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Original Article

# Predictors of Respiratory-induced Lung Tumour Motion Measured on Four-dimensional Computed Tomography

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## Abstract

*Aims:* The delivery of radical radiotherapy in lung cancer is complicated by respiratory-induced tumour motion. The aim of the study was to correlate tumour motion characteristics with tumour and patient factors, particularly the anatomical lobe and pulmonary zone.

*Materials and methods:* Lung tumour volumes on four-dimensional computed tomography were delineated by a single observer at maximal expiration and propagated through all 10 phases of the breathing cycle. Movements were tracked in the superior–inferior (SI), anterior–posterior (AP) and medio-lateral (ML) directions by changes in the tumour centroid coordinates. Tumour motion characteristics were correlated with anatomical lobe, pulmonary zone, tumour volume, T-stage, smoking status and spirometry.

*Results:* In 101 consecutive patients, the median magnitude of tumour motion in the SI direction was significantly larger in tumours located in lower lobes compared with upper lobes and middle/lingular lobes (0.70 cm versus 0.09 cm versus 0.26 cm, $P < 0.01$). No significant difference was found in median tumour motion between lower, upper and middle/lingular lobes in the AP (0.16 cm versus 0.13 cm versus 0.16 cm, $P = 0.45$) and ML (0.08 cm versus 0.08 cm versus 0.13 cm, $P = 0.32$) directions, respectively. When assessed by zone, the median tumour displacement in the SI direction was significantly larger in the lower zones (0.81 cm) as compared with the middle zones (0.30 cm) and upper zones (0.11 cm), $P < 0.01$. No difference was observed in the AP ($P = 0.45$) and ML ($P = 0.73$) directions. Tumour volume, T-stage and forced expiratory ratio were not statistically significant predictors of respiratory-induced tumour motion.

*Conclusion:* Respiratory-induced tumour motion in the SI direction was significantly greater in lower lobe and lower pulmonary zone tumours compared with apical tumours. Tumour volume, T-stage and spirometry did not correlate with the magnitude or direction of respiratory-induced tumour motion. During curative radiotherapy in lung cancer, attention should be paid to motion management, especially for lower lobe tumours.


*Key words:* Four-dimensional computed tomography; motion; respiratory induced

## Introduction

Respiratory-induced lung tumour motion is a well-established cause of inter-fraction and intra-fraction geometric uncertainty during radiotherapy [1,2]. Traditional simulation methods rely on three-dimensional computed tomography (CT) for treatment planning, but this captures lung tumours at a random time point within the breathing cycle. Studies have shown that structures within the thorax can be significantly distorted during respiration, giving rise to motion artefact as well as ambiguity in tumour size, shape and position [3].

A uniform margin of tissue is added to the clinical target volume during planning, forming the internal target volume (ITV) that compensates for this phenomenon. The addition of standard respiratory motion margins, however, does not account for individual lung tumour movement. Consequently, ITV margins must be wide enough to prevent geographical miss during the delivery of high dose, radical

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radiotherapy. This can result in unnecessary irradiation of surrounding normal tissue, increasing the risk of treatment-related toxicities, such as oesophagitis, lung fibrosis and radiation pneumonitis [4–6].

Numerous motion management techniques have been used during radiotherapy delivery, many of which are described in a recent review article by Cole *et al.* [7]. They divide these strategies into the broad categories: imaging, breath-hold, abdominal compression, tracking and gating. Specifically, several imaging modalities have been used to characterise respiratory-induced tumour motion, including fluoroscopy, breath-hold CT scans and dynamic magnetic resonance imaging studies [8–11]. Trials using real-time tracking of fiducial markers have also been conducted, showing the greatest movement in the superior–inferior (SI) direction in tumours located within the lower lobes [12]. In recent years, the advent of four-dimensional CT (4DCT) has further improved our ability to image tumour motion throughout respiration [13–15]. The clinical role of 4DCT in radiotherapy planning has evolved over the last decade, giving rise to improved gross tumour volume (GTV), ITV and planning target volume delineation [16,17].

This study was designed to evaluate the magnitude and direction of respiratory-induced lung tumour motion using 4DCT, in patients treated with radical radiotherapy. We tested for associations between tumour motion and patient and tumour characteristics. We hypothesised that the magnitude and direction of lung tumour motion can be predicted based on tumour and patient factors.

## Materials and Methods

This was a single-institutional, retrospective study of radical lung cancer patients of the Peter MacCallum Cancer Centre with accessible 4DCT scans between December 2009 and May 2013. This study was approved by the Ethics Committee of the Peter MacCallum Cancer Centre (reference number 13/105).

### *Patient Data Collection*

Patients eligible for this study had a diagnosis of lung cancer and also underwent 4DCT planning for radical radiotherapy in the treatment position (arms up) on a flat table top. Identical CT scanners at different campuses were used. Maximum intensity projection and average intensity projection image sets were archived. As such, not all full 4DCT sets were available for evaluation. Only patients with accessible 4DCT images were included. Exclusion criteria in this study included 4DCT images of inadequate quality, non-identifiable GTV (T0), extensive tumours involving chest wall or pleural invasion as defined by tumour contact with pleural surface or mediastinal invasion (T4). Patients with co-morbid disease considered to significantly compromise respiration were also excluded from the study. These conditions included very large pleural effusions, phrenic nerve palsy or tumours associated with lobar collapse. Although we did not exclude patients based on tumour size, most patients recruited into our study had T1 or T2 disease.

Patient information was retrospectively collected and included patient age, gender, coexisting respiratory disease, respiratory function tests and smoking status. Tumour characteristics were collected and included anatomical lobe, pulmonary zone, tumour volume and T-stage. Anatomical lobe was classified as upper, lower or middle/lingular lobes. Tumour volume (ml) was measured by the analysis software at the $T_{50\%}$ phase. The pulmonary zone was determined by dividing the maximum lung vertical dimension into thirds.

### *Simulation Four-dimensional Computed Tomography Scans*

At the Peter MacCallum Cancer Centre, all patients were simulated in the arms-up position. A respiratory-sorted 4DCT dataset was generated using the Philips Brilliance® Widebore (Royal Philips Electronics, Amsterdam, the Netherlands) CT scanner coupled with a Philips Bellows System®. The bellows system consisted of an elasticised belt worn around the abdomen that expanded and contracted with respiratory motion. The bellows contained a pressure transducer that converted the pressure waveform into a voltage signal, which was digitised and transmitted to the CT scanner. The resultant data were presented as a trace demonstrating respiratory motion and the calculated number of breaths per minute. The calculated respiratory rate was used to select an appropriate pitch for couch motion during CT scanning. The CT scanner was commissioned to acquire 4DCT scans in helical mode and to bin the CT slices into 10 phases for image reconstruction. The patients were imaged using 140 kVp, 3 mm slice thickness, 3 mm increment and 0.44 s rotation time; images were reconstructed with $\sim$35 $mm^3$ voxel resolution (3 mm slice thickness $\times$ 1.0742 mm pixel spacing). The images were sorted into 10 datasets, corresponding to 10 equally spaced phases of the respiratory cycle, in which $T_{50\%}$ represented the end-expiratory point and $T_{0\%}$ represented the end-inspiratory point.

### *Image Analysis Methodology*

4DCT image datasets were analysed using MIM v5.6 software (MIM Software Inc., Cleveland, Ohio, USA). GTVs were delineated by a single observer in the maximal expiration phase ($T_{50\%}$). Subsequent volumes were delineated through the respiratory cycle using a deformable propagation algorithm of MIM. Immediately following the propagation process, GTV contours on all 10 phases were verified for accuracy and corrected if necessary. Tumour movements were tracked in the SI, anterior–posterior (AP) and mediolateral (ML) directions by a single observer, through changes in the GTV centroid coordinates.

### *Statistical Analyses*

The greatest distance in lung tumour motion for each patient was obtained from the MIM software. These measurements were recorded in the AP, SI and ML directions