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Full length Research paper

The efficiency of using audio prompting method to regulate the patient's breathing during radiation therapy treatment of NSCLC

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Advanced radiotherapy treatments for Non-Small-Cell Lung Cancer (NSCLC) rely on conforming the radiation dose to the tumor geometry as tightly as possible; this increases the probability of destroying the tumor cells while simultaneously reducing the radiation dose to nearby tissues and to organs at risk, subsequently reducing normal tissue toxicity. Unfortunately, patient breathing is likely to compromise the method during implementation, as the breathing motion causes the tumor to move periodically out of the planned radiation beam. The aim of this study is to establish a simple breath-monitoring method which is easy to follow and patient friendly; this could be achieved by developing training method and monitoring device that are considered to be non-invasive, and which also do not rely on connections to the treatment machine. A total of twelve volunteers participated in this study. Two methods of breathing were used: free-breathing and audio-prompted breathing, with synthesized breathing as the 'ideal' pattern. The result showed that audio prompting resulting in large amplitude and phase variations, compared to the free breathing method. It is concluded that the audio promoting method that is used to regulate breathing in patients undergoing radiotherapy for lung tumors is inappropriate to be used during the treatment of NSCLC.

Key words: Non small cell lung cancer, respiratory gating, three-dimensional conformal radiotherapy, free-breathing, intensity-modulated radiation therapy, audio prompting.

INTRODUCTION

External beam radiation therapy is an important modality in treating cancer, alone or in combination with other modalities such as surgery or chemotherapy. Progress over the last two decades in the area of radiation therapy technology has been exemplified by the development of state-of-the-art radiation treatments, such as 3-dimensional conformal radiotherapy (3-DCRT) and intensity-modulated radiation therapy (IMRT), which have ultimately increased the chances of recovery for cancer patients, improved the tumor control probability (TCP), and reduced the normal tissue complication probability (NTCP) (Webb, 2003). IMRT is an advanced technique of 3-DCRT, whereupon the beam intensity is modulated by the planning computer system in order to deliver a higher dose to the tumor with a reduced margin. The application of the IMRT technique is unique for each patient since it can be modified according to each tumor shape with the use of a multi-leaf collimator (MLC), which creates an irregular field, providing the best coverage of the tumor (Bortfeld et al., 2002).

The main two goals of radiation therapy are to destroy the cancerous cells and to increase the survival rate of patients with cancer (Haas, 2008). These two goals are best achieved when the radiation therapy dose prescribed to the planning target volume (PTV) is delivered to a tumor, which is a static relative to the radiation beam. This provides the opportunity to maximize control over the dose delivered to the tumor as well as that delivered to normal healthy tissues and organs at risk. There are three main types of patient-controlled breathing manoeuvres, which can be used in order to control the respiratory motion during radiotherapy on lung tumors: Deep inspiration breath hold (DIBH), deep expiration breath hold (DEBH) and self-breath holding during the inspiration or expiration phases (Mageras et al.,2004). The above methods of motion control are all under the direct control of the patient, and therefore do not involve the use of any external devices in order to modify the breathing pattern or motion of the chest wall. The literature attests to the fact that techniques such as DIBH, DEBH and chest restrictors are not well tolerated by lung cancer patients, who often have some form of lung dysfunction (Giraud et al., 2006). Respiratory gating radiotherapy has been used for some time in medical imaging, such as with the use of Compton tomography (CT) and magnetic resonance imaging (MRI), and with the objective of reducing artefacts and blurring (Liu, 1993; Moerland et al., 1994). This is a method of treating a tumor whereby the radiation beam is turned on only when the tumors is within a narrow range of positions, which is referred to as the gating window. The radiation beam is active only when the tumor is in a certain position, and when the respiratory cycle is at a reproducible point which is defined before the treatment session. If irregular breathing patterns or cycles appear, the beam will then be immediately switched off. However, in order to keep this point reproducible, the patient has to make an effort to actively hold his breath or control his breathing cycle (Kubo et al., 2000). The problem with using respiratory gating radiotherapy increased treatment time, cost, and requires more personnel.

The aim of this study is primarily aimed to improve our knowledge of NSCLC patient's response and tolerance to different breath-training regimes, each of which has been designed with the objective of promoting a regular and controlled breathing pattern over a time interval commensurate with conventional radiotherapy treatment times.

METHODS

Twelve subjects were recruited for participation in this study; all were unpaid volunteers and presented a variety of profiles, from the young, healthy non-smoker with no medical conditions or pulmonary problems to the elderly smoker with an unspecified pulmonary problem. Prior to the taking of measurements, participants were shown the measuring system and were made to feel comfortable in the room and surroundings; heating and lighting were adjusted for their comfort. During measurement, volunteers were placed in supine position with their arms in the sides. Although the literature suggests that breathing is predominantly controlled abdominally when the arms are placed above the head. A custom-made belt and strain gauge with a variable resistive element constructed from a rubber capillary tube and a liquid metal filling, and an operational amplifier (with its integral sensor using the USB connection to a laptop running the dedicated software was designed to measure the chest wall expanding during the breathing cycles.

Our initial investigation during the testing phase showed that a more consistent measurement could be taken if the belt was placed above the xyphoid process, slightly towards the nipple. Consequently, all measurements were taken with the belt placed in this position, unless this was non-optimal for a specific subject. In order to ensure that the sensor was placed in the correct position, a short measurement (of less than one minute) was carried out prior to the actual data collection session. This allowed the sensor, belt position and tightness, monitor location and lighting to be optimally adjusted; all of these parameters were then fixed for each of the data collection/training sessions for that particular subject.

Prior to the taking of each measurement, subjects were asked if they were comfortable and ready to start. If so, they were asked to relax as much as possible and not to move or fidget as, in a radiotherapy session, patient movement would cause a radiographer to terminate a treatment and reposition/settle the patient. Unless the subject specifically requested a halt, the researcher observed discomfort, or some other significant problem occurred, the data recording continued even if the subject coughed or moved slightly, thereby simulating a real patient treatment session. Each data collection session lasted 4 min. There was an interval of 10 min between sessions for the subject to rest.

The subjects of this study, were 18 to 74 years, were able to understand and discuss their participation, did not require oxygen or any other form of breathing aid, have no pre-existing heart condition or other medical condition that could be exacerbated during the data collection episode, be able to lie or sit in the supine position for the duration of approximately one hour and provide full signed consent. The recording session was done following Keall 2006 and Kini et al. (2003), procedure to train patients during radiotherapy treatment for each subject, a series of 4 min breathing traces were collected under different training and feedback situations. The agreed protocol was to take the following measurements in the same order each time: free-breathing and audio prompting (therapist's voice providing prompt commands to breathe in and out) The data collection was organized in the above way in order to facilitate the most natural free-breathing response, that is, one that was not influenced by any form of training or relaxation. Certainly, it was recognized that relaxation and/or fatigue could influence the later collections in the sequence, but analysis of the data showed no such effects. The data collected in all sessions were recorded and each recording contained the numerical data to enable the full 4 min waveforms to be reconstructed in time correlation with any prompting or feedback waveform. Thus, the period, amplitude and phase patterns of the subject's breathing could be analyzed against the different prompt or feedback waveforms. The data was exported directly to Excel spreadsheets.

PROCEDURE DURING THE BREATHING SESSIONS

Free-breathing session

The first session of breath training was in free-breathing. The subject was asked to lie on a clinical bed for a total of four minutes, and the respiratory belt was placed between the lower part of the chest and the upper part of the abdomen. The subject was asked to breathe normally, with no requirement to perform any particular kind of breathing. During this time, the breathing cycle was recorded via the sensor to the laptop computer. No images, sounds or any other feedback were presented to the subject. After the recording of the breathing cycles, which lasted for four minutes, the subject was told the session had concluded and was asked to rest prior to the next collection session. During this time, the time-averaged natural amplitude and frequency of the subject's breathing was extracted from the data set collected. The amplitude and period of participants' breathing varied with time over the 4 min period, and so it was deemed necessary to establish an average for these parameters.

There are two alternatives to setting up a training waveform: either the training waveform has approximately the same parameters as the natural breathing averages for the subject, or the period and amplitude of the training waveform are chosen simply for the convenience of the treatment, and so the training pattern is different from the subject's normal breathing. In all of the training

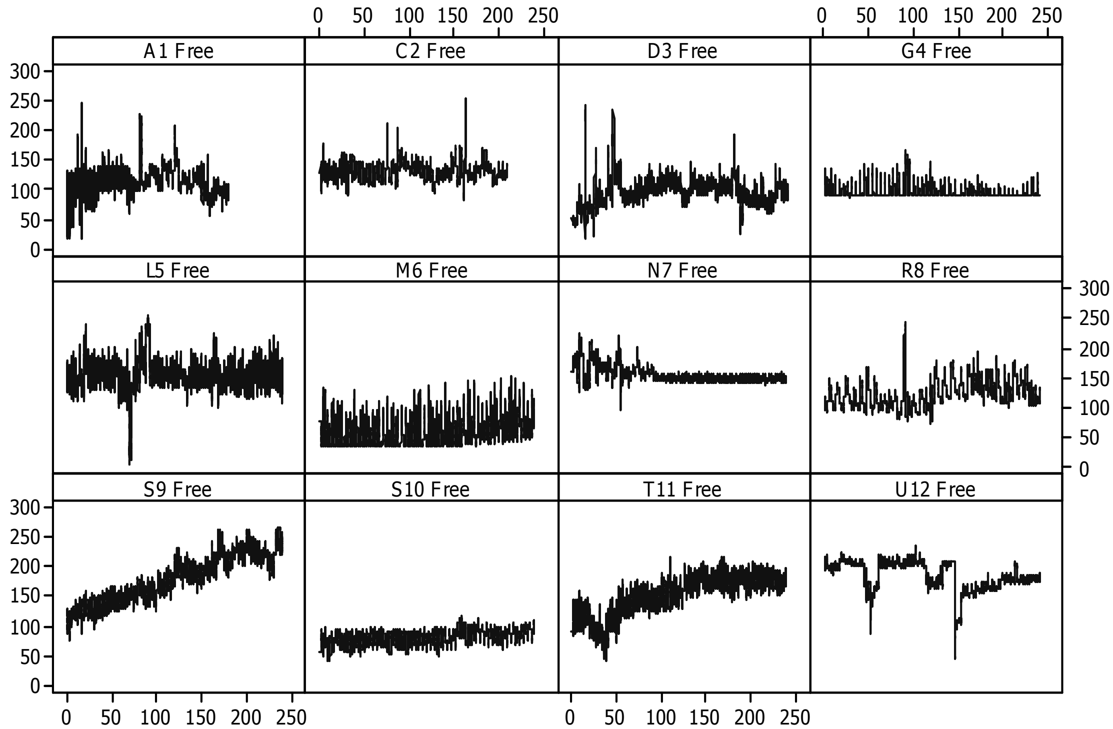

Figure 1. Free breathing patterns without and promotion.

sessions, time-averaged data from the free breathing pattern were used in order to establish the parameters of a regular training pattern.

Audio prompting session

For the audio prompting session, the breathing belt was left on the patient from the free breathing session and the monitor software was set to produce a sine wave with a frequency and period was determined. The sine wave was presented to the researcher (not the subject). During the session, the researcher would issue the simple verbal commands to 'breathe in' and 'breathe out' for the subject to follow. The aim here was to cause the subject to breathe regularly within a consistent period and amplitude via simple commands, such as could be issued over an intercom system in a conventional treatment room. The researcher was prompted by the visual comparison of the subject's breathing and the 'ideal' signal provided by the software. Again, four minutes of data were collected for each subject.

STATISTICAL ANALYSIS

A spectral analysis of the breathing patterns was performed using GraphPad, Prism (Graphpad Software, 2236 Avenida de la Playa, La Jolla, CA 92037, USA). Multi-factorial repeated measures ANOVA (assuming a General Linear Model) was used to determine the effects of the two factors on the four response variables. A post-hoc analysis was performed using Tukey's method for the pair-wise comparison of mean values. The significance levels were conventionally truncated to: not significant ($P > 0.1$); marginally significant ($P = 0.05$-0.1); significant ($P = 0.01$-0.5); highly significant ($P = 0.001 – 0.0001$); and highly significant ($P = 0.000 – 0.001$).

RESULTS

For several years, it has been a common practice, as advocated by several research groups, to treat a patient's breathing pattern effectively as a single sine wave with a fixed period and amplitude. Hence, it is often assumed that treatment gating can be set using a single period with the patient breathing freely. Contrary to this assumption, our evidence suggests that such a technique is inadequate for deriving a gating procedure which agreed with Keall (2006) that showed the audio instructions tended to increase the amplitude when compared with the FB. Figure 1 shows the patterns of free breathing without any control for the twelve subjects, where it showed unstable breathing patterns as compared with the audio breathing. It can be observed "at a glance" that the breathing patterns of the 12 subjects varied both within and between the two breathing motilities controls (free breathing and audio mentoring).

Audio mentoring appeared to stabilize the breathing patterns as shown in Figure 2; however it increased the amplitudes in most of the subjects, compared with the diverse free patterns observed without mentoring. The subsequent analysis includes objective tests to determine whether the apparent differences observed in Figure 3 are statistically significant. The trace shows a characteristic changing baseline, which corresponds to the subject slowly changing the style of breathing by not

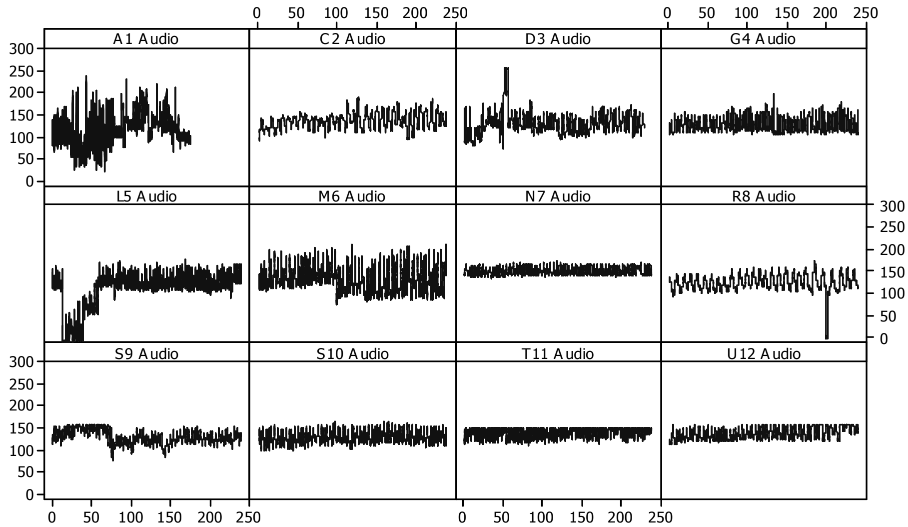

Figure 2. Breathing patterns with audio promotion.

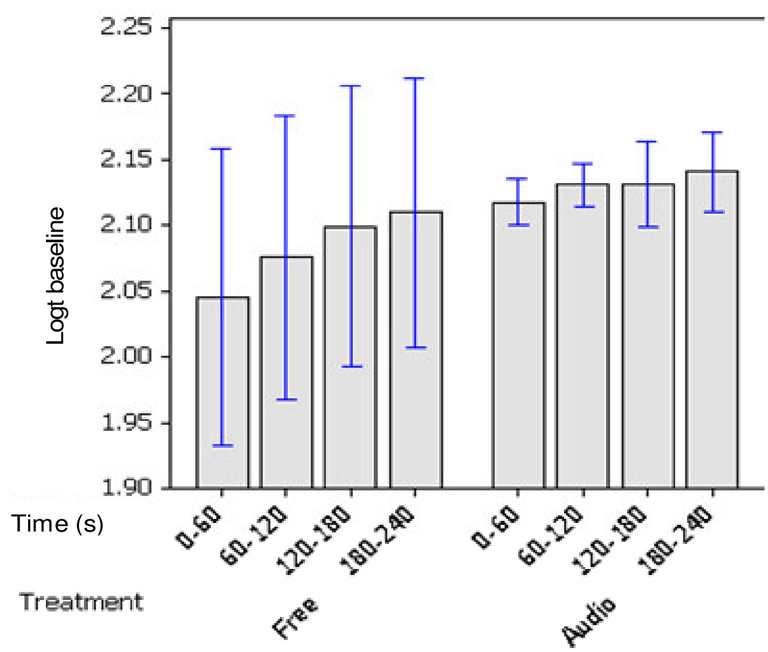

Figure 3. Comparison of mean baselines ± 95% confidence intervals with respect to times and breathing modalities.

completely emptying the lungs during the exhale portion of the cycle.

DISCUSSION

The aim of this study is to develop methods of monitoring the chest wall motion as well as developing a robust method of analyzing the data. As a subsidiary aim, it is hoped that the study will ultimately lead to the development of a simple and cost-effective device which can, in principle, be used to control breathing without the need for support from the treatment machines, or other sophisticated machines.

The more advanced the techniques used to treat cancer, the higher the level of complexity, and so the risk of errors will ultimately increase. The advance techniques and modality are a good example of conformal radiotherapy, which aims is to conform the dose around the target volume while sparing the adjacent normal tissue and the organs at risk (OAR) (Ramsey et al., 1999) and it includes 3-DCRT, stereotactic radiotherapy (SRT) and IMRT. The major problem with using conformal radiotherapy with its modalities to treat lung and abdominal tumors is that the movement of the tumors due to respiration could cause a geometric miss and increase the dose to the critical organs in the area, such as the heart, coronary artery or lungs. Intra-fraction motion may also cause about 20% error in the dose when using the IMRT technique (George et al., 2003). Intra-fraction motion defeats the purpose of using IMRT, since the dose will not be delivered to the planning target.

Audio prompting is a technique that is used before radiation therapy treatment to stabilize the patients breathing which could lead to limited tumor movement. Furthermore, the exact correlation between the tumor motion and externally-measured breathing has not yet been established, although it is fair to say that all the evidence gathered from the fluoroscopic measurements suggests a strong direct correlation. What is clear, however, is that the more tightly the dose is conformed to the tumor (as in the now-routine use of IMRT), the greater the risk of the tumor partially moving out of the field during treatment, ultimately leading to under dosing and an inhomogeneous dose distribution; the consequence will be an increase in the probability of incomplete tumor kill and hence of tumor cell repopulation.

However, from our result, it demonstrates quite graphically an interesting problem which can arise if we choose to deliver the radiation beam with audio prompting. From the result is showed that the amplitudes of every subject changed dramatically, compared with the diverse free patterns observed without mentoring. The problem increases if we choose to gate the radiotherapy beam on amplitude criteria. If, as is usual practice, we set an amplitude window based on the exhale portion of the breathing pattern, then the shifting baseline will eventually force the treatment to a halt; although the phase may be correct, the patient is breathing outside the window. In such a case, the treatment would stop even though it is likely that the tumor is within the treatment beam. During the real-time treatment with gating, the verification for tumor position would be checked using electronic portal imaging, portal film or by tracking, here we are estimating the shift from the subject's real-time breathing trace and studying what might happen if the gating window were set either at the maximum exhale amplitude or the maximum inhale amplitude. Figure 3 shows the comparison of mean baselines ± 95% confidence intervals with respect to times and breathing control modalities (FB and AB). Figure 4 shows the comparison between the two modalities of breathing control where there was increased amplitude during the audio promoting modality. The variation in amplitude and phase shown in Figures 4 and 5 show that it is inappropriate to attempt to gate a treatment under the assumptions of consistency in amplitude or phase for Free-breathing.

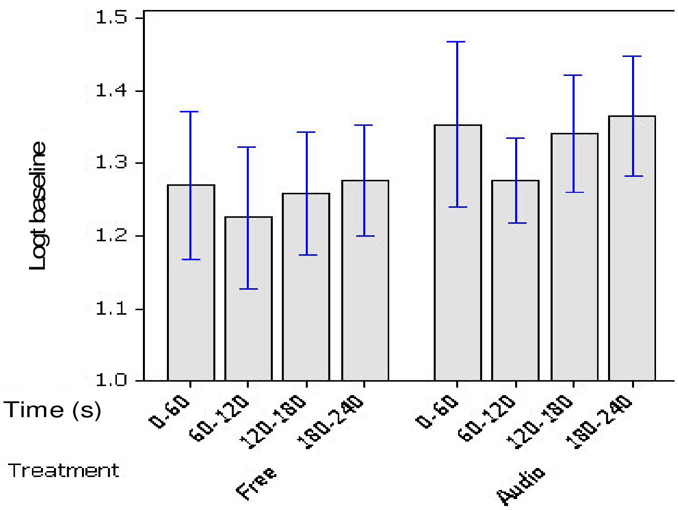

Figure 4. Comparison of mean amplitudes ± 95% confidence intervals with respect to times and breathing modalities.

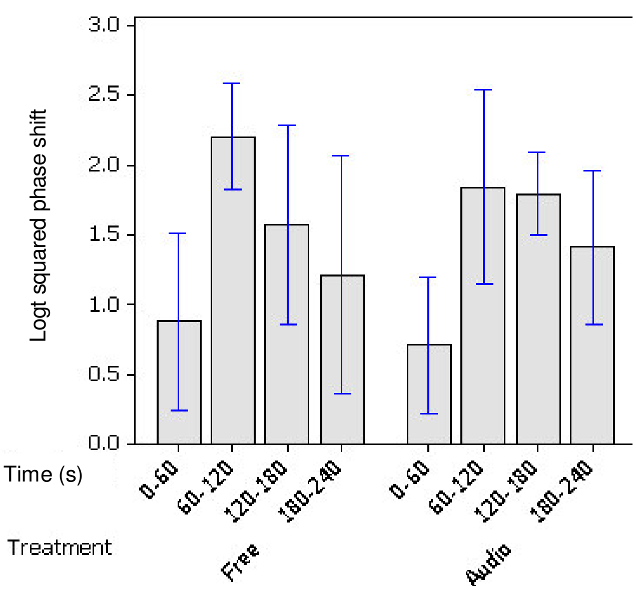

Figure 5. Comparison of mean phase shifts ± 95% confidence intervals with respect to time and breathing modalities.

CONCLUSION

The effects of different techniques designed to regulate a patient's breathing were investigated in a population of some 12 subjects, each of whom were randomly chosen and ranging in age from 18 to 74 years. Two regulation techniques were investigated: Free-breathing and audio prompting, with the latter being the method most commonly used in order to regulate a patient's breathing. It has been demonstrated that the commonly-held assumption that FB can be described by a simple sine wave with a single period and amplitude is false, and that gating a radiotherapy treatment on amplitude — the most common practice and founded on the above assumption —unreasonable using AP can have a worsening affect on the breathing pattern of a subject by producing exaggerated amplitude swings. Audio prompting appears to improve the phase-control of breathing over free-breathing, it also results in more abrupt and larger swings in amplitude, thus presumably driving the tumors out of the beam further than would occur in free-breathing and thereby destroying the desired uniform dose distribution over the tumors, reducing both the tumors dose and the TCP. Concomitantly, more healthy tissue would be driven into the beam, distorting the desired isodose distribution, increasing the non-tumor dose and thus the NTCP. Together, these would presumably reduce the efficacy of the treatment and the patient's survival probability.

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