ACTA ONCOLOGICA, 2018
VOL. 57, NO. 2, 211–218
https://doi.org/10.1080/0284186X.2017.1360511

ORIGINAL ARTICLE

Results from a clinical trial evaluating the efficacy of real-time body surface visual feedback in reducing patient motion during lung cancer radiotherapy

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ABSTRACT

Introduction: Optical surface measurement devices are a maturing technology in radiotherapy. The challenge for such devices is to demonstrate how they can improve clinical care. We present results from a phase 1 clinical trial designed to test the hypothesis that if presented with live data from a novel optical measurement device, showing their deviation from an ideal radiotherapy treatment position, patients will be able to better control their motion and increase their geometrical conformance.
Method and materials: Fourteen lung cancer patients were enrolled in a prospective clinical study and asked to use a variety of visual feedback schema from a novel in-house developed optical surface measurement device. The magnitude and regularity of their body surface motion using the different schema was compared to that when free-breathing at three time-points throughout their radiotherapy treatment schedule. Additionally, 4D Cone Beam CT data, acquired simultaneously with the optical measurements, was used to test if improvements in external motion are reflected in changes in internal tumor motion.
Results: The primary endpoint of the trial, device tolerability assessed by the fraction of participants completing all study sessions, was 86%. Secondary endpoints showed that use of the visual feedback device was found to statistically significantly decrease body surface motion magnitude by an average of 17% over the study cohort, although not universally. Similarly body surface motion variability was decreased by 18% on average. Internal tumor motion magnitude was also found to be statistically significantly decreased by an average of 14% when using the feedback device. Reduction in external motion was predictive of reduced internal motion but no evidence of a simple correlation between changes in internal and external motion magnitude was found.
Conclusions: Visual feedback of live motion is well tolerated by lung cancer patients and can reduce both body surface and tumor motion.

ARTICLE HISTORY
Received 15 February 2017
Accepted 20 July 2017

Introduction

Optical imaging of the body surface, or markers upon it, is becoming an accepted image guidance technique in radiotherapy, finding application in 4D scan acquisition [1], patient set-up [2,3], treatment gating [4] and tumor tracking [5]. Optical imaging complements traditional and emerging IGRT imaging technologies: it is radiation free and can thus be deployed during patient irradiation instead of just immediately before or afterwards as for standard cone beam CT (CBCT) usage; in contrast to 4D CT/CBCT, it makes direct measurements of patient motion rather than inferring them retrospectively from a surrogate signal; unlike current MR technology it is capable of true 3D real-time, high speed, low lag, performance; but it is self-evidently only able to capture a patient's external body topology, not internal anatomy.

Traditionally radiotherapy optical devices could be divided into two broad classes: fast marker based systems capable of real-time performance but limited to sparse measurement points [1,6], sometimes combined with orthogonal X-ray units [7,8]; and wide field whole body measurement devices that provide static snapshots or operate much more slowly [9,10] unless the field size is clipped to a smaller area [11]. Previously we developed a novel system that combines the advantages of both types of system, measuring the whole body surface at high resolution in real time [12]. More recently both commercial medical devices [13] and investigations of alternative technologies in the clinic [14,15] have demonstrated similar performances. In short, real-time, high resolution measurement of patients' whole body surface in the treatment room is becoming a mature technology. The challenge is to demonstrate how such devices can improve clinical radiotherapy care.

Intra-fraction patient motion remains a problem in radiotherapy, especially in treatment of the thorax where respiratory motion is most evident [16]. Whilst gold-standard IGRT techniques in which patient set-up is verified through imaging are becoming widespread, treatment is nearly always

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delivered relying only upon closed circuit television observation for catastrophically large movements. Additionally, other than attempting to 'remain still' during irradiation, the patient currently has a wholly passive role during their therapy. The UK National Cancer Research Institute's Consumer Liaison Group expressed both feelings of isolation and lack of control during treatment, and a desire for meaningful engagement during their therapy delivery.

Using the novel in-house developed optical sensor previously described [12], we hypothesized that if presented with a clear representation of their current pose and position with respect to a reference, patients would be able to both reduce their respiratory motion and better conform to their specified reference position. We developed a series of visualization schema and were able to demonstrate in a prospective study in healthy volunteers that using the device reduced periodic motion amplitude and overall position variability in all subjects by up to 40% [17]. This work built upon previous visual feedback studies in which single parameter surrogates for patient respiratory motion (e.g. thoracic pressure belt [18,19], spirometry [20], and body markers [21]) were used to encourage patients to adopt a stable breathing pattern [22] or breath hold to increase gated treatment duty cycle [23,24] and help sparing of critical organs [25]. A concise review of some of the literature is provided by Pollock et al. [26].

Although results from the volunteer study were encouraging, the study recruited from the hospital workforce and participants were thus relatively young and technologically literate. Tolerability and efficacy of the device needs to be demonstrated in a representative patient population who are often elderly and commonly present with severe co-morbidities. Furthermore, there is no data demonstrating the effect of the device in reducing internal tumor motion. The feasibility study we present here was designed to provide preliminary answers to these questions and demonstrate proof of principle for use of the device in lung cancer patients.

Method and materials

Optical surface measurement and visual feedback system

The optical device providing the underlying measurement data to the feedback system was developed in-house and is described in full elsewhere [12]. In brief, a sinusoidal fringe pattern is projected onto the body surface, allowing its topology to be recovered by analysis of the fringe modulation. The system operates, from image acquisition to data display, at 22Hz and 85-ms latency, and measures 512 by 512 points per frame (spatial resolution <1 mm), resulting in a data density of 46 Mbps (Mega-bits per second) [27]. The optical measurements are validated to be geometrically accurate to 1mm over 62% and 2 mm over 90% of an anthropomorphic phantom's surface as compared with cone beam computed tomography data [12]. Measurement stability over repeated imaging of a static surface is 0.03 ± 0.13 mm.

The feedback device analyzes the real-time measurement data from the surface sensor and displays the results, live, to the patient. Comparison with a reference surface, an average optical surface or the planning CT scan body outline is performed by subtraction of reference surface points from their corresponding live surface locations. For the sensing geometry of our system, correspondence between surfaces can be rapidly established with sufficient accuracy (offset error <0.5 mm) by simple gridded two-dimensional closest-point search [27]. Computationally more expensive strategies such as point projection and 3D feature tracking can be employed if a sensing geometry that introduces greater errors is used.

The feedback visualization schema used to display the discrepancy between live and reference surfaces are shown in Figure 1: a thresholded colorwash of displacement magnitude over the live 3D surface, a 'lamina' residual surface resulting from the subtraction of the reference surface from the live surface, and a 'traffic light' showing the mean displacement of the residual surface as a single parameter. The color coded threshold levels are individually determined at each session as described below. A video recording of the display schema is available as Supplementary material.

The visual feedback is provided to the patient via a screen attached to the rear of a standard lung board and a mirror that is angled to allow the patient to view the screen. A mirrored system was preferred to the video glasses used in the volunteer study [17] as this was both easier to clean, and allowed the patient to be aware of their overall environment in addition to the feedback display.

Study design

A non-randomized, single center, feasibility study under the sponsorship of The Christie NHS Foundation Trust was designed (ClinicalTrials.gov identifier: NCT02068378, research ethics committee reference 14/NW/0037) to test our hypotheses that: (i) the visual feedback device will be tolerated in lung cancer patients; (ii) use of the device will reduce patients' body surface motion amplitude and variability as compared to free-breathing; and (iii) reduction in external motion correlates to reduced internal tumor motion.

The study recruited 14 adult radical radiotherapy stage I–III lung cancer patients. Stage IV non-small cell lung cancer patients, those unable to give informed consent, and those suffering from epilepsy or migraine, for whom the bright lights of the optical sensor may not be suitable, were excluded from the study.

Each study participant was asked to undergo four imaging sessions (one training session and three study sessions spread over the patient's treatment schedule) where they used the optical feedback display to assist in controlling their motion. The images acquired during these sessions were in addition to any used to make clinical decisions, with no changes to the patients' standard care. At each study session the patient was set up by radiographer staff as per their treatment. The reference surface used during that session was then acquired as the average surface measured by the optical sensor over 20s. The individualized visualization thresholds for that day were calculate as integer multiples of the standard deviation of the measurement points' amplitudes during reference surface acquisition. Optical surface

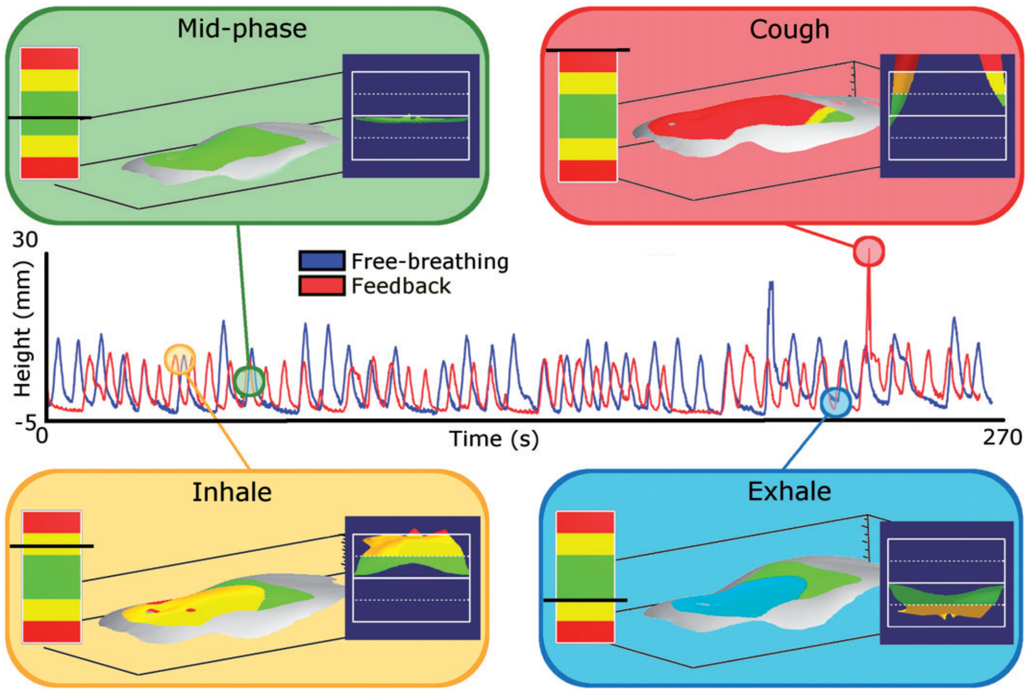

Figure 1. A patient surface (Pat05) as measured using the in-house developed optical device at different points during breathing. The three visualization schemes used to show deviation from ideal set-up position are shown for each selected time-point: (central) colorwash over the live surface; (right) 'lamina' residual between the live and ideal surfaces; (left) 'traffic light' single parameter reduction of the deviation. The single parameter respiratory signal of the patient free breathing (blue) and using the traffic light feedback device (red) during the same example study session is shown for illustration.

measurements were then taken with the patient free-breathing (i.e., without visualization aids) and whilst using each of the visualization schema. Whilst using the visualization device patients were asked to breathe smoothly and try to limit their motion to within the green and amber portions of the display. Simultaneous 4D Cone Beam CT images were captured during free-breathing and use of the 'traffic light' display. The trial protocol is illustrated in Figure 2.

Analysis

The trial collects data from three sources: (i) optical surface measurements when free breathing and using the different visualization schema; (ii) 4D cone beam CT images acquired simultaneously with free breathing and traffic light display optical measurements; and (iii) a patient questionnaire completed following each final study session.

The primary trial endpoint, the tolerability of the device to lung cancer patients is assessed simply as percentage of patients who complete all three study imaging sessions.

External body surface motion is assessed by evaluating respiratory magnitude and stability over patients' whole body surface using the optical surface sensor (recording time 90 s optical alone or 240 s with simultaneous 4D CBCT – Figure 2). An offline wavelet transform approach (described in detail in Supplementary materials) is used to filter the individual motion signals to physically meaningful timescales and estimate the mean and standard deviation of each surface measurement point's amplitude during an acquisition. The optical measurements for each schema from an imaging session can therefore be summarized by two parameters: the surface average of signals' mean amplitudes (μ_μ) corresponding to motion magnitude; and the surface average of the standard deviation of the measurement points' amplitudes (μ_σ) corresponding to motion regularity or consistency.

Internal tumor motion is determined from the 4D cone beam CT images. Image data were acquired using an Elekta Synergy linear accelerator with integrated Elekta XVI system (200 degrees gantry rotation, 1320 frames, S20 field size and F1 filter, at 120 kV and 20 mA/16 ms), and reconstructed in 10 respiratory phases [28]. Each phase image in the 4D CBCT datasets was matched to the first using rigid registration of the region of interest defined by the clinical target volume, in line with standard clinical practice. For each phase we recorded the Cartesian components of registration translation. The magnitude of the motion for a 4D image is then parameterized as the peak-to-trough amplitude of the periodic change in registration components. The resultant motion amplitudes were validated against those calculated using the CE marked clinical XVI workstations (v4.0) as an independent check. This process is described in greater detail in the Supplementary materials.

Inter-comparison of patients' motion parameters is performed using a linear mixed effects model that allows for multiple measurements per patient by including patient identity as a random effect alongside the controlled fixed effects. Statistical significance was assessed via the likelihood ratio test, in which the linear mixed model was compared using an analysis of variance (ANOVA) test to its corresponding null model in which the feedback schema fixed effect is excluded. The relationship between external (optical) and internal (4D CBCT) motion is assessed both by analysis of the confusion

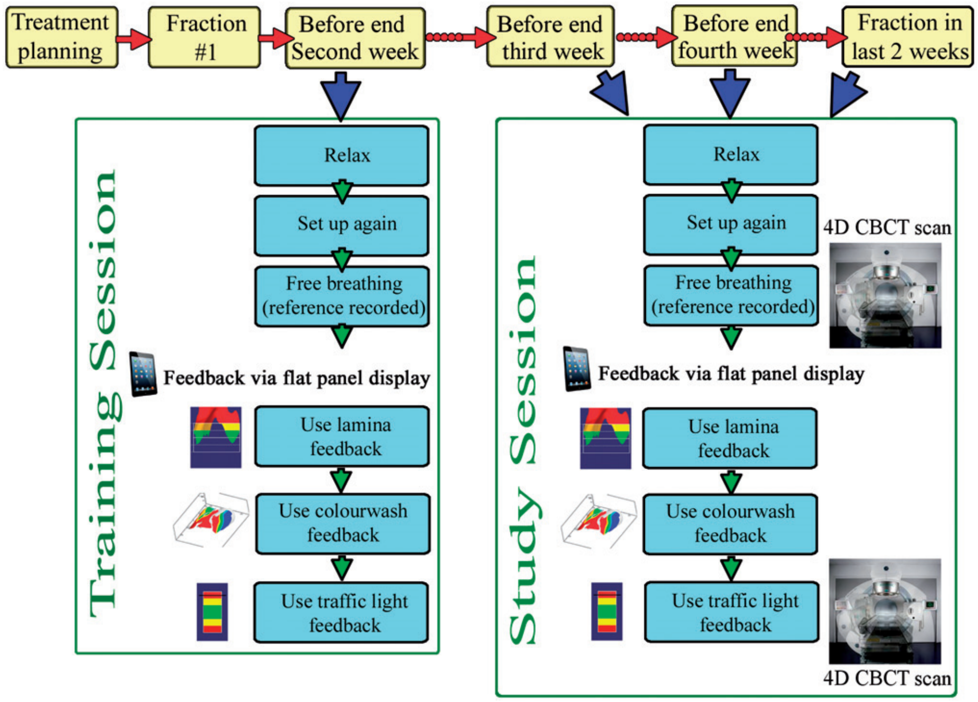

Figure 2. The trial protocol and scheduling.

matrix testing whether or not reduced external motion is predictive of reduced internal motion, and by Pearson and Spearman correlation of changes in corresponding motion magnitudes at each study session. Analysis was performed using the *lme4* [29] package in *R* [30] after Winter [31].

Patient experience and satisfaction with the feedback device was assessed by questionnaire following their last study session (for both those who did and did not complete all sessions). The questionnaire can be found in full in the Supplementary materials.

Results

Of the 14 patients recruited to the study, two did not complete all three imaging sessions. We therefore score the device tolerability on our lung cancer patient cohort at 86%.

All patients completed their end of study questionnaire. Whilst 79% of participants wore glasses and 45% reported additional eyesight issues, none reported any visual problems with using the mirrored viewing system we adopted. Comfort of device use, ease of device use, and perceived benefit of device to patients were scored at 4.4 ± 0.5, 4.4 ± 0.7, and 4.4 ± 0.7 respectively in the range 1–5 (disagree strongly – agree strongly) by grouping responses to related questions. The single parameter traffic light display scheme was ranked as favorite by 86% of patients, with 50% each selecting the colorwash and lamina displays as their least favorite. Free-text comments although anecdotally positive were excluded from analysis.

Optical measurements

The surface averages of the mean and standard deviation of the measurement points' amplitude for all study sessions are shown in Figure 3 grouped by patient and visualization schema. Table 1 summarizes the overall fixed effect size of the different visual feedback schemes on the external motion parameters. The likelihood ratio test shows the effect to be statistically significant for both signal mean ($\chi^2(3) = 14.86$, $p = .002$) and standard deviation ($\chi^2(3) = 18.56$, $p = .0003$). Example distributions of the mean and standard deviation of the signal amplitude over two patients' body surfaces are shown in Figure 4.

4D cone beam CT measurement

Table 2 and Figure 5 show the change in internal tumor motion amplitude as a fixed effect of using the visualization device (with the traffic light schema). Inter-comparison of 4D motion magnitudes calculated using the method presented above with those calculated with the CE marked clinical XVI software reveals a Pearson correlation coefficient of $R = 0.9$.

The correlation between absolute internal and external motion magnitude is $R = 0.12/\rho = 0.11$ and $R = -0.06/\rho = 0.01$ for free breathing and using the traffic light feedback display, respectively. Reduced external motion when using the feedback device is predictive of reduced internal motion with an accuracy of 0.68, sensitivity of 0.75 and specificity of 0.65, with the changes in motion magnitude having Pearson and Spearman correlation coefficients of $R = 0.0$ and $\rho = 0.25$. When split into upper and lower lung cohorts the correlation coefficients separate to $R = -0.11/\rho = 0.17$ and $R = 0.27/\rho = 0.34$, respectively ($R = 0.39/\rho = 0.43$ for lower left tumors).

Discussion

Having already established the utility of the device in a healthy population [17], the primary endpoint of the study is

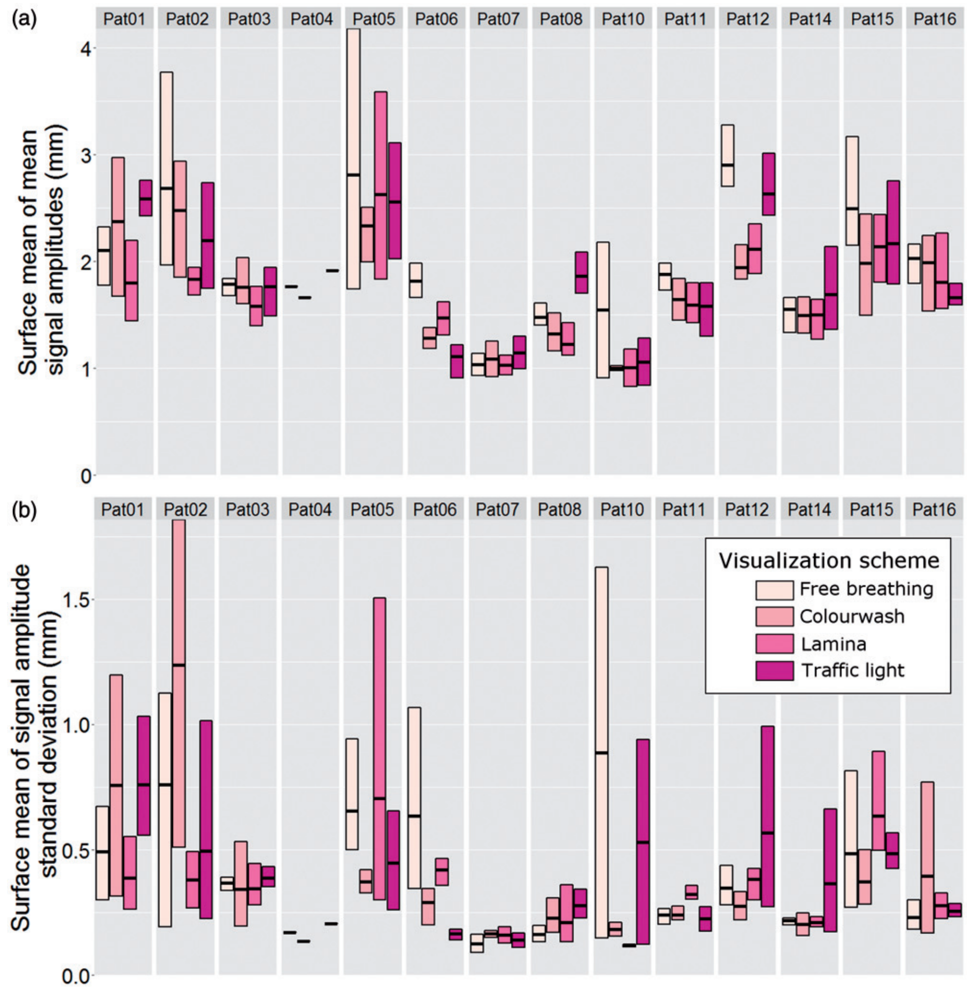

Figure 3. Surface average of the (a) mean and (b) standard deviation of the external measurement points' signal amplitude (μ_μ and μ_σ), grouped by patient and visualization schema, for all of the study imaging sessions of each patient. The data is displayed as the minimum, mean and maximum value recorded. Note Pat04 attended only one session.

Table 1. Overall effect size of the different visualization schema on the surface average of the signals' mean and standard deviation, as shown by a linear mixed effect model comparing the different feedback strategies as a fixed effect whilst controlling for patient variation as a random effect.

Visualization scheme	Free breathing	Color wash	Lamina	Traffic light
Surface average of mean signal amplitude (μ_μ): motion magnitude				
Surface average of signals' mean amplitudes (mm)	2.0	1.74	1.66	1.84
Change from free breathing (mm)	N/A	−0.26 ± 0.09	−0.34 ± 0.09	−0.16 ± 0.09
Change from free breathing (%)	N/A	−13 ± 5	−17 ± 5	−8 ± 5
Surface average of standard deviation of signal amplitude (μ_σ): motion regularity				
Surface average of signals' standard deviation (mm)	1.06	0.91	0.87	0.89
Change from free breathing (mm)	N/A	−0.15 ± 0.05	−0.19 ± 0.05	−0.17 ± 0.05
Change from free breathing (%)	N/A	−14 ± 5	−18 ± 5	−16 ± 5

the tolerability of the device in a representative patient demographic. With 86% of patients completing all three study sessions, and questionnaire feedback rating the comfort, ease of use, and perceived benefit at 4.4 out of 5 we can state that the device was well received by the study participants. The two patients who did not complete their study sessions withdrew through unrelated injury (radiotherapy not completed) and treatment complications.

With respect to the secondary endpoints, use of the visual feedback device statistically significantly reduces body surface (Table 1) and internal (Table 2) motion amplitude and increases surface motion stability (Table 1). Unlike our previous study using healthy volunteers [17] the effect is not universal, but over the whole cohort, on average, patients were able to better control their motion when using the device.

In our previous healthy volunteer study the patients' mean amplitude (μ_μ) was reduced from 2.7 to 1.7 mm (37%) when using the device and their standard deviation (μ_σ) from 1.4 to 0.6 mm [17]. The average respiratory magnitude we measured in this study was 2.0 ± 1.06 mm reduced to 1.66 ± 0.87 mm when using the device (17%). As one might expect, the lung cancer patients in this study's cohort do not

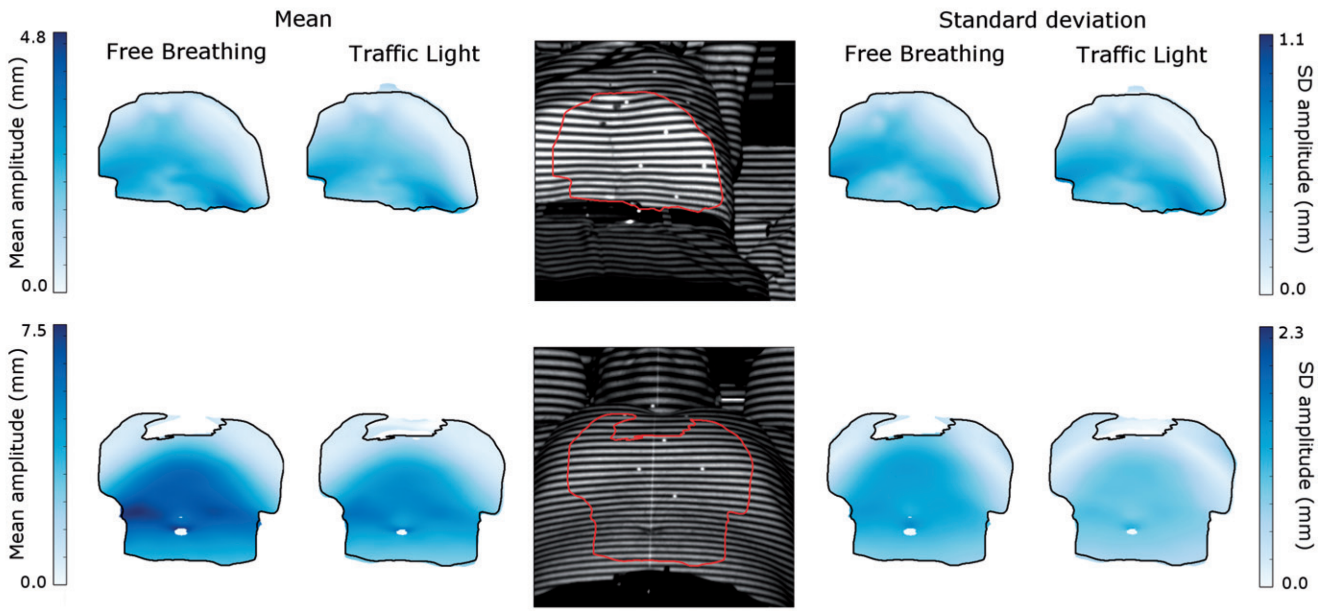

Figure 4. Example distributions of the mean signal amplitude (left two columns) and signal standard deviation (right two columns) at each measurement point over a patient's surface. The figure shows the distributions for two patients (Pat03, top, and Pat05, bottom) both free breathing and using the traffic light visual feedback schema (Figure 1).

Table 2. Overall effect of use of the feedback device on tumor motion magnitude, as assessed by 4D CBCT scan versus unassisted free-breathing.

	Tumour amplitude no feedback (mm)	Tumour amplitude with feedback (mm)	Change from free breathing (mm)	Change from free breathing (%)	Likelihood ratio test significance
Left–right amplitude	1.76 ± 0.34	1.72 ± 0.35	0.04 ± 0.09	2 ± 5	$X^2(1) = 0.001$ $p = .97$
Ant–post amplitude	2.08 ± 0.34	2.07 ± 0.36	0.01 ± 0.12	1 ± 6	$X^2(1) = 0.001$ $p = .97$
Inf–sup amplitude	5.03 ± 0.86	4.33 ± 0.89	0.70 ± 0.23	14 ± 5	$X^2(1) = 8.6$ $p = .003$

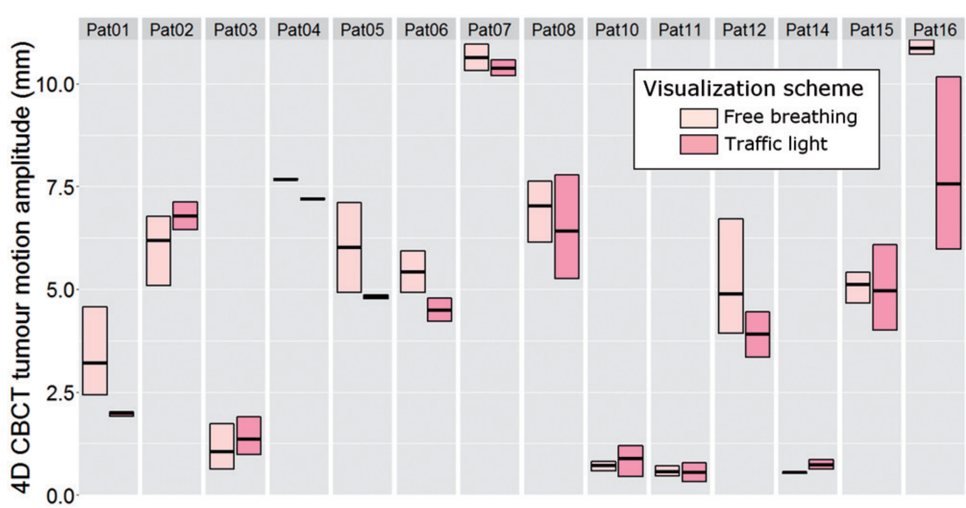

Figure 5. The minimum, mean and maximum tumor inferior-superior amplitudes measured with 4D CBCT for each patient with and without the visual feedback device. Note Pat04 attended only one session.

perform quite as well as the healthy volunteers from the previous study. Whilst the majority of the studies in the literature [26] focus on improving motion stability, Masselli et al. [19] share our aim of reducing motion magnitude. They report a similar reduction in healthy volunteer motion to ourselves of 40%, but find a 37.5% improvement in a cohort of five lung cancer patients. The discrepancy in lung cancer patient performance suggests there may be scope for further optimizing the presented feedback schema.

Interestingly, as for the volunteer study, the lamina visualization schema, despite being the least popular was the most effective at reducing motion. The simplicity of the traffic light display probably explains its attraction. However, condensing a whole sensor frame to single parameter necessarily results in a loss of detailed information from the visualization. It seems that despite the more complex information presented in the more detailed schema perhaps being a more daunting prospect, the trial volunteers were generally capable of processing that data to better moderate their motion. An important anecdotal point is that the first patient to use the device (Pat01) was observed holding their breath in an attempt to stay in the green and amber feedback zones and subsequently having to gasp for air. This highlighted the need for thorough patient training that emphasized smooth breathing. It also raised the issue of feedback schema design – might there be psychological associations with designs and/or colors that affect behavior (e.g., red with 'bad'/'stop')? Certainly something the authors took from the experience is that appropriate specialists should be consulted when designing feedback displays.

There is no obvious correlation between the magnitude of external surface and internal tumor motion ($R=0.12/\rho=0.11$). From a physiological standpoint large body surface motion would not necessarily be expected to equate to large tumor motion. Rather tumor motion magnitude depends upon its internal position, composition, and binding to surrounding tissues. What one might expect is that changes in a patient's external motion magnitude would correlate to corresponding changes in tumor motion. A reduction in external surface motion is a reasonably good predictor of reduced internal motion (sensitivity/specificity 0.75/0.65). However, there is no linear relationship between the scale of the changes ($R=0.0$), and only a weak positive non-linear monotonic association ($\rho=0.25$). This relationship is more pronounced in lower lobe tumors ($R=0.27/\rho=0.34$). That is, use of the device will act to reduce a patients' external body surface and internal tumor motion, and reduced external motion is indicative of reduced internal motion, but there is no simple relationship between the external and internal effect sizes. Physiologically, this can be interpreted along similar lines to the lack of correlation between internal and external motion magnitudes: tumor motion is complex and dependent upon local anatomy and pathology amongst other factors in addition to respiratory motion magnitude. Lower lobe tumors are typically more mobile than upper lobe ones, particularly if the tumor is well separated from the mediastinum and chest walls, simply as the lower lobes of the lungs move more. If a tumor is more likely to be free to move, it stands to reason that its relationship with changes in external motion would be stronger.

There are two approaches to dealing with respiratory motion. The first, and the aim of this study, is to attempt to reduce motion magnitude thereby decreasing the internal target volume (ITV) necessary to ensure tumor coverage, and hence reducing the planned amount of irradiated healthy tissue. The second is to try and ensure motion regularity so that the patient's geometry at treatment is the same as that at planning. Baseline shifts to patient geometry and motion between treatment planning and delivery can result in significant changes to the desired dose distribution. As the use of the feedback device reduces tumor motion (by 0.7 ± 0.23 mm) from that when free breathing this would certainly count as a baseline shift if used only on the treatment machine. The wider discussion to this point is whether or not the motion captured and accommodated during treatment planning is representative of that exhibited during treatment even if a device is not used. Comparison of tumor motion amplitude in the study cohort's 4D CT planning scans with that during their free breathing study session 4D CBCT scans, using the same mixed model approach described above, reveals there to be a fixed effect reduction in inferior–superior respiratory motion amplitude of 1.85 ± 0.46 mm ($\chi^2(2)=24.17$, $p<.001$). The interpretation is that (in this small feasibility study dataset) there is a large baseline shift in motion amplitude between planning and treatment in the absence of the use of any feedback device. On this basis, there is a strong argument for using feedback type approaches throughout the therapy pathway to both reduce motion magnitude and increase consistency.

In conclusion, the presented device was uniformly well received and generated significant improvements in motion control without use of physical constraints in a representative sample of lung cancer patients. A final and important point to note is that not only are many patients wholly capable of tolerating and using such devices, our experience is that there is a substantial appetite to do so and to play an active role in optimizing treatment.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by The Christie Charity through the Christie Pilot Study Fund 2013 round. Gareth J. Price acknowledges support through Cancer Research UK via funding to the Cancer Research Manchester Centre [C147/A18083]. Corinne Faivre-Finn acknowledges support from Astra Zeneca and Merck.

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