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Real-time direct diaphragm tracking using kV imaging on a standard linear accelerator

Nicholas Hindley

ACRF Image X Institute, University of Sydney, Central Clinical School, Eveleigh, NSW 2015, Australia; Tel: +61405908920; E-mail: nicholas.hindley@sydney.edu.au

Paul Keall

ACRF Image X Institute, University of Sydney, Central Clinical School, Eveleigh, NSW 2015, Australia

Jeremy Booth

Northern Sydney Cancer Centre, Royal North Shore Hospital, St Leonards, NSW 2065, Australia

Institute of Medical Physics, School of Physics, University of Sydney, Camperdown NSW 2015, Australia

Chun-Chien Shieh

ACRF Image X Institute, University of Sydney, Central Clinical School, Eveleigh, NSW 2015, Australia

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Purpose: As the predominant driver of respiratory motion, the diaphragm represents a key surrogate for motion management during the irradiation of thoracic cancers. Existing approaches to diaphragm tracking often produce phase-based estimates, suffer from lateral side failures or are not executable in real-time. In this paper, we present an algorithm that continuously produces real-time estimates of 3D diaphragm position using kV images acquired on a standard linear accelerator.

Methods: Patient-specific 3D diaphragm models were generated via automatic segmentation on end-exhale 4D-CT images. The estimated trajectory of diaphragmatic motion, referred to as the principal motion vector, was obtained by registering end-exhale to end-inhale 4D-CT images. 2D diaphragm masks were generated by forward-projecting 3D models over the complement of angles spanned during kV image acquisition. For each kV image, diaphragm position was determined by shifting angle-matched 2D masks along the principal motion vector and selecting the position of highest contrast on a vertical difference image. Retrospective analysis was performed using 22 CBCT image sequences for six lung cancer patients across two datasets. Given the current lack of objective ground truth for diaphragm position, our algorithm was evaluated by examining its ability to track implanted markers. Simple linear regression was used to construct 3D marker motion models and estimation errors were computed as the difference between estimated and ground truth marker positions. Additionally, Pearson correlation coefficients were used to characterize diaphragm-marker correlation.

Results: The mean ± standard deviation of the estimation errors across all image sequences was -0.1 ± 0.7 mm, -0.1 ± 1.8 mm and 0.2 ± 1.4 mm in the LR, SI and AP directions respectively. The 95th percentile of the absolute errors ranged over 0.5 – 3.1 mm, 1.6 – 6.7 mm and 1.2 – 4.0 mm in the LR, SI and AP directions respectively. The mean ± standard deviation of diaphragm-marker correlations over all image sequences was -0.07 ± 0.57, 0.67 ± 0.49 and 0.29 ± 0.52 in the LR, SI and AP directions respectively. Diaphragm-marker correlation was observed to be highly dependent on marker position. Mean correlation along the SI axis ranged over 0.91 – 0.93 for markers situated in the lower lobes of the lung, while correlations ranging over -0.51 – 0.79 were observed for markers situated in the upper and middle lobes.

Conclusion: This work advances a new approach to real-time direct diaphragm tracking in realistic treatment scenarios. By achieving continuous estimates of diaphragmatic motion, the proposed method has applications for both markerless tumor tracking and respiratory binning in 4D-CBCT.

1. Introduction

In cancer radiotherapy, the success of any motion management strategy depends on its ability to reliably track tumour position. This becomes particularly important in the treatment of thoracic cancers where respiration introduces a constant source of irregular motion[1]. In seeking to address this challenge, several approaches to real-time tumor tracking have been reported to-date and these can be placed into three main categories. First, tumor position can be determined via direct fluoroscopic imaging. This presents the most intuitive and

straightforward approach and, encouragingly, several direct imaging technologies are under current investigation.[2-5] However, poor contrast between cancerous and healthy tissue remains a recurrent difficulty for these methods and further development is required in order to ensure safe clinical implementation.

Second, tumor localization can be achieved by implanting radiopaque fiducial markers[6] or electromagnetic transponder beacons[7,8]. This presents an alternative to direct fluoroscopic imaging which overcomes the issue of low contrast. However, implantation is an invasive and costly procedure that introduces the risk of pneumothorax.[9] Additionally, since fiducial markers may migrate away from the intended site[10] or exhibit surrogacy errors[11-15] this does not provide a robust strategy for respiratory motion management.

The final class of strategies uses anatomical landmarks as surrogates for respiratory motion. By positing correlations between surrogate motion and anatomic motion, thoracic structures such as the abdominal surface, carina or diaphragm can be used to establish tumor motion models. Critically, the accuracy of these models depends strongly on the choice of surrogate, with the most common choice being anterior-posterior (AP) displacement of the abdominal surface.[16,17] However, relying on external surrogates alone can lead to residual tumor motion not contemplated in the original treatment plan.[18]

The ideal anatomical surrogate will exhibit a direct and consistent relationship with respiratory motion. Intuitively, internal surrogates will harbor stronger correlations with internal anatomy changes than their external counterparts. However, where intrafraction images are used for monitoring, it is crucial that the surrogate remains persistently visible. Direct diaphragm tracking seeks to address both these challenges. First, the diaphragm serves as the most important muscle for respiration. Indeed, it has been demonstrated that the first two principal components of longitudinal diaphragm motion are sufficient to describe 3D

thoracic organ motion.[19] Additionally, owing to its high intrinsic contrast with the surrounding anatomy, the diaphragm is typically identifiable on kV images of the thorax. Therefore, the focus of this study was to develop a robust method for direct diaphragm tracking during kV image acquisition.

Previously reported tracking algorithms typically rely on a thresholding technique or impose various optimization constraints during imaging. For instance, in a recent paper, diaphragm identification was considered as a constrained linear regression optimization problem.[20] Under this approach, thresholding was achieved using Otsu's method, the geometry was approximated by parabolas and the temporal redundancy of diaphragmatic motion was modelled by applying both band and algebraic constraints. Critically, since these computations were carried out for each image individually, execution of the algorithm was not achievable in real-time. Additionally, as boundary detection was performed by thresholding, tracking failures at the lateral side were inevitable on CBCT images due to interference from overlapping anatomic structures.

In contrast, our approach achieves real-time tracking by accounting for the bulk of computational complexity prior to kV image acquisition. This is achieved by using 4D-CT images to build patient-specific models of the diaphragm, which subsequently serve as geometric constraints during imaging. Coupling these constraints with a maximum gradient algorithm then ensures that our approach tracks only those structures that exhibit both high geometric similarity to the pre-built diaphragm model as well as high intrinsic contrast.

Evaluating the performance of diaphragm tracking algorithms has typically involved manual delineation of the diaphragm by a clinician.[20-23] This has two important limitations. First, such judgments must be made subjectively. Since there is no standard way of identifying the diaphragm on fluoroscopic images, interoperator variability is inevitable.

Second, the ability to confidently identify the diaphragm is highly dependent on imaging angle. Indeed, interference from overlapping structures at the lateral side is a key challenge which this work seeks to address. Therefore, since the ultimate goal of this work was to enable real-time motion management, the proposed algorithm was evaluated by examining its ability to accurately track implanted markers.

This study centers on achieving three aims:

- Developing an algorithm which utilizes pre-built, patient-specific models of the diaphragm in order to achieve real-time tracking.
- Evaluating the performance of this method both by using simple linear regression to construct 3D motion models and by examining correlations between tracked diaphragm positions and implanted marker positions.
- Demonstrating the feasibility of the proposed method for real-time motion management using datasets that represent realistic treatment settings.

2. Materials and methods

2.1 Workflow

The workflow for the proposed method (Figure 1) can be divided into steps 1 – 3 occurring post 4D-CT acquisition and steps 4 – 5 which occur during kV image acquisition:

1. A 3D model of the diaphragm is constructed by segmenting the end-exhale image of the pre-treatment 4D-CT.
2. The 3D diaphragm model is registered to the end-inhale image of the pre-treatment 4D-CT to compute a principal motion vector.

3. A 2D diaphragm model is generated by projecting the 3D model onto the detector space over the complement of angles spanned by full gantry rotation.
4. A vertical difference image is generated for each kV image in order to highlight the intrinsic contrast of the diaphragm.
5. The diaphragm is tracked using a maximum gradient algorithm.

Algorithmic development was performed in MATLAB (The MathWorks, Inc., Natick, MA) and latency testing was performed in C# (Microsoft Corp., Redmond, WA).

2.1.1 Building the 3D diaphragm model

Patient-specific models of the diaphragm are generated by segmenting the end-exhale phase image of a pre-treatment 4D-CT. Candidate segments are identified using transitions in the superior-inferior (SI) direction from pixels labelled as lung tissue to pixels labelled as soft tissue. Label maps are computed by applying an intensity threshold together with a connectivity constraint to exclude small cavities. For each lung, the optimal diaphragm segment is selected by searching over each coronal slice according to the following criteria. First, the optimal segment should span the largest distance in the left-right (LR) direction. Second, the outermost points of the optimal segment will extend the furthest from the image centre. Third, the optimal segment will exhibit negative curvature. To account for motion artefacts, the segment is regularized by a smoothing spline in both the LR and anterior-posterior (AP) directions. Finally, the optimal segment is propagated to each coronal slice by selecting those candidate segments with maximal overlap.

2.1.2 Computing the principal motion vector

Since the diaphragm moves in the inferior-anterior direction during respiration, diaphragmatic motion was parameterized along an artificial axis constructed by taking linear combinations of the SI and AP axes. That is, the diaphragm was regarded as shifting over a patient-specific principal motion vector $(v_0 \quad d)$ where v_o is the position of the diaphragm at end-exhale and d is the direction of diaphragmatic motion. The direction of diaphragmatic motion was estimated by registering the 3D diaphragm model, extracted from the end-exhale image, to the diaphragm position in the corresponding end-inhale image, assuming zero LR motion and zero rotation. Each candidate position v was then computed by:

$$v = (v_0 \quad d)\begin{pmatrix}1\\ s\end{pmatrix}$$

$$= v_0 + sd,$$

where s is a scaling factor reflecting the distance from the diaphragm position at end-exhale.

2.1.3 Generating a 2D diaphragm model

A 2D diaphragm model is built by forward-projecting the 3D model over the complement of angles spanned by full gantry rotation. An angular increment of 0.5° was found to yield sufficient angular resolution. By identifying the visible pixels at each angular view, this approach does not model the diaphragm as a curve but as a collection of angle-specific binary maps which are then shifted along the principal motion vector. Therefore, considering $M_{\alpha,v}$ as the binary map at gantry angle α shifted to position v, each pixel within the field of view p_i can be classified according to the indicator function:

$$\delta_i(\alpha, v) = \begin{cases} 1 \; if \; p_i \in M_{\alpha,v} \\ 0 \; otherwise \end{cases}$$

This constrains the maximum gradient search to those pixels within each shifted, angle-matched diaphragm map. Since the imaging geometry is often known beforehand, these maps are generated prior to treatment in order to reduce computation time in step 4.

2.1.4 Generating the vertical difference image

The diaphragm is tracked by selecting the position of highest contrast along the principal motion vector. For each kV image, a vertical difference image is generated by computing the difference between mean intensity values 2 mm above (superior to) and below (inferior to) each pixel. This can be considered as transforming the set of pixel intensities $i_1, \ldots, i_n$ for a kV image with n pixels to a set of gradient values $g_1, \ldots, g_n$ in the difference image. In contrast to traditional approaches, this method only considers vertical intensity changes, since the diaphragm is always positioned inferiorly to the lungs (Figure 2). A 2 mm window is used to account for the observation that, on kV images, transitions from the lung to the diaphragm often span across several pixels.

2.1.5 Applying a maximum gradient algorithm

During imaging, the logical map which represents the closest angular view to the current gantry angle is selected. Candidate positions are then generated by shifting the map pixel-wise along a pre-determined search window. For the first image, a search window extending 10 mm in the SI direction from the end-exhale position is used. This is reduced to a 3 mm window centered at the previously tracked diaphragm position for all subsequent images. Search windows of 3 and 10 mm were found to adequately capture diaphragm motion between frames, given at the acquisition rates of the image sequences used in this

study. To improve recovery from tracking failures, a rolling mean of all previous diaphragm positions is computed and used to center an additional 3 mm search window. Each candidate position is scored by taking the sum of gradients for every pixel delineated by the 2D map. The candidate with the highest gradient-sum is selected as the current diaphragm position. In other words, the diaphragm is tracked by computing:

$$\bar{v} = \arg\max_{v} \sum_{i=1}^{n} g_i \, \delta_i(\alpha, v)$$

Critically, while the maximal gradient search is performed over the 2D projection space, by shifting each map along the principal motion vector, the algorithm produces estimates of 3D diaphragm position.

2.2 Patient data

Retrospective analysis was performed on a total of 22 image sequences for six patients across two datasets. This included images from both the 4D-Lung dataset24 in The Cancer Imaging Archive as well as the LIGHTSABR trial8. In this study, patient selection was based solely on whether the diaphragm remained persistently visible during image acquisition. This restricted our analyses to 3 of the available 7 patients in the 4D-Lung dataset and 3 of the available 15 patients in the LIGHTSABR trial. 4D-CT scans for the LIGHTSABR trial and the 4D-Lung dataset had 1- and 3-mm slice thickness, respectively. Patient characteristics are summarized in Table 1.

2.2.1 Ground truth marker positions

Patients in the 4D-Lung study were implanted with 2 or 3 radiopaque fiducial markers and a robust template-based segmentation technique was used to estimate tumor position. For patients in the LIGHTSABR trial, tumor position was estimated by implanting 3 electromagnetic transponder beacons. The positions of these implanted markers were considered as ground truth in computing estimation errors.

2.2.2 Image sequences

CBCT images from both the 4D-Lung dataset and the LIGHTSABR trial were used in this study. This included 14 image sequences from the 4D-Lung dataset each consisting of 1200 half-fan projections acquired with an on-board Varian kV imaging device (Varian Medical Systems, Palo Alto, CA) at 5 Hz over 360°. Similarly, the LIGHTSABR data consisted of 8 image sequences consisting of approximately 600 half-fan projections acquired at 10 Hz over 360° also using a Varian device. The size of each image was 1024 × 768 pixels with a pixel spacing of 0.388 mm. Audiovisual biofeedback was implemented for breathing guidance during every scan in the 4D-Lung dataset.

2.3 Evaluating tracking performance

Since the ultimate goal of this work is to inform real-time motion management, our algorithm was evaluated by examining its ability to accurately track implanted marker motion. Critically, since principal components analysis can be used to parameterize 3D thoracic organ motion using longitudinal motion of the diaphragm as a surrogate19, there is a strong mathematical basis for using linear regression similarly to predict 3D marker motion.

Therefore, in this study, 3D motion models were built by constructing lines of best-fit, in the least-squares sense, using the first 10 percent of images in each sequence. Errors were computed as the difference between estimated and ground truth marker positions across the remaining 90 percent of images. Additionally, diaphragm-marker correlation was examined by computing Pearson correlation coefficients between tracked diaphragm positions and ground truth marker positions for each imaging sequence in its entirety.

Each 3D motion model was built by individually considering marker position in the LR, SI and AP directions as a function of diaphragm position. Critically, since the diaphragm was modelled as shifting along a 1D motion vector, this translates as a simple linear regression problem of the form:

$$\widehat{m_j} = \alpha V + \beta,$$

where $\widehat{m_j} = [\hat{m}_{j,1}, \hat{m}_{j,2}, \dots, \hat{m}_{j,i}]$ is set of estimated marker positions for i images in the jth direction, $V = [\bar{v}_1, \bar{v}_2, \dots, \bar{v}_i]$ is the set of tracked diaphragm positions along the principal motion vector, α is the regression coefficient and β is the bias term. Defining $m_j = [m_{j,1}, m_{j,2}, \dots, m_{j,i}]$ as the corresponding set of ground truth marker positions, estimation error in the jth direction is then defined as:

$$e_j = m_j - \hat{m}_j,$$

where j = 1, 2 or 3 for the LR, SI and AP directions, respectively. Each model was evaluated using the mean and standard deviation of the estimation error along each axis as well as diaphragm-marker correlations. Additionally, the mean 95th percentile of absolute error is also reported, where absolute error in the jth direction is defined as $|e_j|$.

3. Results

3.1 3D motion models

The mean ± standard deviation of the estimation errors across all image sequences was -0.1 ± 0.7 mm, -0.1 ± 1.8 mm and 0.2 ± 1.4 mm in the LR, SI and AP directions respectively. Additionally, the mean 95th percentile of the absolute errors ranged over 0.5 – 3.1 mm, 1.6 – 6.7 mm and 1.2 – 4.0 mm in the LR, SI and AP directions respectively. These data are summarized in Tables 2 and 3.

In terms of the predominant axis of motion, the image sequence with lowest mean SI error corresponds to the last scan of Patient 6 (Figure 2) at 0.0 ± 0.6 mm. One striking observation of these data is that the model performed well in spite of capturing very little of the dynamics in the LR direction. In this case, these semi-periodic fluctuations were likely due to cardiac motion. However, it is hypothesized that this lack of nuance produced little overall effect as motion in the LR direction was restricted to a range of approximately 1 mm. Indeed, marker motion for this patient was confined to the narrowest range observed in this study

Conversely, the highest mean SI error was observed for the last scan of Patient 5 (Figure 3) at 1.7 ± 3.4 mm. For this sequence, a persistent shift in estimation accuracy seems to have occurred approximately midway through the scan. It is hypothesized that this reflects an apparent shift in diaphragm position as the dominant hemisphere in the field-of-view shifted from left to right. Indeed, subtle anatomic differences over certain imaging angles appear to yield corresponding differences in the visibility of the surrounding structures. Additionally, the breathing traces for Patient 5 were characterised by their large amplitude.

As shown in Table 1, Patient 5 exhibited the widest range in terms of tumor motion. This was due, in part, to a rapid spike resembling a cough during the first scan for Patient 5. As a consequence, Patient 5 also exhibited the largest 95th percentile error along the SI axis at 6.7 mm.

3.2 Diaphragm-marker correlation

The mean ± standard deviation of diaphragm-marker correlations over all image sequences was -0.07 ± 0.57, 0.67 ± 0.49 and 0.29 ± 0.52 in the LR, SI and AP directions respectively. Critically, the SI axis represented the predominant direction of marker motion for every patient, except Patient 4 who presented with an upper lobe tumor and exhibited the lowest correlation along this axis. Conversely, correlations along the SI axis ranged over 0.91 – 0.93 for Patients 3, 5 and 6 who presented with lower lobe tumors and over 0.76 – 0 .79 for Patients 1 and 2 who presented with middle lobe tumors. These data are summarized in Table 4.

4. Discussion

The proposed methodology has two important clinical implications for respiratory motion management. First, strong correlations between the diaphragm and the lung[21] as well as the liver,[25] open up the possibility of using the proposed method to achieve markerless tumor tracking for both cancer sites. Indeed, one could envisage extending the benefits of direct diaphragm tracking to lesions in additional thoracic and abdominal organs such as the pancreas. Second, direct extraction of diaphragmatic motion from CBCT scans provides more accurate respiratory signals for 4D-CBCT projection binning. Indeed, as an anatomic

surrogate, the diaphragm offers more realistic representations of internal thoracic motion than its external counterparts.[26,27] Moreover, in contrast with projection-based techniques,[28,29] the proposed method extracts an absolute rather than relative respiratory signal, entirely de-coupled from gantry angle.

A key contribution of the present work consists in shifting the bulk of computational complexity prior to kV image acquisition. Indeed, the construction of pre-built models has three major advantages. First, pre-projection onto the detector space allows for two-dimensional mappings which reflect the three-dimensional nature of the underlying anatomy. Second, confining the maximal gradient search to a pre-determined window ensures robustness against extraneous and overlapping structures. Third, generating patient-specific maps prior to imaging drastically reduces computation time. When implemented in C# and run on an Intel® Core™ i7-6700HQ CPU @ 2.60GHz with 16 GB RAM, the proposed workflow was successfully executed at 80 – 120 ms per frame. This demonstrates the feasibility of the proposed method for real-time implementation.

One limitation of the present work is that ground truth positions were determined using implanted markers. While these methods typically provide an excellent surrogate for tumor motion, surrogacy errors can occur. For instance, errors ranging over 0 – 3 mm were reported in [21] for electromagnetic transponder beacons. Similarly, tumor localization errors ranging over 0.6 – 4.3 mm were observed in [20] for fiducial markers. However, 3D motion models were built only to demonstrate the feasibility of real-time tracking for targets influenced by respiratory motion and their precision should be read within this context.

In terms of tracking accuracy, we believe that there are three main reasons for differences between the tracked and actual diaphragm edges (Videos S1 – S6). First, the appearance of the diaphragm varies across imaging angles. Indeed, in this study, the largest

errors were observed for an imaging sequence in which the apparent position of the diaphragm differed as the left hemisphere became occluded from view and the algorithm began to track the right hemisphere. This yielded lower estimates of diaphragm position which, in turn, lead to mispredictions in tumor positon. It is hypothesized that these apparent changes in diaphragm position arise due to subtle differences in attenuation as the surrounding anatomic structures enter the field-of-view. However, it is envisaged that this may be overcome by tracking the left and right hemispheres of the diaphragm independently. Therefore, extending the workflow to account for this apparent independence will form the basis of future study.

Second, tracking errors were consistently more frequent when a smaller proportion of the diaphragm was visible within the field-of-view. As mentioned earlier, this arises because a reduction in the total number of visible pixels in the 2D model diminishes the differences between candidate positions in terms of their gradient-sums. Consequently, tracking performance may decrease in instances where markers are positioned distal to the diaphragm and the imaging isocenter is adjusted accordingly. Coupling this observation with the reported diaphragm-marker correlations it is anticipated that, given the current status quo, the proposed algorithm would impart the greatest benefit to those patients with lower- and middle-lobe tumors. However, it should be noted that the geometries of the image sequences studied in the present work, reflect an intent to track the tumor rather than the diaphragm. Therefore, these results can be taken to reflect a lower-bound for direct diaphragm tracking. Indeed, were the field-of-view expanded to encompass both the diaphragm and the tumor simultaneously, the benefits of this technology could be extended to a greater number of patients.

Finally, sudden changes in respiration may yield motion patterns which lie outside the narrowly-defined search windows. As mentioned in the Methods section, our algorithm uses a restricted search window based on previous diaphragm positions in order to ensure real-time implementation. However, in instances of coughing or deep inspiration, the algorithm may produce less accurate estimates of diaphragm position. Therefore, investigating the precise tuning of these windows to reflect both patient-specific respiration patterns and image acquisition rates should form the basis of future study.

In terms of 3D tumor motion estimation, the accuracy of the linear regression models strongly depended on marker location relative to the thoracic anatomy. On the one hand, close proximity of the marker to the heart can introduce nuance not captured by diaphragm tracking alone. On the other hand, close proximity of the marker to the diaphragm will induce larger overall motion ranges as well as more sudden changes in marker position. Therefore, there is great scope both for extending the proposed workflow to account for additional thoracic structures such as the heart and for exploring more sophisticated motion models.

5. Conclusion

The methods advanced in this paper achieve real-time direct diaphragm tracking on kV images acquired using a standard linear accelerator. A key contribution of this work consists in the ability to directly track diaphragm position as opposed to producing phase-based estimates. Simple linear regression between tracked diaphragm positions and ground truth marker positions yielded 3D motion models with mean errors of -0.1 ± 0.7 mm, -0.1 ± 1.8 mm and 0.2 ± 1.4 mm in the LR, SI and AP directions respectively. These results

demonstrate the feasibility of using the proposed method for real-time motion management during thoracic cancer irradiation. Extending tracking to additional thoracic structures as well as building more intricate models of internal anatomic motion will form the basis of future study.

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Disclosure of Conflicts of Interest

Varian Medical Systems have partially funded the patient study that enabled this analysis. The results of this work have led to the submission of a record of invention.

References

1. Suh Y, Dieterich S, Cho B, Keall P. An analysis of thoracic and abdominal tumour motion for stereotactic body radiotherapy patients. Physics in Medicine & Biology. 2008;53(13):3623.

2. Colien H, Max D, Hassan M, Lineke van der W, Ben S, Wilko V. Markerless positional verification using template matching and triangulation of kV images acquired during irradiation for lung tumors treated in breath-hold. Physics in Medicine & Biology. 2018;63(11):115005.

3. Lin T, Lin Y. Markerless Tumor Gating and Tracking for Lung Cancer Radiotherapy based on Machine Learning Techniques. In: Suzuki K, Chen Y, eds. Artificial Intelligence in Decision Support Systems for Diagnosis in Medical Imaging. Cham: Springer International Publishing; 2018:337-359.

4. Nguyen K, Haytmyradov M, Mostafavi H, et al. Evaluation of Radiomics to Predict the Accuracy of Markerless Motion Tracking of Lung Tumors: A Preliminary Study. Frontiers in oncology. 2018;8:292-292.

5. Yan H, Tian Z, Shao Y, Jiang SB, Jia X. A new scheme for real-time high-contrast imaging in lung cancer radiotherapy: a proof-of-concept study. Physics in medicine and biology. 2016;61(6):2372-2388.

6. Harada T, Shirato H, Ogura S, et al. Real-time tumor-tracking radiation therapy for lung carcinoma by the aid of insertion of a gold marker using bronchofiberscopy. Cancer. 2002;95(8):1720-1727.

7. Shah AP, Kupelian PA, Waghorn BJ, et al. Real-Time Tumor Tracking in the Lung Using an Electromagnetic Tracking System. International Journal of Radiation Oncology*Biology*Physics. 2013;86(3):477-483.

8. Booth JT, Caillet V, Hardcastle N, et al. The first patient treatment of electromagnetic-guided real time adaptive radiotherapy using MLC tracking for lung SABR. Radiotherapy and Oncology. 2016;121(1):19-25.

9. Geraghty PR, Kee ST, McFarlane G, Razavi MK, Sze DY, Dake MD. CT-guided Transthoracic Needle Aspiration Biopsy of Pulmonary Nodules: Needle Size and Pneumothorax Rate. Radiology. 2003;229(2):475-481.

10. Nelson C, Starkschall G, Balter P, Morice RC, Stevens CW, Chang JY. Assessment of lung tumor motion and setup uncertainties using implanted fiducials. International Journal of Radiation Oncology*Biology*Physics. 2007;67(3):915-923.

11. van der Voort van Zyp NC, Hoogeman MS, van de Water S, et al. Stability of Markers Used for Real-Time Tumor Tracking After Percutaneous Intrapulmonary Placement. International Journal of Radiation Oncology*Biology*Physics. 2011;81(3):e75-e81.

12. Imura M, Yamazaki K, Shirato H, et al. Insertion and fixation of fiducial markers for setup and tracking of lung tumors in radiotherapy. International Journal of Radiation Oncology*Biology*Physics. 2005;63(5):1442-1447.

13. Hong JC, Eclov NCW, Yu Y, et al. Migration of implanted markers for image-guided lung tumor stereotactic ablative radiotherapy. Journal of applied clinical medical physics. 2013;14(2):4046-4046.

14. Takamiya M, Nakamura M, Akimoto M, et al. Multivariate analysis for the estimation of target localization errors in fiducial marker-based radiotherapy. Medical Physics. 2016;43(4):1907-1912.

15. Hardcastle N, Booth J, Caillet V, et al. MO-FG-BRA-06: Electromagnetic Beacon Insertion in Lung Cancer Patients and Resultant Surrogacy Errors for Dynamic MLC Tumour Tracking. Medical Physics. 2016;43(6Part31):3710-3711.

16. Kubo H, Hill B. Respiration gated radiotherapy treatment: a technical study. Physics in Medicine & Biology. 1996;41(1):83.

17. Vedam SS, Kini VR, Keall PJ, Ramakrishnan V, Mostafavi H, Mohan R. Quantifying the predictability of diaphragm motion during respiration with a noninvasive external marker. Medical Physics. 2003;30(4):505-513.

18. Berbeco RI, Nishioka S, Shirato H, Chen GTY, Jiang SB. Residual motion of lung tumours in gated radiotherapy with external respiratory surrogates. Physics in Medicine and Biology. 2005;50(16):3655-3667.

19. Zhang Q, Pevsner A, Hertanto A, et al. A patient-specific respiratory model of anatomical motion for radiation treatment planning. Medical Physics. 2007;34(12):4772-4781.

20. Wei J, Chao M. A constrained linear regression optimization algorithm for diaphragm motion tracking with cone beam CT projections. Physica Medica. 2018;46:7-15.

21. Cerviño L, Chao A, Sandhu A, Jiang S. The diaphragm as an anatomic surrogate for lung tumor motion. Physics in Medicine & Biology. 2009;54(11):3529.

22. Karami E, Wang Y, Gaede S, Lee T-Y, Samani A. Anatomy-based algorithm for automatic segmentation of human diaphragm in noncontrast computed tomography images. Journal of medical imaging (Bellingham, Wash). 2016;3(4):046004-046004.

23. Sundarapandian M, Kalpathi R, Siochi RAC, Kadam AS. Lung diaphragm tracking in CBCT images using spatio-temporal MRF. Computerized Medical Imaging and Graphics. 2016;53:9-18.

24. Roman NO, Shepherd W, Mukhopadhyay N, Hugo GD, Weiss E. Interfractional Positional Variability of Fiducial Markers and Primary Tumors in Locally Advanced Non-Small-Cell Lung Cancer During Audiovisual Biofeedback Radiotherapy. International Journal of Radiation Oncology*Biology*Physics. 2012;83(5):1566-1572.

25. Yang J, Cai J, Wang H, et al. Is diaphragm motion a good surrogate for liver tumor motion? International journal of radiation oncology, biology, physics. 2014;90(4):952-958.

26. Yan H, Yin F-F, Zhu G-P, Ajlouni M, Kim JH. The correlation evaluation of a tumor tracking system using multiple external markers. Medical Physics. 2006;33(11):4073-4084.

27. Hoisak JDP, Sixel KE, Tirona R, Cheung PCF, Pignol J-P. Correlation of lung tumor motion with external surrogate indicators of respiration. International Journal of Radiation Oncology*Biology*Physics. 2004;60(4):1298-1306.

28. Zijp L, Sonke JJ, van Herk M. Extraction of the Respiratory Signal from Sequential Thorax Cone-Beam X-Ray Images. 2004.

29. Yan H, Wang X, Yin W, et al. Extracting respiratory signals from thoracic cone beam CT projections. Physics in Medicine and Biology. 2013;58(5):1447-1464.

Figure 1. A pictographic representation of the workflow for the proposed diaphragm tracking method.

Figure 2. Tracking performance for the image sequence with the lowest mean SI error, including (a) individual projections overlaid with tracked diaphragm models, in blue and (b) motion traces for the ground truth marker position, in green, and the retrospective correlation model, in blue, along each axis (below). The shaded region corresponds to the data used for training. The panels in Figure 2a indicate instances where the algorithm has accurately registered the diaphragm. This results in 3D marker position estimates with low error as shown in Figure 2b.

Figure 3. Tracking performance for the image sequence with the highest mean SI error, including (a) individual projections overlaid with tracked diaphragm models, in blue and (b) motion traces for the ground truth marker position, in green, and the retrospective correlation model, in blue, along each axis (below). The shaded region corresponds to the data used for training. In the third panel of Figure 3a, the algorithm misregisters the diaphragm due to an apparent difference in hemisphere position. This yields persistent mispredictions in tumor position as seen for the remainder of the scan in Figure 3b.

Table 1 Patient characteristics. RML means right middle lobe; RLL means right lower lobe; LML means left middle lobe; LLL means left lower lobe; LUL means left upper lobe; SABR means stereotactic ablative body radiotherapy; LR means left-right direction; SI means superior-inferior direction; AP means anterior-posterior direction

Patient	Dataset	Number of image sequences	Tumor location	Motion range (mm)[a]		
				LR	SI	AP
1	4D-Lung	4	RML/RLL	2.3 [0.7]	7.1 [1.0]	2.0 [0.3]
2	4D-Lung	5	LML	2.3 [0.6]	8.6 [2.2]	4.4 [0.9]
3	4D-Lung	5	LLL	0.9 [0.2]	13.0 [4.5]	4.0 [0.7]
4	LIGHTSABR	3	LUL	6.5 [0.2]	5.4 [0.9]	7.5 [0.4]
5	LIGHTSABR	2	RLL	3.2 [1.5]	17.9 [0.2]	6.1 [1.5]
6	LIGHTSABR	3	LLL	1.2 [0.2]	3.9 [0.5]	2.5 [0.4]
Overall	-	22	-	2.5 [1.9]	9.1 [4.8]	4.2 [1.9]

[a] Motion range is reported as the mean [standard deviation] of the 5^{th} to 95^{th} percentile difference in marker position for all image sequences

Table 2 Mean and standard deviation of the estimation errors across all image sequences. LR means left-right direction; SI means superior-inferior direction; AP means anterior-posterior direction.

Patient	Mean error [standard deviation] (mm)		
	LR	SI	AP
1	0.0	0.1	0.2
	[0.6]	[1.2]	[0.7]
2	-0.3	-0.3	0.3
	[0.8]	[1.9]	[1.6]
3	0.0	-0.5	0.3
	[0.2]	[1.9]	[1.5]
4	-0.5	0.2	0.0
	[1.5]	[1.8]	[2.0]
5	-0.1	0.7	0.5
	[0.9]	[3.3]	[2.3]
6	-0.2	0.2	-0.3
	[0.5]	[0.7]	[0.5]
Overall	-0.1	-0.1	0.2
	[0.7]	[1.8]	[1.4]

Table 3 Mean 95th percentile of the absolute errors across all image sequences. LR means left-right direction; SI means superior-inferior direction; AP means anterior-posterior direction.

Patient	95th percentile error (mm)		
	LR	SI	AP
1	1.3	2.3	1.5
2	1.9	3.9	3.2
3	0.5	4.2	2.8
4	3.1	3.4	4.0
5	1.9	6.7	3.1
6	1.1	1.6	1.2

Table 4 Diaphragm-marker correlation. LR means left-right direction; SI means superior-inferior direction; AP means anterior-posterior direction.

Patient	Mean Pearson correlation coefficient [standard deviation]		
	LR	SI	AP
1	0.14 [0.48]	0.76 [0.06]	0.5 [0.12]
2	-0.21 [0.51]	0.79 [0.13]	0.47 [0.25]
3	-0.35 [0.61]	0.93 [0.03]	0.00 [0.30]
4	0.78 [0.05]	-0.50 [0.11]	-0.68 [0.06]
5	-0.59 [0.08]	0.91 [0.08]	0.78 [0.12]
6	-0.16 [0.11]	0.91 [0.01]	0.84 [0.05]
Overall	-0.07 [0.57]	0.67 [0.49]	0.29 [0.52]