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Esophagus and spinal cord motion relative to GTV motion in four-dimensional CTs of lung cancer patients

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Summary

Respiration-related variations in the distance between the center of mass of gross tumor volume and both esophagus and spinal cord in the transversal plane were on average 3 mm (range 1-10 mm) and 2 mm (range 1-5 mm), respectively. Depending on the tumor location and treatment technique, variations might become important for treatment planning.

Keywords

Four-dimensional computed tomography; lung cancer; radiotherapy; respiratory motion; normal tissue

Introduction

Temporospatial tumor variations are increasingly being investigated with the aim to improve tumor targeting, reduce dose to normal tissue and potentially escalate tumor dose. Radiotherapy of the thorax region is a particularly challenging task due to intrafractional respiratory motion. For established methods that account for respiratory tumor motion such as gating [1,2] or treatment techniques currently in development such as real-time tumor tracking [3,4], the main focus of respiration management has been to target tumor motion.

With higher treatment conformality and increasing tumor doses normal tissue toxicity has become a dose limiting factor [5]. Besides lung and heart, spinal cord and esophagus are among the most critical organs at risk in patients undergoing radiotherapy for thoracic tumors. For physiological reasons thoracic motion does not only affect lung tumors, but all intrathoracic structures including esophagus and spinal cord. Four-dimensional CTs (4D CTs) allow measurement of respiration-related motion of tumor, normal tissue and their relative positional variations during respiration [6,7]. In the present analysis GTV motion relative to esophagus and spinal cord motion are measured based on 4D CTs. The inclusion of information on normal

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tissue variations in treatment planning enables selection of appropriate breathing phases for treatment and a more accurate estimate of the delivered dose.

Material and Methods

Data acquisition

This study is based on 4D CTs of 14 patients with lung cancer ranging from stage T1N0 to T3N2 and T4N0. The tumor volume ranged from 1.1 to 317.7 cm³. For a detailed description see reference [7].

For all patients, respiration-correlated 4D CTs were acquired on a 16-slice CT scanner in cine mode (GE Healthcare Technologies, Waukesha, WI) using the respiration-monitoring system RPM (Varian Medical Systems, Palo Alto, CA). No contrast agent was applied. Images were binned with equal length in 10 respiratory phases T0 to T9 with T0 representing end-inspiration and T5 approximately end-expiration.

Image segmentation

Image segmentation was performed manually by four experienced observers for all patients and all phases using Pinnacle, Version 6.2 and 7.7 (Philips Medical Systems, Milpitas, CA). To avoid contouring errors the following steps were taken:

- Contouring followed a detailed protocol.
- To avoid interobserver variations, all structures of one patient were delineated by one observer.
- To reduce intraobserver errors, observers were encouraged to reference contours of other phases of the same structure.
- All contours were inspected for consistency by one observer.
- All contours were compared with automatically created contours using deformable image registration [8].

For the purpose of this study, contours of the gross tumor volume (GTV), the esophagus and spinal cord were relevant. GTV, esophagus and spinal cord were contoured slice by slice for all respiratory phases. The GTV was defined as all macroscopic tumor, including lymph nodes with a diameter of at least 1 cm in the short axis on CT. Esophagus and spinal cord were contoured over the complete craniocaudal extension of the CT scan. In transversal directions, the spinal cord was contoured using a circular contour with a diameter chosen according to the individual anatomy, while the esophagus contour was based on the outer esophageal wall contour. For contouring, the CT window level was adjusted on the location of the respective structure, e.g., lung window, if the GTV was located in the lung, thorax window for esophagus and spinal cord or GTVs infiltrating the mediastinum.

Data analysis

Since esophagus and spinal cord extend beyond the range of a regular thorax CT and centroid motion could therefore not be measured in three dimensions, all analyses were performed in transversal planes. Considering the serial structure of spinal cord and esophagus, circumscribed dose changes in short sections of these two organs are highly relevant. Analysis of organ motion in the transversal plane is therefore particularly important.

The transversal plane for analysis of each respiratory phase was defined as the CT slice containing the centroid (center of mass) of the GTV.

The calculation of organ location and respiratory motion was performed using IDL (RSI, Boulder, CO). The distance of the GTV centroid to the center of the esophagus and spinal cord in a reference breathing phase (end-inspiration, or T0) as well as respiration-related motion of each of the three structures per se was calculated. For the latter, the average maximum vector length of respiration-related centroid motion of GTV, esophagus and spinal cord in the transversal plane was measured by calculating the maximum path length of centroid motion during the respiratory cycle for each patient and averaging the results over all patients for each structure.

The variations in distance of the GTV centroid relative to the centers of esophagus and spinal cord were calculated for all respiratory phases and normalized to the distance in end-inspiration (T0). To calculate the average maximum variation in distance, the maximum amount of variation in distance between GTV and esophagus or spinal cord observed in each patient was averaged over all patients. The amount of organ displacement towards versus away from each other was compared and tested for significance using a two-tailed t-test with significance being assumed for $p < 0.05$. Variations in GTV-esophagus and GTV-spinal cord distance were compared for the position of the GTV centroid relative to mediastinal structures. Due to the limited number of patients and the large amount of potential variables that potentially influence respiratory motion, no attempt was made to relate clinical and anatomical findings with variations in GTV, esophagus and spinal cord motion.

Results

Position and motion of GTV, esophagus and spinal cord

In end inspiration the distance of the GTV centroid to the center of the esophagus in the same transversal plane, averaged over all patients, was 5.1 cm (range 1.2 – 7.8 cm) and to the center of the spinal cord 7.6 cm (range 5.1 – 11.3 cm).

The average maximum vector lengths were 4 mm (range 1 to 11 mm), 2 mm (range 1 to 5 mm) and 1 mm (range 0 to 2 mm) for GTV, esophagus and spinal cord, respectively, and ranged in mediolateral direction from 1 to 6 mm, 0 to 5 mm and 0 to 1 mm and in anteroposterior direction from 1 to 10 mm, 0 to 2 mm and 0 to 2 mm, respectively, with the spinal cord motion being smallest.

Displacement of GTV relative to esophagus and spinal cord in the transversal plane

Figure 1a and b show the displacement for esophagus and spinal cord relative to GTV. Normalized to end inspiration the maximum amount of variation in GTV centroid position relative to the esophagus was on average 3 mm (range 1-10 mm) and relative to the spinal cord 2 mm (range 1-5 mm). A relative displacement between GTV centroid and esophagus/spinal cord > 3 mm was observed in 3 patients each. During expiration the distance between GTV centroid and esophagus/spinal cord became smaller (negative numbers) in 8 and 7 of 14 patients and larger in 6 and 7 of 14 patients (fig. 1). When considering the direction of displacement (distance becoming larger or smaller), the maximum variation in the distance between GTV and esophagus/spinal cord averaged over all patients was less than 1 mm for both esophagus and spinal cord. The amount of displacement towards versus away from each other did not differ significantly both for GTV-esophagus and GTV-spinal cord ($p > 0.05$). An example of GTV, esophagus and spinal cord location for in- and expiration is shown on corresponding 4D CT scans in figures 2 a and b.

The measurement position for the relative motion of the GTV centroid relative to esophagus and spinal cord was in the aortic arch area in 3, at the carina level in 7 and in the lower mediastinum in 4 patients. Relative motion of GTV to esophagus was on average 3 mm at the

aortic arch level, 2 mm at the carina level and 4 mm in the lower mediastinum, for spinal cord it was 4 mm, 2 mm and 1 mm. Increase or decrease in distance was not related to the location of the GTV.

Discussion

Upper dose levels in lung cancer radiotherapy have mostly been confined by normal tissue toxicity with esophagus and spinal cord being among the most relevant organs [5]. Improved tumor targeting and normal tissue sparing would therefore facilitate dose increases to the tumor and potentially increase tumor control.

In the present study both respiration-related esophagus and spinal cord motion were observed with esophagus motion being larger than spinal cord motion, and both being smaller than GTV motion in the transversal plane. The observed amount of esophagus motion in our study was similar to the results by Dieleman et al. [9] and Yaremko et al. [10] also using 4D CTs. It was less compared to the motion found at the gastroesophageal junction where motion due to respiration and motion of the diaphragm is largest [11]. Data using implanted markers showed larger motion which is probably due to a longer observation time [12,13].

The observed maximum spinal cord motion was 2 mm. We believe that the actual amount of spinal cord motion is minimal in supine patient position [14]. Part of the spinal cord motion should therefore be attributed to contouring variations that occur also in the presence of a well-designed contouring procedure and a well visualized structure. Imaging artifacts in 4D CTs are relevant mostly in craniocaudal direction where most of the respiration occurs and should have only limited influence on the present study looking at displacement in the transversal plane.

More important for treatment planning than organ motion per se, is how the distance between tumor and normal tissue varies during treatment. The distance between GTV centroid and esophagus/spinal cord increased between inhale and exhale in about half of the cases, respectively, despite the lung volume decreasing from inhale and exhale. This means that for tumor coverage with maximal esophagus or spinal cord sparing it cannot be predicted *a priori* which phase would be most appropriate for respiratory-gated delivery.

We did not observe any relation between the measurement location in the mediastinum and an increase or decrease in the distance of GTV and normal tissue structure. With the GTV contributing most to distance variations, factors like tumor size, fixation to thoracic wall or mediastinal invasion might play a more important role, but were not investigated because of the limited patient number. The distance between GTV and esophagus or spinal cord may change differently from phase to phase due to differences in the motion of each structure and organ deformation. Variations in the distance therefore depend on complex 3D motion patterns. While the present study focuses on centroid motion, organ deformation and consecutive variations in the distance of organ surfaces might also play a role in the spatial variations during respiration.

11/14 patients showed changes in the distance between GTV and esophagus/spinal cord of less than 3 mm. Relative displacement in the observed range is important particularly for settings where esophagus or spinal cord are located in the steep dose gradient of the planning target volume where small motion results in large dose variations. The observed displacements of up to 10 mm for GTV relative to esophagus and 5 mm for GTV relative to spinal cord are therefore relevant for highly conformal treatment techniques, such as intensity modulated radiotherapy [15] and particularly stereotactic radiotherapy with high single fractions, in connection with respiration management methods. When using gated treatment, selection of respiration phases where the distance of GTV and esophagus/spinal cord is largest would therefore be useful to

spare normal tissue and to increase the therapeutic ratio. As can be observed from fig. 1, this selection is patient-dependent.

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Figure 1a

Figure 1b

Figure 1.

Figure 1a: Respiration-related esophagus displacement relative to GTV centroid for 14 lung cancer patients. Displacement is normalized to end inspiration. Negative numbers on the y-axis indicate GTV and esophagus moving towards each other, positive numbers indicate GTV and esophagus moving away from each other.

Figure 1b: Respiration-related spinal cord displacement relative to GTV centroid for 14 lung cancer patients. Displacement is normalized to end inspiration. Negative numbers on the y-axis indicate GTV and spinal cord moving towards each other, positive numbers indicate GTV and spinal cord moving away from each other.

Figure 2.

Respiratory motion of GTV relative to esophagus and spinal cord. Change in distance between a) inspiration and b) expiration in CT slices containing the GTV centroid. The GTV (red), the centroid of the GTV (blue), the esophagus (green) and the spinal cord (yellow) are shown. The distance of GTV centroid to center of esophagus is 8.1 cm in inspiration and 7.1 cm in expiration, the distance of GTV centroid to spinal cord is 7.2 cm in inspiration and 7.4 cm in expiration. The GTV centroid motion in craniocaudal direction is 2.5 cm during respiration.