Fluoroscopy as a surrogate for lung tumour motion

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Objectives: The aim of this article was to test a simple approach of using pixel density values from fluoroscopy images to enable gated radiotherapy.

Methods: Anterior and lateral (LAT) from images were acquired from 18 patients referred for radical radiotherapy for non-small cell lung cancer for a period of 30–45 s. The amplitude of movement and the number of breathing cycles were determined in the right–left (RL) and superoinferior (SI) directions on the anterior images and the anteroposterior (AP) and SI directions on the lateral images. The breathing pattern was created by analysing the variation in a summation of pixel values within a defined area. The greatest and lowest 30% of pixel values were set as the duty cycle to represent inhale and exhale amplitude-based gating.

Results: A median of eight breathing cycles was captured for each patient with a duration of 2.2–11.8 s per cycle. The mean (range) motion was 4.7 mm (2.4–5.8 mm), 7.2 mm (2.3–17.6 mm), 6.2 mm (1.9–13.8 mm) and 4.8 mm (2.4–11.3 mm) in the RL, SI (AP), SI (LAT) and AP directions, respectively. A total of 10/14 anterior videos and 7/11 LAT videos had correlations between motion and breathing of >0.6. Margins of 5.5 mm, 6.8 mm and 6.6 mm in the RL, SI and AP directions, respectively, were determined to gate in exhale. The benefit of gating was greater when motion was >5 mm.

Conclusion: The simple approach of using pixel density values from fluoroscopy images to distinguish inhale from exhale and enable gating was successfully applied in all patients. This technique may potentially provide an accurate surrogate for tumour position.

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Tumour motion remains one of the challenges when delivering radical radiotherapy, particularly in lung cancer. The large margins required to encompass motion can increase the radiation dose to normal tissue. Techniques used to reduce margins involve synchronising the treatment delivery to the motion, which conventionally requires a surrogate for tumour location. Such surrogates for tumour location include infrared marker blocks placed on the xiphoid process (RPM; Varian Medical systems, Palo Alto, CA), spirometers [1] and temperature of breathing airflow [2].

Fluoroscopy has been used to determine lung tumour motion either on its own [3, 4] or in combination with CT [5], and has the advantage of being available on the majority of the new generation linear accelerators. However, verifying the tumour position using fluoroscopy either requires the tumour to be visible or requires markers to be implanted in the tumour. Implanting markers is an invasive procedure with associated morbidity, which lung cancer patients may not tolerate.

This study tests a simple approach of using pixel density values from fluoroscopy images as a surrogate of tumour motion [6], to distinguish inhale from exhale and to enable gated radiotherapy and subsequent margin reduction.

Methods and materials

The study protocol was approved by the local committee for clinical research and the local research ethics committee.

Determination of motion

Patients referred for radical radiotherapy for non-small cell lung cancer were invited to participate in the study and 18 consented for extra fluoroscopy screening at the time of the plan verification appointment in a simulator. This was done after the simulation process, with the patient free breathing and without use of coaching techniques. Images were acquired and processed by a system designed in-house consisting of a video acquisition computer which contained a frame grabber and recorded the video onto a hard disk.

Anteroposterior (AP) and lateral (LAT) images were acquired from 18 patients at a rate of 25 frames per second during a period of 30–45 s from each direction and saved as audio video interleave (AVI) files.

Files were corrupted in 2 patients; therefore, 16 AP and LAT fluoroscopy AVI files were transferred to a second computer that ran Matlab (The Mathworks Inc., Natick, MA) scripts, first to remove the geometric distortion and rescale the images, then to allow the video frames to be outlined and finally to extract statistics of the outlines.

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Figure 1. Fluoroscopy image of a lung patient taken on a treatment simulator (a) without geometry correction and (b) with correction.

Geometric distortion was measured using a calibration phantom made of aluminium with a regular array of holes at 1 cm spacing. The image correction process first measured the distortion from the image of the phantom by identifying the position on the image of each hole in the phantom and then generating a polynomial that mapped real co-ordinates to the pixel position in the distorted image (geometric correction map [GCM]). The GCM was then applied to the distorted patient videos to provide a corrected video with a regular pixel spacing of 0.5 mm per pixel at 100 cm from the source. A frame of an uncorrected and a corrected image is shown in Figure 1. The distorted field wires can be seen in

Figure 1a and the straightened (corrected) edges in Figure 1b.

After geometric correction, one clinician outlined the tumour by defining it on the first frame and then scrolling through each frame and re-outlining when tumour movement was observed. Tumour characteristics and digitally reconstructed radiographs with the gross tumour volume superimposed were available to aid the clinician in defining the tumour volume. The statistics gathered using the Matlab script from the outlining were centroid position and area. The amplitude of movement was then determined from the change of centroid position in the right-left (RL) and superoinferior (SI)

Figure 2. An example of one patient's breathing trace (determined by pixel density) and measured motion trace. Bold represents inhale threshold for gating.

Figure 3. Anterior image showing tumour positions in patients screened with fluoroscopy. Numbers 12 and 16 were unable to be outlined.

direction on the anterior images and the AP and SI direction on the LAT images. The number of complete breathing cycles during the fluoroscopy period was counted. The motion measured by the outlining was manually compared with the video images by another observer.

Deformation of tumour during breathing was observed during the breathing cycle, and this was quantified by comparing the movement of the edges of the tumour with the movement of the centre of mass.

Determination of breathing traces for gating

The method for determining the breathing trace from the fluoroscopy images has been described previously [6]. In brief, the breathing pattern is created by analysing the variation in a summation of pixel values within a defined area, with the defined area being hand selected to maximise the breathing pattern signal. The differences in the pixel summation values are due to higher or lower density tissue, *e.g.* tumour or diaphragm, passing through the defined area. The pixel summation method was applied to the fluoroscopy videos to create breathing traces, an example of which is shown in Figure 2.

The pixel summation trace may not be in phase with either the outlined motion traces or their vector sum. A phase shift arises as a result of measuring different parameters and the arbitrary selection of limits for the pixel summation. This phase shift is, however, constant and thus can be easily removed by adding a further phase shift. As such, the pixel summation trace was phase shifted to match a trace formed from the vector sum of both motion traces. As the pixel summation limits are arbitrary, so are the absolute values; thus, the range was also rescaled to match the motion trace. Finally, the Pearson correlation coefficient between the vector motion traces and their respective breathing traces were calculated to determine the degree of linear relationship. The Pearson correlation coefficient was used because the data were continuous and normally distributed.

The centroid position was merged with the breathing trace data using the frame number as a time reference. To simulate gating using the amplitude, the duty cycle was set at the greatest 30% of pixel values and the lowest 30% of values to represent inhale and exhale. A 30% duty cycle was chosen to correspond to the typical duty cycle of 20–30% in other studies; longer cycles, for example of 50%, have been shown to increase residual motion [7, 8]. An example of the duty cycle for inhale is shown in

Table 1. Fluoroscopy time, number of breathing cycles acquired and seconds taken per cycle

	Time (s), median (range)	No. of breathing cycles, median (range)	Duration of breathing cycles (s), median (range)
Anterior	32 (23.4–44.2)	8 (5–17)	4.2 (2.5–6.4)
Lateral	37 (6.8–44.1)	8 (2–17)	4.1 (2.2–11.8)

Table 2. Maximum amplitude motion in each individual patient as measured by fluoroscopy in order of tumour size

Study number	Anterior images (mm)		Lateral images (mm)		Area (mm ²)	
	Max. RL (mm)	Max. SI (mm)	Max. SI (mm)	Max. AP (mm)	Anterior	Lateral
8	2.8	3.8	4.5	4.1	313	826
11	5.1	17.6	12.5	4.1	1001	1417
7	3.4	14.8	5.7	7.8	1169	1527
19	4.5	5.1	n/a	n/a	1183	n/a
10	5.8	6.1	n/a	n/a	1187	n/a
18	5.2	3.5	n/a	n/a	1277	n/a
15	2.4	6.2	4.3	4.8	1512	1612
9	2.5	2.5	3.2	3.3	1672	2244
17	3.9	6.0	8.1	3.7	1676	1986
14	4.9	15.3	13.8	11.3	1867	1719
2	2.4	2.3	3.6	2.7	2014	2349
13	4.1	4.8	3.3	2.4	2144	4277
3	5.8	5.8	7.6	5.9	2788	2444
4	12.6	7	1.9	2.7	3361	2052

n/a, not applicable; RL, right-left; SI, superoinferior; AP, anteroposterior.

Figure 2. The standard deviation of the motion within the duty cycle (residual motion) was determined.

The relationship between inhale, exhale and pixel density was verified by observing the videos. A low-density value did not always correspond to inhale because of the structures used to define the breathing trace. The time spent in exhale and inhale as a percentage of the total time and the residual motion was determined. The margin for gating was calculated as:

$$2.5 \sum + 0.7\sigma[9] \quad (1)$$

This included the residual motion in inhale and exhale (S_{motion}) and the random patient set-up error ($S_{\text{set-up}}$), which was added in quadrature, and the systematic $S_{\text{set-up}}$ patient set-up error.

Results

Motion

Tumour location with respect to the carina for the 16 evaluable patients is shown in Figure 3. In three patients, the tumour was obscured by the vertebral bodies in the LAT view and in one further patient the tumour was obscured by the heart and spine in the AP and LAT views, respectively. For one patient, the AP images did not include the entire tumour and on the LAT image the tumour was not clearly identified. Consequently, 11 patients had both AP and LAT images outlined and 3 patients had AP anterior only.

Of the visible tumours, 2 were in the lower lobe (right lung) and 12 were in the upper and middle lobes (3 in the left lung and 9 in the right lung) (Figure 3).

A median of eight breathing cycles was captured for each patient with a duration of 2.2–11.8 s per cycle. Patients' breathing cycles were of similar duration in the two views even though they were acquired at two different time points. Only two patients had a >1 s difference between the AP and LAT images, both of which showed longer breathing cycles. Patient 3 increased from 6.4 s to 8.4 s and patient 14 from 5.4 s to 11.8 s (Table 1).

The amplitude of motion was greatest in the SI direction, followed by the AP and then the RL direction

(Table 2). The mean (range) of motion was 4.7 mm (2.4–12.6 mm), 7.2 mm (2.3–17.6 mm), 6.2 mm (1.9–13.8 mm) and 4.8 mm (2.4–11.3 mm) in the RL, SI (AP), SI (LAT) and AP directions, respectively. There are two measurements of the SI motion, one from the AP images and one from the LAT images, which were recorded 2–3 min apart. Movement >5 mm was seen in nine patients in the SI direction and seven had movement of >5 mm in at least one other direction. Additionally, in three patients, there was tumour movement of >10 mm in the SI direction; two of these tumours were located in the lower lobes. In two patients, motion of >10 mm, one in the AP and one in the RL direction, was observed.

The difference in the magnitude of motion in the SI direction between the AP and LAT images was <2 mm in eight patients and 5.1 mm, 9.1 mm and 5.1 mm in each of three patients.

There appeared to be no correlation between the tumour size and magnitude of movement.

Gating and breathing traces

Correlations between motion and breathing of >0.6 were found in 10 out of 14 anterior videos and 7 out of 10 LAT videos (Table 3). Examples of good correlation and poor correlation are shown in Figure 4.

Table 3. Correlation of two-dimensional motion vector and breathing trace

Patient no.	Correlation anterior	Correlation lateral
2	0.5	0.5
3	0.6	
4	0.6	0.6
7	0.8	0.6
8	0.6	0.8
9	0.4	0.1
10	0.7	n/a
11	0.6	0.9
13	0.2	0.4
14	0.7	0.8
15	0.9	0.7
17	0.9	0.7
18	0.3	n/a
19	0.6	n/a

The mean (range) phase shift was 0.59 s (0.045–1.66 s). The mean time (range) spent in inhale and exhale was 10.4 s (6–16 s) and 12.2 s (5.2–18.8 s), respectively, in the anterior videos, and 11 s (2–17.6 s) and 10.9 s (3.1–18.4 s), respectively, in the LAT videos. The time spent in exhale as a percentage of total breathing time was 37.5% (19–54%) in the AP views and 31% (11.5–59%) in the LAT

views. The time spent in inhale as a percentage of total breathing time was 35% (13–41%) in the AP and 36% (24–57%) in the LAT views. The irregularity in breathing cycles affected the time spent in inhale and exhale and the magnitude of the residual motion (Figure 5).

The residual motion in the inhale and exhale was not significantly different but was less than the maximum

Figure 4. Examples of breathing and motion traces with the corresponding scattergraphs in three different patients. (a,b) Illustrating poor correlation (patient 1); (c,d) illustrating strong correlation (patient 2); and (e,f) illustrating mid-correlation (patient 3).

Figure 5. Irregular breathing motion from (a) anteroposterior and (b) lateral views in a patient (patient 14), illustrating different times spent in inhale and exhale.

motion (Table 4). To establish the margins when using gating, the residual motion in exhale σ_{motion} and the random and systematic patient set-up error was used. The reduction in margin compared with a conventional margin of 10 mm, 15 mm and 10 mm in the RL, SI and AP directions, respectively, was greatest in the SI direction followed by the RL and then AP directions (Table 5).

Discussion

Determining motion

Prior to testing the use of fluoroscopy to gate radiotherapy treatments, it was necessary first to determine the motion. Using fluoroscopy and a video system developed in-house, images on 18 patients were captured and those from 16 patients were analysed. In two patients, data were corrupted; the reason for this is unknown. The tumour was more easily visualised in the anterior images than in the LAT images; 82% (14 out of 16) had a visible tumour in the anterior images and 65% (11 out of 16) in the LAT images owing to the heart obscuring the tumour in the anterior views and the vertebral bodies in the LAT views.

The number and length of breathing cycles agreed with previous studies and hence were representative of the population [3, 10]. Longer breathing cycles in the LAT compared with the AP images occurred in two patients in this study, possibly because the images were acquired after the plan check procedure, which lasts

~20 min. Patients may have been fatigued, although it may have been expected that the time per cycle would have decreased, owing to patients hyperventilating, rather than increased. It could be that patients were concentrating on maintaining their position because of the extended time or were more relaxed and taking slower, longer breaths at the end of the process.

The greatest motion was observed in the SI direction followed by the AP and RL directions. This is in agreement with other studies using fluoroscopy and when individual rather than population motion is described [5, 11]. Reproducibility of magnitude of motion in the SI direction from the AP and LAT images was <2 mm in eight patients. In two out of three of the remaining patients the difference could be explained by a small sample size because the video terminated after 6.8 s (patient 4) and by an irregular breathing pattern in which the tumour moved a further 1 cm in addition to the regular motion (patient 7). The other patient had no discernable reason from the videos for the difference in pattern.

Contrary to expectations, one patient had movement of >10 mm in the RL direction (patient 4). This was associated with atelectasis of the right lung adjacent to the tumour, with a raised diaphragm and deviation of the trachea to the right, resulting in an unexpected pattern of movement (Figure 6).

The limitations in this study included using one observer to outline the tumour and the method of outlining. However, an independent observer viewed all images and confirmed maximum movement, which would reduce outlining errors. The images were also

Table 4. Residual motion in inhale and exhale over all patients, and exhale split into two groups of patients with <5 mm and >5 mm movement in any direction

	RL (mm)	SI (mm)	SI (mm)	AP (mm)
Inhale ($n=14$)	1.1 (0.1–3.8)	1.7 (0.5–4.5)	1.4 (0.3–4.1)	1.0 (0.4–1.8)
Exhale ($n=14$)	1.2 (0.5–3.5)	1.7 (0.7–5.4)	0.9 (0.3–2.3)	1.5 (0.2–3.2)
Exhale (>5 mm)	1.5 (0.5–3.5)	2.2 (0.8–5.4)	1.1 (0.3–2.3)	1.8 (0.2–3.2)
Exhale (<5 mm)	0.8 (0.6–0.9)	1.0 (0.7–1.2)	0.6 (0.4–1.0)	1.0 (0.9–1.0)

AP, anteroposterior; RL, right-left; SI, superoinferior.
Values are given as mean (range).

Table 5. Margins calculated using residual motion in exhale and patient set-up error

	RL (mm)	SI (mm)	AP (mm)
$S_{\text{motion, exhale}}$	1.1	1.7	1.5
$S_{\text{motion, exhale}} < 5 \text{ mm}$	0.8	1.0	1.0
$S_{\text{motion, exhale}} > 5 \text{ mm}$	1.5	2.2	1.8
$S_{\text{set-up}}$	2.4	2.9	2.2
$S_{\text{set-up}}$	1.5	1.9	1.9
Margin	5.5	6.8	6.6
Margin, $< 5 \text{ mm}$	4.3	5.5	5.5
Margin, $> 5 \text{ mm}$	5.4	6.8	6.6

AP, anteroposterior; RL, right-left; SI, superoinferior.

acquired on 1 day at one session, and breathing motion may not be reproducible between sessions or days. However, there was close agreement in the SI motion in the majority of patients (8 out of 11) from the AP and LAT views, which were acquired 2–3 min apart.

Gating using breathing traces

The primary aim of this study was to determine whether radiotherapy could be gated using the pixel density function as a surrogate for motion. This method has already been tested to detect breathing traces [6] and has a potential advantage over using external surrogates for lung motion because internal lung tissue and/or tumour is used to determine the breathing trace. The correlation with motion was strong ($r > 0.6$) in 68% of images. It did not follow that patients with irregular cycles had poor correlation or that patients with more motion had greater correlation. When the traces of patients with weak and strong correlations were examined, the traces with weaker correlations had spiky motion traces and the stronger correlations had smoother traces (Figure 4). The noise in the motion measurement would have resulted in the more spiky traces.

The equal time spent in inhale and exhale is not in agreement with other studies. However, this is because of the method used to determine inhale and exhale by the greatest and lowest 30% of pixel density values, which would result in equal phases; consequently, either phase could be used to gate the treatment.

The use of fluoroscopy for gating reduced the margin compared with the conventional margin of 15 mm, 10 mm and 10 mm in the SI, RL and AP directions, respectively. In patients with movement $< 5 \text{ mm}$, set-up error had the greatest contribution to size of margin, which is in agreement with other studies [12, 13]. Methods to improve the reproducibility and stability of patient set up should be investigated alongside methods used to compensate for tumour motion.

The residual motions in exhale were 1.2 mm, 1.7 mm and 1.5 mm in the RL, SI and AP directions, respectively. Similar results were found in the SI direction when fluoroscopy and a synchronised spirometer signal were used to determine the residual motion (σ_{SI}); this was the same with amplitude-based gating. The mean (range) of residual motion was 1.5 mm (1.1–2.0 mm) [12]. The residual motion in the AP and RL directions was estimated as $\sigma_{\text{AP}} = 0.4\sigma_{\text{SI}}$ and $\sigma_{\text{RL}} = 0.2\sigma_{\text{SI}}$ because of poor visibility in the fluoroscopy images. Using the formula suggested by Burnett et al [12] with our SI residual motion would result in $\sigma_{\text{AP}} = 0.7 \text{ mm}$ and $\sigma_{\text{RL}} = 0.3 \text{ mm}$, which is smaller than we reported. Our larger residual motions in these directions illustrate that errors can be introduced when typical motion in patients with lung cancer is assumed to calculate margins.

The irregularities in breathing cycles are recognised and coaching techniques using audio, audiovisual and visual methods have been assessed to improve this, although no method has improved both amplitude and frequency [12, 14]. However, improving the reproducibility of the breathing cycle may not reduce residual motion [7].

The fluoroscopy images in this study were acquired on 1 day at one point in time, and there are conflicting reports as to whether residual motion changes significantly during a treatment course [15–17].

To implement this system clinically, potentially the in-room kilovoltage three-dimensional imaging linear accelerators could be used to acquire a sequence of frames with the patient in the treatment position. The software used in this study could read the breathing trace and the set up adjusted to the centre of the motion. The amplitude of the motion could then be observed to check that the margin was adequate. This process would also overcome the problem of baseline shifts.

Figure 6. (a) Anterior and (b) lateral chest radiograph of patient 4 showing atelectasis in the right lung and the displaced trachea.

Conclusion

Using fluoroscopy and a video system developed in-house, it was possible to measure tumour motion in 82% of anterior images and 65% of LAT images. The variation in motion between patients and in each direction, independent of location and size, demonstrates the need for motion-compensating techniques or patient-specific margins.

The simple approach of using pixel density values from fluoroscopy images to distinguish inhale from exhale and to enable gating was successfully applied in all patients. Poor correlations between the motion and breathing traces were possibly due to the method of motion measurements. This technique may potentially provide an accurate surrogate for tumour position; however, clinical implementation would require daily verification of the baseline tumour position.

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