2-dimensional (2D) coronal and sagittal cine-MRI scans. The slice (7 mm) was placed through the longitudinal axis of the esophageal tumor. The cine-MRI scans consisted of 2D balanced steady-state free precession sequences to gain a sufficient signal-to-noise ratio. The following scan parameters were used: flip angle 50°, TE 1.44 ms, TR = 2.9 ms, NSA 1, pixel size 2.01 mm × 2.01 mm for the coronal images. The parameters for the sagittal images were identical except for the pixel size: 1.43 mm × 1.43 mm. A series of images was collected during 60 seconds of free breathing at a rate of 2 Hz.

Cine-MRI scans were recorded with a bandwidth of 1935.6 Hz/mm (sagittal) and 2662.6 Hz/mm (coronal). Considering a maximum field inhomogeneity in the tumors of approximately 100 Hz, the maximal geometric error remained <0.05 mm. Given that this is considerably smaller than the voxel sizes used, the imaging distortion was considered negligible for measurement of the tumor motion.

**Quantification of tumor motion**

To quantify movement, a reference point on the caudal tumor border was marked by a single physician on the 10th frame of each cine-MRI, skipping the prior frames because the contrast of the steady-state of the cine-MR sequence had not yet been established (Fig. 1). This point was automatically tracked in subsequent frames by use of a minimum output sum of squared error (MOSE) adaptive correlation filter (13). The selected point provided the center of a search window (64 pixels × 64 pixels). Correlating the filter over the search window in the next frame tracked the point. The filter was determined by requiring that correlation with the initial frame produced a compact Gaussian peak centered on the tracking point. The location corresponding to the maximum value in the correlation output indicated the new position of the target. The caudal tumor border was chosen to track because its sharper contrast with the surrounding tissues made it suitable for tracking.

Tracking provided coordinates of the tumor reference point in each frame, which were used to calculate tumor movement. Tumor motion in the craniocaudal (CC) direction was determined on both the coronal and sagittal scans. Left–right (LR) and anteroposterior (AP) movement were evaluated on coronal and sagittal images, respectively. If images were acquired in an angulated plane with respect to these 3 directions, vectors were corrected to represent the actual CC, LR, and AP directions. Individual patient data were evaluated and summarized by use of the peak-to-peak amplitudes of motion in each direction. Furthermore, the smallest range to cover 95% of excursions from the time-average over all instances (c95) was also calculated. This c95 provided a more robust measure for tumor motion by excluding outliers caused by sporadic movement (eg, swallowing, hiccups) seen on the scans.

**Craniocaudal motion and the respiratory cycle**

The length and frequency of the cine-MRI acquisition made it possible to measure tumor motion throughout multiple breathing cycles. For each patient, the CC motion pattern was inspected and analyzed (Fig. 2). The peaks and troughs of each motion pattern were defined as inhale or exhale peaks (ie, the greatest deviation from the mean [time-averaged] position at the end-inhale phase and end-exhale phase). For each patient, the inhale and exhale peaks were grouped and the mean and standard deviation (SD)
was calculated to assess the stability of tumor position in each phase.

### Tumor location

To investigate the relationship between mobility and location along the longitudinal axis of the esophagus, tumor location was determined. Tumors were classified into 3 groups (upper, middle, and lower tumors) according to the American Joint Committee on Cancer staging guidelines (14).

### Statistical methods

All analyses were executed with SPSS, version 20.0. Tumor movement in the CC, LR, and AP directions was determined for each patient. The peak-to-peak amplitude and c95 of each patient was then used to calculate the mean and standard deviation in each direction for the whole group. To analyze the stability of the end-inhale and end-exhale phase of the respiratory cycle, a paired-samples $t$ test was done on the standard deviations of inhale and exhale peaks per patient. To assess differences in motion between upper, middle, and lower tumors, an analysis of variance was performed. If a significant difference was found between these 3 groups, pairwise comparisons with a Bonferroni correction were performed to identify which group contributed to this difference. For all statistical tests performed, a value of $P<0.05$ was considered statistically significant.

### Results

#### Clinical characteristics of patients

Thirty-six patients were included in this study. The patient characteristics are summarized in Table 1. In 1 patient only coronal cine-MRI was performed, and in another patient only sagittal cine-MRI was acquired. Six sagittal scans were excluded because of an erroneously set slice thickness (3 mm instead of 7 mm), causing insufficient signal-to-noise ratio in the images. As a result, 35 coronal and 29 sagittal cine-MRI scans were available for analysis.

#### Quantification of tumor motion

Tumor registration within the individual images was typically done at a millisecond time scale. In 28 patients, both coronal and sagittal cine-MRI scans were obtained, making it possible to measure CC motion in both planes. CC motion on sagittal images was 9% less than CC motion tracked on coronal images. To prevent underestimation of movement, further analysis of CC motion was done on the coronal images. Motion for each direction is summarized in Table 2. The greatest motion was found in the CC direction, with a mean (SD) peak-to-peak amplitude of 13.3 (5.2) mm, followed by the AP (4.9 [2.5] mm) and the LR (2.7 [1.2] mm).

---

**Fig. 1.** (A) Coronal and (B) sagittal cine-magnetic resonance image of a lower esophageal tumor, with the reference point (white) for the tracking filter shown on the caudal tumor border.

**Fig. 2.** Representative craniocaudal motion pattern in 1 patient of a point tracked on the caudal tumor border. The variety in the end-inhale phase (peaks) and the stability of the end-exhale phase (troughs) are evident.
mm) directions. The large standard deviations and ranges reflect a high interpatient variability in tumor motion.

**Cranio-caudal motion and the respiratory cycle**

Visual inspection of the cine-MR images showed a relationship between tumor and diaphragmatic motion consistent with the close correlation between the respiratory cycle and CC motion described in the literature (8, 15). Analysis of inhale and exhale peaks per patient showed a statistically significant difference with overall mean (SD) values of 4.4 (2.1) mm and 3.2 (0.7) mm, respectively (P < 0.001). The greater variation in standard deviation of the inhale peaks indicated more variation in tumor position in the end-inhale phase (Fig. 3). Last, the stability of exhale peaks in comparison with inhale peaks remained in very mobile tumors (Fig. 3).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td>Male 24 (66.7) Female 12 (33.3)</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>68 (10.5)</td>
</tr>
<tr>
<td>Tumor volume, mL, mean (SD)</td>
<td>68.5 (60.8)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td>SCC 16 (44.4) AC 20 (55.6)</td>
</tr>
<tr>
<td>Stage, n (%)</td>
<td>IIA-B 9 (25.0) IIIA-C 10 (27.8) IV 6 (16.7) Unknown 11 (30.6)</td>
</tr>
<tr>
<td>Tumor location, n (%)</td>
<td>Upper 8 (22.2) Middle 7 (19.4) Lower 21 (58.3)</td>
</tr>
<tr>
<td>RT treatment, n (%)</td>
<td>Neoadjuvant 21 (58.3) Palliative brachytherapy 5 (13.9)</td>
</tr>
</tbody>
</table>

**Association between tumor location and esophageal mobility**

Figure 4 shows the relationship between mobility and location of the tumors for the 3 directions of motion studied. There were 8 tumors located in the upper, 7 in the middle, and 21 in the lower part of the esophagus (14). The lower tumors had the greatest movement, requiring a mean (SD) range of 11.5 (3.4) mm to cover 95% of movement from the mean position (c95) in the CC direction. These ranges were 10.7 (3.6) mm in the middle group and 6.1 (1.3) mm in the upper group. A significant difference (P = .001) was found in CC movement between the 3 groups. The upper group differed significantly from the middle (P = .023) and lower (P = .001) groups, but no difference was found in comparing the middle and lower groups (P = 1.000) (Fig. 4A).

A trend was also seen in the AP movement, with a mean (SD) c95 in the lower, middle, and upper groups of 4.7 (1.7) mm, 3.2 (2.2) mm, and 2.0 (0.4) mm. Differences between the 3 groups in AP motion were significant as well (P = .003). The movement of the upper group tumors differed significantly from that of the lower tumors (P = .003) but not from the middle tumors (P = .585) (Fig. 4C). Again, the middle and lower tumors did not differ significantly (P = .162).

No significant difference was seen between tumor location for the LR direction (P = .313) (Fig. 4B), with mean (SD) c95s of 2.3 (1.1) mm, 1.7 (0.37) mm, and 1.8 (0.49) mm in the lower, middle, and upper groups, respectively.

**Discussion**

The greatest esophageal tumor motion was found in the CC direction, followed by the AP direction and minimal movement in the LR direction. The end-exhale phase provided the most stable position independently of the mobility of the tumor. Last, in our study an association was identified between the position of the tumor along the longitudinal axis of the esophagus and its mobility. Tumors in the lower esophagus showed more movement in the CC and AP direction than did higher tumors. This greater movement of lower esophageal tumors may be explained by anatomy (eg, proximity to the diaphragm and influence of respiratory movement).

Several other studies have also identified tumors in the lower esophagus as the most mobile tumors (5,7). Dieleman et al (5) studied esophageal motion in 29 patients with nonsophageal malignancies on normal breathing 4D-CT and described larger margins needed to encompass all movement in the lower esophagus. In the LR and AP directions, these margins were 5 mm for the proximal esophagus, 7 mm and 6 mm in the midesophagus, and 9 mm and 8 mm in the distal esophagus. Motion in the CC direction was not analyzed in their study. Similarly, Patel et al (6) found distal tumors to have significantly greater CC and AP motion than proximal or midesophageal tumors. In that study, 30 patients underwent 4D-CT scans, and movement in 3 directions was analyzed. An association between tumor location and magnitude of motion in the CC and AP directions was found, but not for the LR movement. A study by Yaremko et al (7) also showed a consistent increase in average gross tumor volume displacement with descent along the esophageal axis. This was done by determining the motion for 31 tumors in the distal esophagus on respiratory-gated 4D-CT images by mapping the gross tumor volume on the CT images at maximal inspiration and maximal expiration.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Summary of tumor motion in 3 directions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direction</td>
<td>Peak-to-peak amplitude (mm)</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Cranio-caudal</td>
<td>13.3</td>
</tr>
<tr>
<td>Left-right</td>
<td>2.7</td>
</tr>
<tr>
<td>Anteroposterior</td>
<td>4.9</td>
</tr>
</tbody>
</table>

**Abbreviation:** SD = standard deviation.

* c95 represents the bandwidth covering 95% of tumor motion.

† n = 35 (coronal cine-MRI).

‡ n = 29 (sagittal cine-MRI).
The studies mentioned above have all quantified esophageal movement using 4D-CT images, where the respiratory cycle is binned into inhale and exhale phases and the precise position of the tumor at the end of these phases cannot be determined. In fact, the fourth dimension of these images does not represent the time directly. Therefore, irregularities in the breathing pattern cannot be captured with 4D-CT. An exception is research by Yamashita et al. in which volumetric 4D-CT scanning was used to acquire a full 3D image every 0.5 seconds during 20 seconds. Their study analyzed the 3D movement of 22 markers placed near esophageal malignancies in 12 patients. Similarly to other studies, Yamashita et al. analyzed CC motion separately for upper, middle, and lower tumors and determined an increase in esophageal mobility for lower tumors. They concluded that margins of 4.3 mm, 7.4 mm, and 13.8 mm were required to cover 95% of the tumor motion in the CC direction for upper, middle, and lower tumors, respectively. These findings were in line with our results (10.1 mm for the entire group).

To our knowledge, this is the first study in which cine-MRI has been used to quantify esophageal tumor motion. It also represents the largest group of esophageal tumors (n=36) in which intrafraction motion is examined. Cine-MRI provides sufficient soft-tissue contrast for the visualization of esophageal tumors without the need for invasive fiducial markers. Also, there is no additional radiation exposure for the patient. Use of the MOSSE filter to track the motion on the cine-MR images allowed for fast semiautomatic tracking of the tumor, eliminating the interobserver dependency of contouring the tumor in each frame. Furthermore, it was possible to observe motion patterns directly during 60 seconds, depicting multiple breathing cycles. This allowed the identification of the end-exhale phase as the most stable phase. Radiation field margins typically applied to esophageal tumors are approximately 5 cm in the CC direction and 2 cm radially. The clinical target volume—planning target volume expansion included in these margins is usually 1 to 2 cm. On the basis of our findings, this is sufficient to account for motion in all directions. However, a smaller margin is potentially sufficient in the axial direction to account for LR and AP motion. Our results also suggest that margins could be reduced by individualizing margins after motion measurement. However, before smaller margins are introduced in clinical practice, other uncertainties (eg, setup error) must be investigated.

There were also some limitations to this study. The MOSSE filter works best when tracking a point with distinct contrast in relation to its surroundings; thus, the tumor border was chosen. Also, a difference in CC motion measured on sagittal compared with coronal images was found. The MOSSE filter is susceptible to static structures in proximity of the point being tracked. In the sagittal scans the spinal vertebrae were often near the tumor. This may explain why CC motion in the sagittal images was 9% less...
than motion measured on coronal images, although other factors such as out-of-plane motion or irregular breathing patterns on the consecutively acquired scans may have also contributed to this difference. Also, measurements on cine-MRI do not represent the exact 3D displacement of the esophagus, but the 2D displacement of the point tracked, making it susceptible to effects of out-of-plane motion. However, to minimize the effect of out-of-plane motion, our measurement plane was chosen to depict the greatest length of the tumor, which was closely related to the CC direction. Novel 4D-MRI techniques provide the possibility to resolve the error of out-of-plane motion, offering a promising method for future work (17). Previous work by Crijns et al (18) validated the use of the MOSSE filter as a tracker of kidney motion on cine-MRI. The average measurement errors found for image processing were approximately half a voxel, making it insignificant in comparison with the tumor motion found in our study.

To evaluate the clinical implications of our results, future work should address the dosimetric consequences of esophageal movement on radiation therapy treatment planning for esophageal tumors. Also, with the method used in our study, cine-MRI could be used in the pretreatment workflow for quick assessment of tumor motion. Another application of cine-MRI could be to evaluate the effect of tumor motion on radiation delivery in a brachytherapy (boost) setting. A better understanding of tumor motion makes it possible to individualize radiation delivery strategies accordingly. Further research into assessing benefits of such (individual) motion management strategies could be of value. Moreover, in exploring intrafraction motion management methods, such as gated radiation delivery, our findings on the relative stable tumor position in the end-exhale phase could be used. Last, with advances toward MRI-guided radiation delivery, our method could become increasingly useful and attainable clinically (19).

**Conclusion**

A fast image tracking method was used successfully in this study to quantify the motion of esophageal tumors on cine-MRI non-invasively. The motion of esophageal tumors was found to be highly variable between patients. The greatest mobility was seen in the CC direction, followed by the AP and LR directions. An association was observed between CC and AP movement and the location of the tumor along the axis of the esophagus, with greatest motion in the lower esophageal tumors. Last, our study identified that the most stable tumor position is during the end-exhale phase. This information could be used in the development of strategies for gated radiation delivery. In conclusion, a better understanding of esophageal tumor motion makes it possible to individualize radiation delivery strategies accordingly. Cine-MRI is a successful noninvasive modality to analyze motion for this purpose in the future.

**References**