DEVELOPMENT OF A BREATHING MONITOR AND TRAINING SYSTEM, AND THE ANALYSIS OF METHODS OF TRAINING PATIENTS TO REGULATE THEIR BREATHING WHEN UNDERGOING RADIOTHERAPY FOR LUNG CANCER

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DECLARATION

I hereby declare that I am the sole author of this thesis. I authorise the City University Radiography Department to lend this thesis to other institutions or individuals for the purpose of scholarly research.

DEDICATION

This thesis is dedicated to my family: To my parents — especially my mum — for the unlimited encouragement, support and love; to my husband, Abdullah, who has always brought out the best in me; and to my sons, Salih, Faris and Basim, for their patience and understanding.

ABSTRACT

Purpose: Advanced radiotherapy treatments for Non-Small-Cell Lung Cancer (NSCLC) rely on conforming the radiation dose to the tumour geometry as tightly as possible; this increases the probability of killing the tumour cells while simultaneously reducing the radiation dose to nearby tissues and to organs at risk, subsequently reducing normal tissue reactions. Unfortunately, patient breathing is likely to compromise the method during implementation, as the breathing motion causes the tumour to move periodically out of the path of the radiation beam, while normal, healthy tissue periodically moves into the line of the beam.

The aim of this project is to establish a simple breath-monitoring system which is inexpensive, easy to use and patient friendly; this could be achieved by developing a device that is considered to be non-invasive, and which also does not rely on connections to the treatment machine; it is based on a simple instrumented belt using strain-gauges which monitor the chest-to-wall motion during the breathing cycle.

Methods and Materials: A total of fifty volunteers participated in this study. Three methods of breathing were used: free-breathing, audio-prompted breathing and visual feedback breathing, with synthesised breathing as the 'ideal' pattern. The breathing monitor was used in order to investigate the difference between various training regimes for helping subjects to modify their breathing patterns into a desirable pattern.

Results: The results show that audio prompting — the method most commonly used in the clinic to date — was the least effective of the methods tested, resulting in large amplitude and phase variations compared to the other methods. Visual feedback (not currently used) is demonstrated as being far superior in regulating a subject's breathing: this method produces far tighter control over both the amplitude and phase of the breathing pattern in comparison to any other method investigated.

Conclusions: It is concluded that the current methods of regulating breathing in patients undergoing radiotherapy for lung tumours are inappropriate, and that a far better approach would be to use visual feedback.

NOTATIONS AND ABBREVIATIONS

- ABC: Active Breathing Control (Device)
- ADC: Analogue-to-Digital Conversion
- BEV: Beam Eye View
- CC : Cubic Centimetres
- CT: Computed Tomography
- CTV: Clinical Target Volume
- 3-DCRT: Three-Dimensional Conformal Radiotherapy
- DEBH: Deep Expiration Breath-Hold
- DIBH: Deep Inspiration Breath-Hold
- DMLC: Dynamic Multi-Leaf Collimator
- DRR: Digital Reconstructed Radiograph
- DVH: Dose Volume Histogram
- EPI: Electronic Portal Imaging
- FB: Free-Breathing
- FoM: Figure of Merit
- GTV: Gross Tumour Volume
- Gy: Gray (SI Unit of Absorbed Dose)
- HBSG: Held-Breath Self-Gating Technique
- ICRU: International Commission on Radiation Units and Measurement
- IM: Internal Margin
- IMN: Internal Mammary Nodes
- IMRT: Intensity-Modulated Radiation Therapy
- mDIBH: Moderate Deep Inspiration Breath-Hold
- MHD: Maximum Heart Distance
- MLC: Multi-Leaf Collimator
- MRI: Magnetic Resonance Imaging
- NSCLC: Non-Small Cell Lung Cancer
- NTCP: Normal Tissue Complication Probability
- OAR: Organs at Risk
- OSDB: Obstructive Sleep-Disordered Breathing

- PET: Positron Emission Tomography
- POPS: Proof of Principle System
- PTV: Planning Target Volume
- RoM: Range of Motion
- RPM: Real Time Position Management System, Varian Medical Systems, Palo Alto, CA 994304
- SBF: Stereotactic Body Frame
- SCLC: Small-Cell Lung Cancer
- SD: Standard Deviation
- SM: Setup Margin
- SPO_2 : Oxygen Saturation
- SRT: Stereotactic Radiotherapy
- TCP: Tumour Control Probability

CHAPTER 1: INTRODUCTION

External beam radiotherapy (or radiation therapy) is an important modality in treating malignant tumours. 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 Tumour Control Probability (TCP), and reduced the Normal Tissue Complication Probability (NTCP). The aim of 3-DCRT is to conform the dose around the tumour, plus some extended volume, and then progress to escalate the dose to the tumour in order to improve the TCP and finally reduce the NTCP (Webb, 2001). 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 tumour with a reduced margin. The application of the IMRT technique is unique for each patient since it can be modified according to each tumour shape with the use of a Multi-Leaf Collimator (MLC), which creates an irregular field, providing the best coverage of the tumour (Bortfeld *et al*., 2002).

The use of 3-DCRT is critical in the treatment of unstable tumours, such as those in the thoracic area, where respiratory motion takes place and where most of the critical organs — such as the lung, heart, spinal cord and liver — are located. Since the field is modified and shaped around the tumour, any inter-fraction error (due to day-to-day setup) or intra-fraction error (due to organ movement) can cause geometric uncertainties and failure to deliver the right dose to the right target (Ramsey *et al*., 1999); if these errors are not corrected and subsequently persist throughout the treatment, a geographical miss will take place, whereby the dose prescribed for the tumour (Armstrong *et al*., 1998) will differ from that actually delivered to the tumour, which will result in a poor treatment outcome, a reduced TCP and a higher NTCP.

Inter-fraction motion occurs because the patient is typically treated using multiple treatment fractions; for each fraction, the patient has to be positioned on the treatment couch in a manner which reproduces the planned alignment with the radiation beam. Despite efforts to deliver the treatment as accurately as possible, the position will nevertheless differ from day to day. To date, in most radiation therapy

departments, problems associated with inter-fraction movement have been controlled as much as possible, through the use either of patient immobilisation devices — such as the alpha-cradle (Bentel *et al*., 1997), the body foam-bag and the T-bar (Halperin *et al*., 1999) — or of portal films or electronic portal imaging devices and image-guided radiotherapy, which are designed to reduce setup errors and to increase the accuracy of everyday treatments (Stroom *et al*., 1999).

A number of devices and techniques are also used in order to limit intra-fraction or internal organ motion as much as possible, in addition to any changes in internal organs due to the treatment; this may be achieved by using respiratory gating radiotherapy, adaptive radiotherapy, an Active Breathing Control (ABC) device, or different patterns of breath control which the patient has been/could be trained in, such as Deep-Inspiration Breath Hold (DIBH) and moderate Deep Inspiration Breath Hold (mDIBH) (Halperin *et al*., 1999). While the control of intra-fraction motion nevertheless remains a challenge, the introduction of respiratory manoeuvres and gating radiotherapy with the objective of controlling intra-fraction motion has shown a significant outcome in reducing the Planning Target Volume (PTV) margin for respiration and for limiting the exposure of normal tissue to radiation (Keall *et al*., 2001).

Treatment of Non-Small Cell Lung Cancer (NSCLC) with radiation therapy is always a challenge for two key reasons: Firstly, the presence in the thoracic area of critical organs — such as the spinal cord posteriorly, the heart inferiorly, and the lungs located left and right of the oesophagus — are considered as limiting factors for escalating the dose; and, secondly, the effect on the tumour of respiratory motion may cause an inadequate dose to be delivered to the PTV (Mechalakos *et al*., 2004).

The movement of a tumour due to respiratory motion will range from 0-22 mm in the superior-inferior direction and from 0-10 mm in the anterior-posterior direction (Mechalakos *et al*., 2004). In studies carried out by Mechalakos *et al*. (2004), the effects of respiratory motion on the dose coverage for Gross Tumour Volume (GTV) and the effect of TCP were investigated and monitored; the researchers analysed twelve different treatment plans for patients who had each been previously treated for NSCLC, either by IMRT or by static beam. The GTV ranged from 1.2 cc to 97.3 cc. PTVs were generated by adding 1 cm margin around the GTV. A further 0.6 cm was added in the transverse direction and 1 cm in the superior–inferior direction in order to allow for beam penumbra. The total dose was assumed to be 70 Gy. The

breathing motions were measured using fluoroscopic images; this was done during the free-breathing period. Systematic errors due to respiration motion were investigated. The study concluded that by using the recommendations, the margin for PTV would be sufficient to cover for respiratory motion; however, this needed to be carefully evaluated if the patient was seen to be breathing heavily or if the tumour otherwise had an irregular shape; in some cases, it might be up to 3.8 cm (Ahn *et al*., 2004). It is important to recognise that these ranges differ from one patient to another and will also depend significantly on the location of the tumour and the patient's breathing pattern (Kong *et al*., 2005). Figure 1 shows the movement of the PTV outside the treatment field due to respiratory movement.

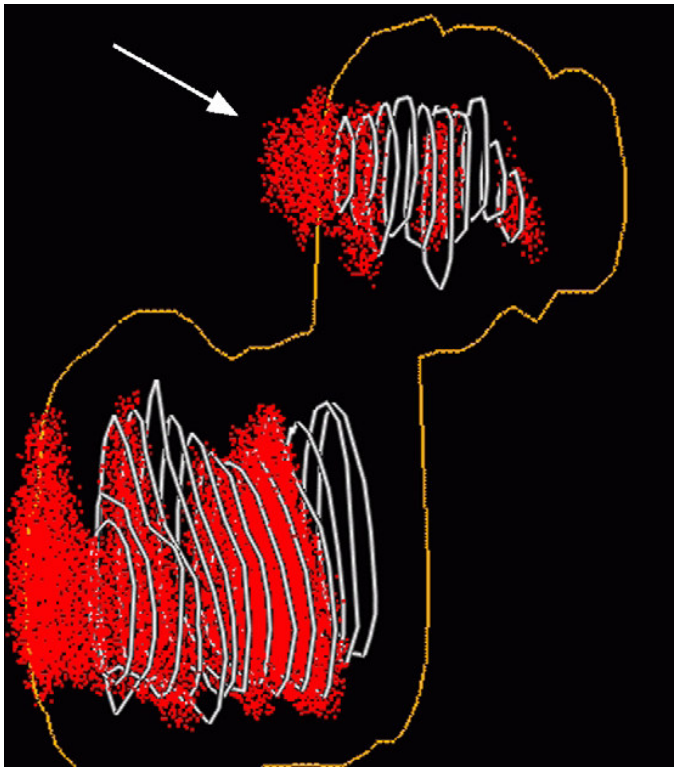

Fig. 1: The effects of respiratory motion

The effective increase in volume and blurring of the shape of the tumour due to its periodic motion is shown in red; the PTV (volume to be irradiated) is shown by the grey coil. Notice how the tumour moves beyond the grey lines, which would constitute an underdose to the tumour with the potential of leaving cancerous cells untreated.

(Image with kind permission of Mechalakos, J. Radiotherapy and Oncology 71:191-200, 2004)

1.1 RESPIRATORY MANOEUVRES AND GATING RADIOTHERAPY

Respiratory manoeuvres — which has the goal of immobilising the organs and tumours during treatment — requires specific patient participation for it to be effective. There are several such manoeuvres, including ABC, DIBH, mDIBH and respiratory gated radiotherapy, as well as tumour-tracking techniques. The ABC, DIBH and mDIBH techniques will all produce significant effects in reducing the volume of normal tissue in the treatment field, but they also have the disadvantage of limitations: For example, they require patient participation; patients must have adequate pulmonary function; and they must have the ability to hold their breath to the full capacity of their lungs (Hanley *et al*., 1999). DIBH requires patients to hold their breath for 10-20 seconds at the end of inspiration under spirometer-based monitoring techniques, which measures lung volume through the measurement of the inhaled and exhaled air, and records it as a function of time. When DIBH is to be used, the patient usually attends a pre-simulation training session, during which he or she is coached by a radiation therapist in the reproduction of the same deep inspiration level during the simulation and treatment.

Techniques, such as DIBH and the use of chest restrictors (devices which apply external pressure to the chest with the aim of limiting its motion and hence the patient's ability to breathe), are poorly tolerated by lung cancer patients, who often have some form of lung dysfunction. In order to overcome these difficulties, techniques that try to capitalise on the patient's Free-Breathing have been investigated; such methods rely on providing patients with some form of feedback signal (audio, visual or audio-visual) which enables them to match their breathing patterns to a predefined pattern. However, the development of these methods has occurred without detailed analysis of the best methods of presenting the feedback signal or of the best breathing pattern to be followed by the patient.

This project is primarily aimed at improving our knowledge base concerning a patient's response to and tolerance of different breath-training regimes which are designed in order to promote a regular and controlled breathing pattern over a time interval commensurate with conventional radiotherapy treatment. In general, this means developing methods of monitoring the chest motion as well as developing a robust method of analysing the data. As a subsidiary aim, it is hoped that the project will lead to the development of a simple and cost-effective device which can, in principle, be used either to control or to support the way in which the patient

maintains a stable breathing pattern without the need for extra equipment, such as Computed Tomography (CT), fluoroscopy imaging machines and treatment units.

1.2 AIMS

The aims of this project are fourfold:

1. To develop a simple breath-monitoring system which is inexpensive, easy to use and patient friendly;
2. to develop an appropriate method/methods for displaying the bio-feedback signal to the patient;
3. to develop a robust method of determining a figure of merit for each method tested; and
4. to use a random sample of healthy individuals in order to establish the best training signal to use (i.e. a simple sine wave based on treatment parameters, a square wave or a signal based on the patient's normal Free-Breathing pattern).

1.3 LAYOUT OF THE THESIS

This thesis is divided into seven chapters. The present chapter has outlined the background of the investigation and the overall objectives of the project. This is followed by Chapter 2 which provides a short introduction concerning the ideas and goals of radical (curative) external beam radiotherapy, together with an overview of the background information available on the various types of lung cancer and its biology. Chapter 2 also discusses the concepts of the various volumes used in defining a treatment, as well as the ideas behind the all-important normal tissue complication probability and tumour control probability.

Chapter 3 reviews in detail the methods and approaches adopted to control respiratory motion in patients with cancer. It considers most of the current techniques, including respiratory gating, breath-hold techniques and respiration synchronized radiotherapy; it also discuses the benefits of each of these techniques in relation to reducing the effects of motion on radiotherapy treatment and setup. Furthermore, the chapter reviews studies of respiratory gating previously used in response to different cancer diagnoses, the control of breathing and the variability of

respiratory motion, the effects of motion on the treatment of lung cancer and, finally, investigations of the benefits of biofeedback in radiotherapy.

Chapters 4 and 5 compose the core of this thesis. Chapter 4 begins by describing the design and construction of a respiratory breathing device, which was built in-house with the view of training patients to control their breathing during radiotherapy treatment. The chapter then progress to providing reports on investigations by way of examining the device and its ability to record breathing patterns.

Chapter 5 describes the methods and the breathing data which were collected during the project. Several models are proposed: free-breathing, audio instruction breathing, and video feedback breathing; their purpose was to produce more consistent and stable breathing patterns during treatment. This chapter sets details data collected on the breathing patterns for each of the subjects, such as audio instruction breathing patterns and video feedback patterns. It also discusses the eligibility of each subject and the challenges associated with the use of the device by the subjects. Chapter 5 also presents a model for calculating the breathing phase and amplitude for each subject, calculated according to individual breathing patterns.

Chapter 6 summarises the findings of the study based on data collected from the breathing patterns of subjects using the respiratory device. It then moves on to consider the potential for the clinical implementation of the device. It concludes with suggestions for future investigations and recommendations for further work.

Chapter 7 provides the key conclusion points of this work and details the benefits of using breathing modalities manoeuvres, such as audio prompting and video feedback, as a means to providing steady breathing patterns; in addition, it gave the limitation of the device and methods and the further work and recommendations.

CHAPTER 2: GENERAL BACKGROUND

2.1 NON-SMALL CELL LUNG CANCER

Lung cancer is the leading cause of cancerous deaths in both men and women worldwide, accounting for approximately 18% of all types of cancer in men and women and causing over 900,000 deaths each year worldwide (Weitberg and Klastersky, 2002). For example, 7.9 million deaths caused by lung cancer occurred in 2007, which amounts to around 13% of all deaths (Howington, 2008). In the UK, lung cancer is the second most common cancer, with 38,313 newly diagnosed cases being reported in 2004 (Hunt, 2008). The lifetime risk of developing lung cancer is 7.63% in men and 5.71% in women; this risk is increased in smokers (Chua *et al*., 2004). The overall five-year survival rate with all kinds of treatment modalities, such as surgery, chemotherapy and radiation therapy, is still very low at only approximately 10%-15%, and mostly depends on the stage of the disease and the stage of detection of the tumour (Kong *et al*., 2005). Unfortunately, approximately 70% of all cases show signs of metastasis upon detection.

The UK five-year survival rate for men and women with all types of lung cancer is 7% (Hunt, 2008). The progression and management of lung cancer depends on two major factors: Firstly, the involvement of any adjacent structures, regional metastasis, or any regional lymph nodes, such as the hilar, mediastinal and supraclavicular nodes; and secondly, the distant metastasis to other organs, which are the lungs, adrenal glands, liver, bone, and brain (Choi *et al*., 2001).

2.2 AETIOLOGY OF LUNG CANCER

The aetiological factors affecting lung cancer include smoking, which is the leading risk factor and accounts for approximately 85% of all cases. Tobacco smoke contains many carcinogens, which are linked to biological effects including mutations and adduct formation (Chung *et al*., 1995). A lifetime smoker is at 20 to 30 times greater risk of developing lung cancer during his or her lifetime than a non-smoker (Parkin *et al*., 2001). Other factors also play a key role, such as age, genetics and gender; for example, the majority of patients develop lung cancer beyond the age of 50, with the average age being 65 years (Weitberg, 2002) and, in relation to genetics, people who

have a family history of lung cancer will also have a slightly greater risk than those with no such history (Weitberg, 2002). A study of the population of Liverpool, UK, carried out by Cassidy *et al.* (2006) found a five-fold increase in risk for those people who had had a first-degree relative who had experienced the disease. Another risk factor in relation to lung cancer is gender, the disease being more common in men than women, although the incidence in women continues to increase due to smoking (Parkin *et al*., 2001). Timofeeva *et al.* (2009) studied gender risk differences and found an increased risk of developing lung cancer in women compared to men due to oestrogen metabolism and the involvement of a certain enzyme called cytochrome P450 (CYP), especially in the early onset of lung cancer. The specific mechanism by which this enzyme affects women's risk of experiencing lung cancer is beyond the scope of this thesis.

Exposure to environmental factors, such as radon — particularly amongst miners (Parkin *et al*., 2001) — and occupational exposure (such as to asbestos, arsenic or cadmium), are also other factors for consideration and are increasing the risk of lung cancer. For instances, asbestos has the ability to cause abnormal segregation of chromosomes and DNA damage; asbestos exposure alone has been associated with a six-fold relative risk of lung cancer. The presence of related disease in the lung and pre-existent non-malignant lung disease, such as chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, pneumoconiosis and tuberculosis, are also factors which are actively increasing the risk of lung sarcoma (Weitberg, 2002).

Lung cancer risk has also been found to be associated with certain polymorphisms in certain DNA repair genes (Rosel *et al*., 2006). Mutations to the DNA repair genes may stop the process of DNA repair and may ultimately lead to cell death (apoptosis). This event will form proto-oncogenes, and inhibit the activity of tumour suppressor genes, subsequently allowing the conversion of normal cells to malignant ones (Anderson *et al*., 1992).

2.3 CLINICAL PRESENTATION

Lung cancer is usually diagnosed and detected in its later stages, with only 10% being diagnosed in the early stages (Table 1); this is mainly due to the nature of lung tumours, which do not produce any pain or discomfort until they have developed to a stage whereby they are large in size and have started to invade the adjacent

structures and blood vessels, at which time symptoms will then begin to appear. The most common symptom of lung cancer is a cough, shortness of breath or dyspnea, which develops early in approximately 60% of lung cancer patients, and is also a common symptom, but which is usually associated with cough and sputum (Beckles M., *et al*., 2003). Haemoptysis is another very common symptom of lung cancer, although it is also considered to be another reason for late diagnosis of lung cancer, since patients who have smoked often cough up blood and have streaking of the sputum, while in their chest X-rays there are rarely any remarkable findings (Beckles *et al*., 2003). Others symptoms of lung cancer are anorexia, hoarseness, chest or bone pain, fever and weight loss (Weitberg, 2002).

STAGE	FREQUENCY OF DIAGNOSIS	FIVE-YEAR SURVIVAL %
I	10%	>60%
II	20%	30%-50%
IIIA	15%	15%-30%
IIIB	15%	3%-6%
IV	40%	<1%

Table 1: NSCLC stages with frequency of diagnosis and five-year survival rates (Ettinger, D. et al*., Clinical Advances in Non-Small Cell Lung Cancer (NSCLC) and Mesothelioma. The PeerPoint Medical Education Institute, LLC, 2005)*

2.4 DIAGNOSIS

Clinical evaluation will include a physical examination and chest X-ray. The primary diagnosis modality for lung lesions is the chest X-ray, which provides a means of detecting enlarged lymph nodes in the chest or abnormal masses in the lungs; however, it has inadequate sensitivity for detecting early or pre-malignant growths at a stage where intervention can affect mortality. The most commonly used modality after chest X-ray is computed tomography scans for chest and abdomen, which provide early findings of any abnormality in the lungs (Weitberg, 2002). Sputum cytology is also considered a key early detection for lung cancer (Kennedy, 2000). There are some other modalities of diagnosis which can also be helpful in detecting

the advanced stages of the disease and the tumour; these are CT with intravenous contrast, Magnetic Resonance Imaging (MRI) of the chest, Positron Emission Tomography (PET), fine needle aspiration, pulmonary function studies, surgical staging with mediastinoscopy/mediastinotomy or thoracoscopy (Weitberg, 2002). Blood tests may also be carried out with the aim of checking the patient's general health; indeed, those which measure the levels of some proteins which are considered as tumour markers could also indicate the presence of a lung tumour. Such tests include PTH (Parathyroid Hormone), CEA (Carcinogenic Antigen) and CYFRA21-1 (Cytokeratin Fragment 19) (Braun, 2006).

2.5 HISTOLOGY OF LUNG CANCER

Lung cancer is classified into two major groups based on their histology and pathology: NSCLC, which accounts for 80% of all lung cancer cases, and Small Cell Lung Cancer (SCLC), which affects approximately 20% of patients (Weitberg, 2002). NSCLC, which is usually located in the periphery of the lung, includes squamous cell carcinoma, adenocarcinoma and large cell carcinoma. SCLC is usually located in the central mass of the lung and is often widespread at the time of diagnosis; it tends to be more aggressive and spreads sooner to distant sites. It is predominantly caused by a significant smoking history (Weitberg, 2002).

2.6 STAGING OF LUNG CANCER

The staging of lung cancer plays an important role in prognosis, the choice of treatment modalities and survival rate; the higher the stage, the worse the prognosis. Staging was developed in order to drive a relation between anatomic extend of the disease and prognosis of patients with lung cancer. The international system for the staging of lung cancer categorises and combines the variation of staging definition, and has given a consistent meaning and interpolation among physicians and scientists worldwide (Mountain, 2000).

The TNM staging system stands for Tumour, Nodes and Metastasis. T1-2-3-4 explains the increasing primary tumour size, where NX-0-1-2-3-describes the absence or presence of regional lymph node metastasis. M0-1 describes the

presence or absence of tumour spread to distant lymph nodes or organ sites (Mountain, 2000). TNM staging is summarised in Table 2, while the staging of NSCLC is summarised in Table 3.

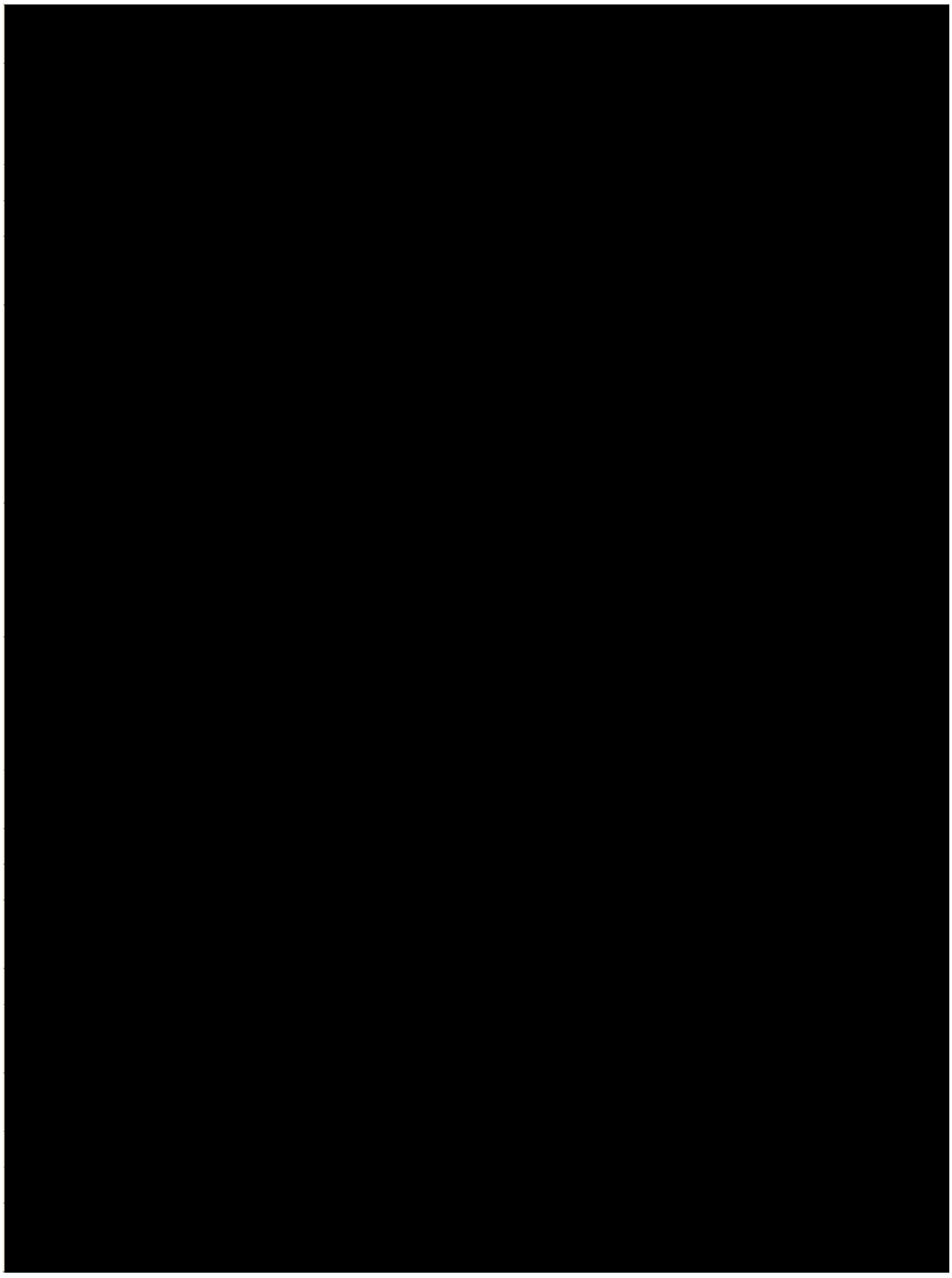

Table 2: The TNM staging of lung cancer

(http://www.oncoline.nl/index.php?pagina=/richtlijn/item/pagina.php&id=22056&richtlijn_id=396)

During the undetected stage, cancer cells are found in sputum (mucus coughed up from the lungs), but no tumour can be found in the lung by imaging or bronchoscopy, or the primary tumour is too small to be assessed.
Stage 0 (carcinoma in situ)
In **stage 0**, cancer is limited to the lung and found only in a few layers of cells. It has not grown through the top lining of the lung.
Stage I
In **stage I,** the cancer is in the lung only, with normal tissue around the tumour. **Stage I** is divided into **stages IA** and **IB**, based on tumour size.
Stage II
In **stage II** cancer has spread to nearby lymph nodes or to the chest wall (the ribs and muscles which make up the area of the body between the neck and the abdomen), the diaphragm (the thin muscle below the lungs and heart that separates the chest from the abdomen), the mediastinal pleura (the thin membrane that covers the outside of the lungs in the area near the heart), or the parietal pericardium (the outer layer of tissue that surrounds the heart). **Stage II** is divided into **Stage IIA** and **Stage IIB**, depending on the size of the tumour and whether it has spread to the lymph nodes.
Stage III
In **stage III,** the cancer has either:
Spread to the lymph nodes in the mediastinum (the middle area between the lungs that contains the heart, major blood vessels, and other structures); or
Spread to the lymph nodes on the opposite side of the chest or in the lower neck.
Stage III is divided into stage IIIA (which is sometimes treated with surgery) and stage IIIB (which is rarely treated with surgery).
Stage IV
In stage IV, cancer has spread to other parts of the body or to another lobe of the lungs.

Table 3: NSCLC Staging

(http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung)

2.7 TREATMENT OF LUNG CANCER

Treatment modalities for lung cancer include surgery, chemotherapy and radiation therapy. The choice of modality is mostly dependent on the stage which the cancer has reached and whether or not the tumour is resectable. Treatment options for patients with NSCLC will also depend on a number of factors, including the stage of the disease, the individual's overall functional and medical status, and patient preferences. Surgery is the primary treatment for patients with early-stage (Stages I and II) cancer who otherwise have a good general health. The goal of surgery is to remove the tumour cells completely and to provide a full cure. Chemotherapy in the late stages of NSCLC shows definite improvement in the median survival rate; however, the overall survival rate is still low (Miller *et al*., 2004). Survival rates and frequencies of diagnosis for the various stages are shown in Table 1.

When chemotherapy is combined with another modality, such as surgery or radiotherapy, there is an improvement in the survival rate. A study by Arriagada *et al*. (1997) showed an improvement in the survival rate in patients with NSCLC if radiation therapy was combined with chemotherapy using an agent such as cisplatin. With this in mind, approximately 3/4 of the patients diagnosed with NSCLC will be at a relatively advanced stage by the time of diagnosis, and so will need another modality, such as radiation therapy (Weitberg, 2002). However, NSCLC is considered to be one of the most difficult malignant lesions to treat with radiation therapy. There are several reasons for this: Geometrical difficulties due to respiratory motion, the number of low-tolerance neighbouring organs, such as the spinal cord and the oesophagus (Dirkx *et al*., 1999), and dosimetric difficulties due to the presence of huge inhomogeneities (Dirkx *et al*., 1999). The role of radiation therapy for the treatment of NSCLC may be either curative or palliative; the treatment is usually delivered via an external photon beam. The field arrangements usually begin with 2 fields — anterior-posterior and posterior-anterior — to a total dose of 45-50 Gy (1.8-2.0 Gy per fraction); boost fields are then applied (usually oblique fields with shielding for the spinal cord) and the total dose is taken up to 60-70 Gy for curative and 30 Gy for palliative therapy (Khan and Potish, 1999).

Some studies have suggested higher doses for NSCLC to increase the local control and survival rate: Martel *et al.* (1999) recommend a total dose of 84 Gy in 42 fractions in order to achieve 50% Local Progression-Free Survival (LPFS) > 30 months without any increasing toxicity for NTCP. The aim of the study was to

estimate the TCP model parameters, which are the doses required for producing 50% probability of tumour control (D50) and the normalised slope (y). The study was based on the clinical experience of using 3-DCRT treatment plans for NSCLC (Martel *et al*., 1999).

The study analysed treatment plans for 76 patients who had been treated for NSCLC between the years of 1986 and 1992. Their dosimetric data included the tumour volume, which ranged from 4.3 cc to 856 cc, the nodal involvement, the tumour stage, histology and other factors such as sex, age and weight. The treatment plans for 66 patients were composed using the conventional AP/PA treatment field for NSCLC, while the remaining 10 were treated using 3-DCRT fields. All patients were prescribed a total dose ranging from 64 Gy to 82 Gy. TCP was calculated using a mathematical model. LPFS was used as a measurement for the local TCP. Although the study suggested that using LPFS with NSCLC is difficult, since it is low in lung cancer patients and reduces with time, the results showed an increase in LPFS when the prescribed dose was higher than 70 Gy (Martel *et al*., 1999). The study, which was comprehensive and ran for about 6 years, showed that in the treatment of NSCLC, increasing the dose would be beneficial, improving the survival rate without causing toxicity to any normal tissue.

Another study, by Kong *et al*. (2005), suggested that the total dose should be up to 70-97 Gy if all the critical criteria of the surrounding normal tissue were taken into consideration; however, it is essential to note that the higher the prescribed dose, the higher the risk of both short- and long-term toxicity to healthy tissue. Overall, conventional external beam radiotherapy suggests a poor outcome, and the result is not completely satisfactory: the median survival rate is still quite low, at only around 8-12%, and the five-year survival rate is 5-10% (Sixel *et al*., 2003).

Treatment of NSCLC with radiation therapy is always a challenge for two main reasons: firstly, there is the presence in the thoracic area of critical organs — such as the spinal cord posteriorly, the heart inferiorly, and the lungs located left and right of the oesophagus — which are considered to be a limiting factor for escalating the dose; secondly, the effects on the tumour of respiratory motion may cause an inadequate dose to be delivered to the PTV (Mechalakos *et al*., 2004).

However, in recent years, the introduction of 3-DCRT and IMRT have brought the hope of better local tumour control, higher survival rates and fewer normal tissue complications (Bradley *et al*., 2002). Dose escalation has improved local control, but

may nevertheless cause chronic pneumonitis, which can lead to death in some cases (Claude *et al*., 2004). There are some basic precautions to be taken when using 3-DCRT in order to reach the goal of successful treatment with a higher tumour control outcome and less normal tissue toxicity: first, the margin around the PTV has to be as tight as possible; second, all inter-fraction and intra-fraction movement has to be controlled (see Chapter 1); and third, the dose has to conform with the lesion and be within tolerance levels for normal tissue. In recent years, 3-DCRT has proven its effectiveness in the treatment of locally-advanced unresectable NSCLC, as it provides excellent coverage for the GTV, allowing the dose to be raised without a concomitant increased risk of harm to normal tissue (Lagerwaarda *et al*., 2002).

A study by Armstrong (2000) investigated the impact of 3-DCRT on the treatment of NSCLC and the potential of the conformal treatment to increase the survival rate. It reviewed every aspect of the 3-DCRT, such as the software and hardware technology, the delineation of target volume used with the 3-DCRT, the techniques available for escalating the dose and the effects of normal tissue toxicity (pneumonitis) when the dose was escalated. The main finding was that 3-DCRT was able to deliver high radiation doses (>70 Gy) with minimum toxicity to lung tissue compared with that of conventional treatment, thus increasing the survival rate for locally advanced NSCLC. However, the study suggested a long follow-up for patients after completing the treatment, for the purpose of detecting any long-term toxicity (Armstrong, 2000).

Xu (2002) conducted a study with the aim of improving the outcome of radiation therapy for NSCLC without increasing the risk of toxicity to normal tissues. The study was carried out on 135 patients with NSCLC, of whom 62 were treated with high-dose 3-DCRT, while the remaining 73 were treated using conventional radiotherapy. Three months after treatment, the rate of remission of the lesions was found to be 44.9% in the conventional therapy group and 77.8% in the 3-DCRT group; there was also a significant difference ($p<0.01$) between the two groups in the efficiency rate. The 1-2 year survival rate was determined to be better under 3-DCRT, at 77.8% in comparison to 42.5% for conventional radiotherapy.

Another study, by Grills (2003), evaluated the benefits of four different techniques for reducing normal tissue toxicity and increasing the tumour dose when treating NSCLC. The techniques evaluated were Intensity-Modulated Radiation Therapy (IMRT), 3-DCRT using multiple beam angles, limited 3-DCRT using only two

or three beams, and the standard technique of radiation therapy, which included Elective Nodal Irradiation (ENI) to treat the mediastinum. The study, which was carried out on 18 patients with stage I to IIIB inoperable NSCLC, concluded that the use of 3-DCRT, especially with only three or four beams, reduced the NTCP by reducing the mean dose and the volume of lung receiving at least 20 Gy (lung V_{20}) compared with the standard technique which includes ENI. It also increased the deliverable radiation dose >80% in comparison with ENI (Grills, 2003).

In another investigation, Miller (2004) attempted to evaluate the GTV coverage and normal tissue complication probability using the conventional 2-dimensional radiation therapy and 3-DCRT. The subjects were 34 NSCLC patients and the results showed that 3-DCRT could provide better coverage for GTV in comparison with 2-D radiation therapy, thus permitting an increased total dose to the target volume without increasing the toxicity to the normal tissues (Miller, 2004).

All of the above studies suggest that increasing the total prescribed dose would ultimately increase the survival rate and local tumour control in NSCLC without increasing the risk of normal tissue damage. However, consideration of toxicity remains under investigation and caution must be applied whenever higher doses are used.

2.8 THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY

Current state-of-the-art radiation therapy makes use of highly advanced modalities in imaging and treatment, and has led to the treatment of cancer becoming more precise and highly conformed, ultimately increasing the accuracy of the treatment and minimising the toxicity to adjacent normal tissue. The most advanced technique in recent years has been 3-DCRT, which has been developed from 3-D imaging modalities, such as MRI, PET and CT, and relies on full anatomic information relating to the patient, which includes the lesion site but is also extended well beyond it to account for any effects of radiation scatter in the area outside the lesions (Purday, 1999). In the patient model, this information will then feed into the radiation planning system. Thus, 3-DCRT is a treatment modality using 3-D anatomic information in order to establish the arrangement of the treatment fields so that the dose can be precisely conformed around the tumour volume in such a way that a higher dose will be delivered to the tumour, while a minimal dose will be delivered to adjacent normal tissue.

The major factor upon which 3-DCRT depends is the delineation of the anatomic structure of surrounding normal tissue and the tumour itself. in order to achieve accurate dose distributions and to arrange the irradiated field in such a way that successfully avoids normal, healthy tissue, radiation oncologists must contour not only the bony landmarks, as in 2-D planning, but also all of the normal tissue in the area of the irradiated field and lesion, which some may consider time-consuming when compared with 2-D treatment planning.

The 3-DCRT plan will be based on contouring the Gross Tumour Volume (GTV), the Clinical Target Volume (CTV) and the Planning Target Volume (PTV), plus the normal adjacent tissue and the Organs at Risk (OAR) in the irradiated area. One major tool of 3-DCRT is the Beam Eye View (BEV) (Figure 2); this is the basic visualising tool (Khan, 2003), providing a 3-dimensional view of the lesion and the adjacent normal tissue, which ultimately helps the planner of the radiotherapy treatment and the radiation oncologist to view the patient in the same orientation as a radiation beam pointing in that same direction, and thus helping them to arrange the treatment fields to target the PTV and avoid healthy normal tissue. Figure 2 shows a BEV of a 3-DCRT field with PTV (red) and the OAR in the area (kidneys, liver, and spinal cord).

Fig. 2: Beam Eye View of 3-DCRT planning
(http://www.radonc.uchicago.edu/typea/scripts/content.cgi?template=defa)

Another tool which is unique to 3-DCRT planning is the Digitally Reconstructed Radiograph (DRR) (Figure 3), produced from the patient's CT images. DRR is mostly used with the aim of localising the volume of interest and the radiation field for delivering radiation treatment. It is produced by calculating the set of volume data which has been produced by the CT images; this produces images similar to the simulation portal image, but with noticeably better contrast and detail of soft tissues and bone structures than regular simulator films. Moreover, it provides greater freedom, enabling viewing of the structures of interest in relation to the central axis of the radiation beam from any viewing angle. It also provides beam geometries of the actual treatment field which the simulation cannot provide due to the geometric limitations of the simulator, such as the restricted physical movement of the apparatus (e.g. gantry and table) (Khan, 2003). The outcome of the treatment with 3-DCRT will depend on how accurate and precise the delineation of GTV, PTV and OAR are; however, the use of PET or CT will no doubt improve the treatment plan.

Fig. 3: DRR of lung field 3-DCRT
(http://www.webtie.org/sots/Meetings/Lung/June192001/
/Bogart/images/slide30_trans.jpg)

Fitton *et al*. (2008) carried out a study with the objective of establishing a protocol to use PET in the delineation of the Primary Tumour (PT) in treating NSCLC, which would lead to a reduced inter-observer variation in gross tumour volume and improve the treatment plan for radiation therapy. The 22 patients in the study all had localised NSCLC. The CT and three-dimensional (3D) PET data images were collected separately before the initiation of the treatments. The patients were then divided into two groups according to the tumour-adjacent organs: the first group comprised patients with a primary lung tumour which was surrounded by the lung and visceral pleura, where there was no invasion or chest wall involvement, while those in the second group had a primary lung tumour with invasion to adjacent nodes, such as hilar nodes, or adjacent structures, such as the heart. The study had two phases with a year between them: the first phase was when the primary tumour was delineated by physicians using CT images, while the second phase was completed a year later when the primary tumour was delineated using fused images of CT and PET.

The result for Group One did not show a reduction in inter-observer variation ($p = 0.1628$) for all regions using CT, while for Group Two there was a strong reduction in inter-observer variation when compared with Group One. A significant difference was detected between the two groups (the difference between the two phases was

significant, i.e. p = 0.0003, paired Student's t-test). In conclusion, it was suggested that using PET imaging improves the segmentation of the primary tumour (Fitton *et al*., 2008). PET images and fused images of CT and PET are considered valuable tools in the treatment of thoracic tumour where the PT is surrounded by healthy normal tissue and tissue which limits the radiation dose, such as heart and hilar nodes, as the study suggested.

Fig. 4: Dose volume histogram, showing dose against percentage of irradiated volume of PTV, Lung and spinal cord

(http://www.tomotherapy.com/images/cases/stAgnes_ctrue_8.jpg)

Figure 4 shows a third important tool in 3-DCRT planning: the Dose Volume Histogram (DVH), which is a graphical display of three-dimensional dose distribution data which presents the dose distributions to the volume of normal tissue and to the lesion; the dose versus volume of the area of interest is displayed, which includes the tumour and the contours of all critical structures. The DVH of a good plan will produce a higher dose to the target volume and a minimum dose to the normal surrounding tissues. DVH is considered to be a major and important tool for analysis of the outcome of the plan, and is ultimately a useful way of making comparisons plans. Using 3-DCRT tools, such as DVH, in the evaluation of individual treatment plans and the development of biological models, such as TCP/NTCP, has also greatly assisted clinicians in designing treatment plans and in prescribing a tumouricidal radiation dose without causing any toxicity to adjacent organs. Tumour Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) are values which are used to quantify the damage to the tumour and to the surrounding

normal tissues respectively. Ideally, treatment with ionising radiation aims to achieve 100% TCP and 0% NTCP; in practice, the estimated value of each depends on clinical experience.

2.9 GTV, CTV AND PTV

It is important to clearly define the three main terms designating tumour volume. The International Commission on Radiation Units and Measurement (ICRU, 1993; 1999) has released two reports offering recommendations, definitions, and suggestions for radiation therapy treatment margins and volumes, the volumes being based on three definitions of GTV, CTV and PTV (Figure 5).

The gross tumour volume is defined by the gross palpable tumour extent. It includes the tumour, the tumour bed, and any microscopic disease, and is defined as 'the confirmed tumour that is palpable or visible by physical or radiological examination' (ICRU, 1993) (Figure 5). The GTV can be defined by physical examination or by any radiological diagnostic method, such as CT, MRI or PET. In NSCLC, the GTV includes the tumour or residual tumour, as well as any lymph nodes involved.

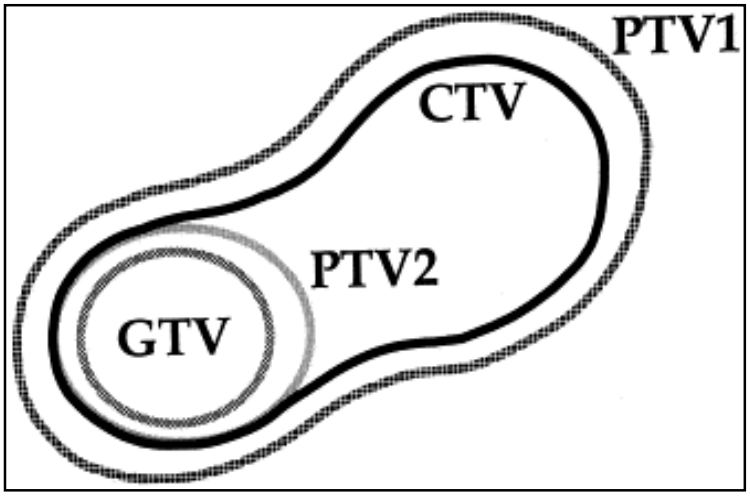

Fig. 5: Gross Tumour Volume (GTV), Clinical Target Volume (CTV) and Planning Target Volume (PTV1 and PTV2) (Graham et al*., 1999).*

The clinical target volume comprises the GTV and any subclinical or microscopic disease, including potential sites which are at high risk of disease, disease extension

or nodal disease. The definition of the CTV is usually based on general oncology principles, and the experience and knowledge of the radiation oncologist. Its determination normally requires the radiation oncologist to consider the local invasive capacity of the lesion, and its ability to metastasise to other areas during the period from diagnosis to treatment. Once the CTV has been defined, the dose and dose distribution will be calculated in mind of achieving the desired treatment goal, which may be curative, palliative or local tumour control treatment. In the case of NSCLC, the CTV is usually defined with a margin around the GTV to cover lymph node regions, such as the ipsilateral hilum and the mediastinum, divided into two values: The ipsilateral hilum and the ipsilateral mediastinum, and the subclavicular fossa (Figure 6) (Graham *et al*., 1999). When a dose is prescribed to the CTV, the radiation oncologist must balance the treated volume in order to produce a Tumour Control Probability with the normal tissue toxicity of the adjacent healthy tissues and Organs at Risk (OAR).

Fig. 6: The thoracic lymph nodes (http://lelaneemeollamokowich.files.wordpress.com/2008/03/lymph-nodes-of-pulmonary-system.gif)

Finally, the planning target volume is calculated by ensuring that all the tissues included in the CTV will receive the prescribed dose, which means that a larger geometrical area will be irradiated (Graham *et al*., 1999; ICRU, 1999). The PTV accounts for variations in patient setup as well as any possible uncertainties or errors, such as inter-fraction setup errors and tumour mobility; it includes a setup margin (SM) (Figure 7, Pg 38), which takes into account all uncertainties in patient-beam positioning in relation to the treatment machine coordinate system. Moreover, included in the PTV is the Internal Margin (IM), which allows for any internal organ motion such as respiratory motion. A study by Graham *et al*. (1999) suggests that the PTV will have two values: The first, PTV1, includes the GTV and CTV, and has a margin for any uncertainties; the second, PTV2, is contoured around the GTV with a margin ranging from 7 to 10 mm (Figure 5). The dose prescriptions are specified to the central points of PTV1 and PTV2 (isocentre). PTV1 will take the initial dose for treatment — which in the study was 50 Gy — while PTV2 will take the boost dose, which was 70 Gy (Graham *et al*., 1999; ICRU, 1999).

Thus, the PTV is larger than the CTV, mostly for the purpose of covering for any geometric uncertainties due to intra-fraction motion or inter-fraction uncertainties and patient setup errors. In the treatment plan, the PTV has to be covered by ≥95% of the isodose line (ICRU, 1993; 1999). The usual margin from CTV to PTV is between one and two cm (Mechalakos *et al*., 2004).

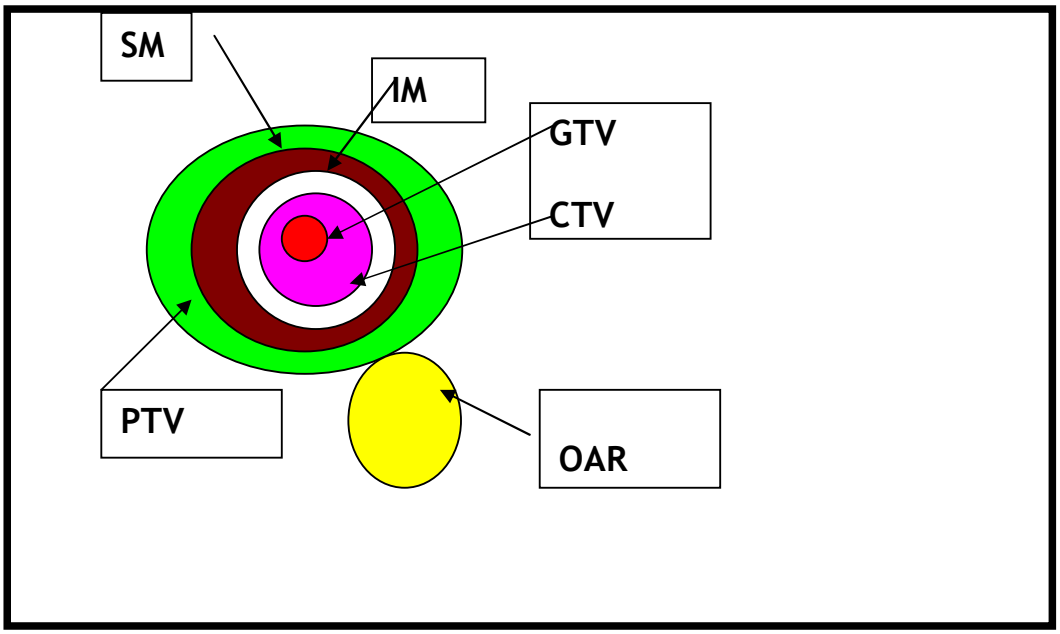

Fig. 7: Target definition (ICRU, 1999)

The GTV is defined as the volume which can be demonstrated to contain tumour cells and can be observed on CT images. CTV is the volume which is created by adding a margin to GTV, to account for subclinical spread of the tumour. PTV is the volume created by adding a margin to the CTV; it accounts for changes in position which include the Setup Margin (SM) and for the intra-fraction motion, which includes the Internal Margin (IM). OAR is an Organ at Risk in the treatment field.

PTV margins should be individually determined and set for each patient, since tumour motion varies from patient to patient depending on tumour location. A study by Sixel *et al*. (2003) investigated the use of a digital fluoroscopy imager attached to CT simulation in order to measure the tumour motion in three dimensions for patients with NSCLC; the overall objective was to reduce the planning target volume for each patient, which would reduce the exposure of normal tissue within the radiation field. The 10 patients in the study, of average age 67.5 years, had unresectable NSCLC with nodal involvement. Their tumours were located in the upper lobe, right middle lobe, right lower lobe, left upper lobe and left lower lobe. The tumour volumes ranged from 13 cc to 276.40 cc. Tumour motion was measured during the simulation using CT and fluoroscopy over periods of several breathing cycles. The radiation oncologist then contoured GTV and CTV, and PTV with a 15 mm margin. The results of the study showed that the tumour could vary in motion from patient to patient, depending on the location of the tumour, with greatest variation (more than 10 mm) in the

superior-inferior direction. This suggested that the margin added to PTV for intra-fraction motion should be calculated individually for each patient and that using a standard PTV margin would be improper (Sixel *et al*., 2003). Although the study used only ten patients, which was considered to be a limiting factor, it shows that each patient's anatomy and tumour is unique, so that PTV margins should be customised and individualised accordingly.

While increasing the radiation dose to 70-80 Gy could give better local control, as reported in other studies referred to above, it could also increase the normal tissue toxicity, particularly if the tumour moves during treatment (Lisbshitz, 1984). Caraig (2001) investigated whether the superior-inferior motion of the tumour was predictable from location or pulmonary functions. Their study, of 22 patients with unresectable NSCLC stage I, IIIA, IIIB and IV, estimated the tumour motion using double exposed orthogonal simulator films which had been taken during the breathing cycles: one exposure was taken at the maximum expiration and the other at the maximum inhalation. The differences in the tumour position between the two films were used to calculate the maximum movement of the tumour. The study found that superior-inferior tumour movement could not be predicted from the tumour position and pulmonary functions; in addition, it suggested that the PTV margin should be individualised for each patient — a recommendation confirmed by Sixel *et al*. (2003) — and that using respiratory gating or breathing control techniques could ultimately improve the outcome of the treatment by reducing normal tissue toxicity (Caraig, 2001). Taken together, the work of Caraig (2001) and Sixel *et al.* (2003) shows that the treatment of NSCLC is always difficult, especially if the movement of the tumour cannot be predicted; hence the importance of limiting respiratory motion, by using respiratory gating or breathing manoeuvres, or by increasing the PTV margin to cover the tumour motion.

The PTV essentially incorporates the safety margin required to allow for the external setup uncertainties in beam alignment and daily patient setup for any internal organ motion and for any organ deformation, such as changes in size or shape due to the treatment (Antolak and Rosen, 1999). Thus, the PTV is the volume that receives the radiation during the treatment, encompassing the tumour and its margins to cover for all geometric uncertainties.

Uncertainties include both systematic and random errors, which have different inputs to the treatment. Systematic errors occur in the treatment in the same direction and with the same timing in each session, and may be attributed to differences in

table sag, laser calibration or mechanical calibration between different rooms (CT, simulator and accelerator) (Craig *et al*., 2001); they may be corrected in the first few fractions by repeating the portal films or using Electronic Portal Imaging (EPI). By contrast, random errors occur in different areas and at different magnitudes in every treatment; they are mostly due to differences in the patient setup error and organ motion, and thus cannot be predicted or corrected. Systemic and random errors will have different radiobiological effects on the treated tumour and the surrounding normal tissues, which can be seen in the TCP or NTCP results of the treatment (Craig *et al*., 2001). Smaller systemic errors will also have a smaller effect on the tumour control probability, whereas larger systemic errors will have a larger effect (Lagerwaarda *et al*., 2002).

Herk (2003) investigated the biological and physical effects of random, systematic geometric errors and respiratory motion in delivering a fractional radiation dose to CTV by using a Gaussian blurring model. A software model was developed in order to calculate the effects and in order to compare the resulting dose plan distribution with the Gaussian model of the planned dose. For physical effects, the model used hypothetical dose distribution with Gaussian distribution and random errors estimated from the normal distribution, with the respiratory motion error added in the craniocaudal direction. For biological effects of the treatment, the study used a linear quadratic model by which the physical dose was converted to the biological effective dose and the number of fractions calculated. The study found that respiratory motion could cause large systematic errors, but did not mention how large these errors were, since this was considered to be beyond its scope. It did, however, suggest that if respiratory motion has a small amplitude it should be treated as Gaussian, while motion of larger amplitude would cause asymmetry and would lead to irregular total dose distributions; this would then help in deciding the margin for random errors, which should be based on the direction of respiratory motion. Regarding the effects of random errors, the results indicated that a shift of 1 cm in CTV away from the radiation source would cause a decrease in the total dose of 6%; however, the direction of the tumour had no effect on random errors (Herk, 2003).

Establishing the PTV is a major factor in achieving successful treatment, because the correct PTV margin will ultimately produce the best coverage of the target volume with the maximum dose delivered to the tumour site, whereas expanding it beyond this limit would expose normal adjacent tissue to excessive radiation, which could cause complications; in the case of NSCLC, these may include pneumonitis or other

major respiratory problems, which can, in some cases, lead to death (Sunyach *et al*., 2000).

The outcome of the treatment and the prognosis of the disease will thus depend on the accuracy of the clinical delineation of the GTV, CTV and PTV, allowing a high homogenous dose to be delivered to the target while also limiting the dose to the adjacent normal tissue. Developing the PTV from the CTV involves many procedures, including the acquisition of data, its transfer to the planning system, and contouring all the critical structures in the area by using all the features available in the planning system, such as BEV and DRR. Meanwhile, patient setup, patient movement, internal organ movement and tumour movement must all be taken into consideration (Armstrong, 1998) as all stages of the delineation of the GTV are usually contoured manually by the radiation oncologist.

GTV delineation for 3-DCRT is done by using the images from a number of planning modalities, such as CT and MRI, which usually covers the thoracic area from the bottom of the larynx to the bottom of the second lumbar vertebra (Armstrong, 1998). The images are then transferred to the planning system, where computer software tools are able to automatically create the CTV and the PTV according to margins which have been determined for each organ. Creating the PTV from the CTV is limited by the surrounding normal structures; the BEV is a useful tool here, providing the planner with all the details of the location of the CTV and the surrounding normal structures. Antolak and his group at the University of Texas MD Anderson Cancer Centre (Antolak *et al*., 1999) recommend that the CTV to PTV margin should have a radius expansion of 1.65 times the Standard Deviation (SD) of geometric uncertainty in all directions (X, Y, Z), which means that each point of the CTV has to be covered by at least 95% of the PTV. The goal of this recommendation is to keep the CTV covered at all times with the prescribed dose, so if the PTV receives 95% of the prescribed dose, the CTV will have a minimum of 90% coverage.

Craig *et al*. (2001) examined CTV-PTV margins and the uncertainties involved, concluding that the judgment of the margin is critical: If it is too tight, there is a probability that the CTV will not receive the full recommended dose, reducing the TCP; if it is too large, the toxicity to adjacent normal tissue will increase, which means an increase in NTCP. Their study presented a model for creating a PTV while evaluating the range of associated uncertainties and their effect on the TCP. The recommendation was a uniformed margin of 0.7 mm which, in the case of a spherical

CTV, would give 95% coverage of the PTV. However, an irregular shape would receive a different coverage.

2.10 ISSUES IN APPLYING IMRT TO MOVING ORGANS

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 major problem with using IMRT to treat lung and abdominal tumours is that the movement of the tumour 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 around 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 PTV as planned. Conformal radiotherapy, which aims to conform the dose around the target volume while sparing the adjacent normal tissue and the OAR (Ramsey *et al*., 2001), includes 3-DCRT, stereotactic radiotherapy (SRT) and IMRT.

In this project, we consider only 3-DCRT and IMRT which, by conforming the dose, allows increased local control and survival rates. From the radiobiological view, 3-DCRT aims to maximise the TCP and minimise the NTCP. IMRT based on modulating the beam intensity across the treatment field, allowing the delivery of a uniformed dose to an irregular target through non-coplanar or coplanar fields, while sparing as much of the adjacent normal tissue as possible. The accuracy of use of both 3-DCRT and IMRT depends on the precise definition of the tumour volume (GTV, PTV and CTV), as any misdelineation could consequently result in a poor treatment outcome and local-distance metastasis.

CHAPTER 3: LITERATURE REVIEW

3.1 INTRODUCTION TO RESPIRATION MANAGEMENT

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 tumour, which is A static relative to the radiation beam. This provides the opportunity to maximise control over the dose delivered to the tumour as well as that delivered to normal healthy tissues and organs at risk. However, as discussed in Chapter 1 and shown in Figure 1, tumours of the lung, liver and kidney are not stationary but move with the patient's breathing cycle: Ohara *et al*. (1989) and Ross *et al*. (1990) have shown that such tumours may move 1-3 cm during quiet breathing. Thus, as already mentioned, the goals of radiation therapy are affected not only by the random and systematic daily setup errors but also by tumour motion, which is directly associated with normal respiratory activity. Respiratory motion not only affects the tumour and PTV, but also plays a role in increasing the toxicity to the healthy adjacent tissues, such as the spinal cord and oesophagus (Weissa *et al*., 2008), which can move into the radiation field during treatment. In order to minimise respiration-induced motion and to limit the effects of intra-fraction motion on tumours, the direct effects of respiratory motion on NTCP and TCP have been investigated by several groups of researchers. Most of the studies previously carried out have assessed the effectiveness of using breath-hold manoeuvres and breath-control devices with the objective of eliminating or reducing intra-fraction motion, thus allowing a reduction of the respiratory margin around the PTV, sparing the normal tissue, and escalating the tumour dose (Weissa *et al*., 2008). Generally, such investigations have involved the study of breath-hold at inspiration or expiration during CT-scanning and treatment.

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 tumours: Deep Inspiration Breath Hold (DIBH), Deep Expiration Breath Hold (DEBH) and self-breath holding during the inspiration or expiration phases. There is also another type of breath hold which is used for breast cancer treatment, called moderate Deep Inspiration Breath Hold (mDIBH).

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. There are, however, other techniques which rely solely on the use of external control devices to actively modify the patient's breathing or chest wall movement, or which otherwise attempt to use the patient's breathing or chest wall movement to control the beam-on and beam-off characteristics of the radiotherapy treatment machine; these methods include the use of a spirometer, the Active Breathing Control (ABC) system, Free-Breathing gating, respiratory gating radiotherapy (coupled with either breath hold, active breathing control devices or IMRT), real-time tumour tracking (robotic radiotherapy) and synchronised respiration techniques. Each method is discussed in the following sections.

3.2 BREATH HOLD

The concept of the breath hold (BH) technique is to immobilise the tumour by holding the breath, which, in theory, improves the outcome of radiation therapy, allows for dose escalation and reduces the toxicity to the surrounding normal tissue (Rosenzweig *et al*., 2000). This technique is mostly used for patients with lung cancer, sometimes in association with external devices such as ABC or a respiratory gating system; alternatively, it may be used alone with or without respiratory mentoring (patient training). Rosenzweig *et al*. (2000) have suggested that the use of the DIBH technique could allow a 10% increase in the prescribed tumour dose with a concomitant reduction in the normal tissue dose, which would therefore improve patient outcomes.

Barnes *et al*. (2001) investigated the benefits of using DIBH in patients with NSCLC to immobilise the tumour, then compared these with free breathing (FB). The study was performed on 10 selected patients with stage I-IIIB NSCLC, Karnofsky performance status ≥ 60% and a tumour mass visible under anterior-posterior (AP) fluoroscopy (Karnofsky performance status is a scale index which is used to classify patients with cancer in order to determine the treatment modality of each patient and the prognosis: the lower the scale, the worse the prognosis and outcome of the treatment (Abernethy *et al*., 2005)). In this study, the selection criterion was the ability of the patients to hold their breath for 15 seconds, with tumour location in different areas of the lungs, such as right lower lobe, right upper lobe, left lower lobe and right

middle lobe. The measurements were taken in two sessions: in the first, fluoroscopy images were taken when the patient was in the treatment position, breathing freely with no instruction, and five breathing cycles were recorded; in the second, the BH manoeuvre was employed, where the patient was asked to hold his/her breath for as long a period as possible, without any other device or manipulation supporting the BH. This session was repeated three times in order to estimate the mean time of DIBH. The tumour position at the superior edge of the FB fluoroscopy was marked and used as a guide for the tumour position during BH.

The maximum superior and maximum inferior tumour positions were recorded for five seconds during DIBH. The average superior-inferior displacement of the tumour was estimated from the three BH recording sessions. For each patient, three 3-DCRT plans were generated with the aim of establishing the margin needed to generate the PTV from GTV: the first PTV was produced from FB scans, the second from DIBH scans and the last from the DIBH scan, but using the FB margin. Each of the plans had the same treatment parameters, with treatment energy of 6 MV and total prescribed dose of 70.9 Gy. The results showed a reduction of 32.5% in lung volume receiving ≥ 20 Gy when the DIBH manoeuvre was applied, for two reasons: the increasing lung volume when the patient performed deep inspiration and the reduction in PTV margin due to tumour immobilisation. Although the results indicate that the technique is a promising one which could reduce the dosimetric effect of tumour motion and reduce the PTV margin, allowing dose escalation, it could nevertheless not be applied to most or all patients with NSCLC, for many reasons. First, the number of patients was limited, with the study being carried out on only 10 patients, yet two of these could not cope with the manoeuvre. Second, the authors of the study warn that before patients could use such manoeuvres, they would have to meet a number of eligibility criteria, such as the ability to hold and control breathing for a certain amount of time (BH ≥15 s). Finally, this manoeuvre involves the use of fluoroscopy imaging, which adds to the exposure dose to patients. This indicates the need to develop a technique to produce stable breathing patterns that would be suitable for all patients with NSCLC and would not rely on the use of a fluoroscope.

In another study, Hanley *et al*. (1999) used the DIBH technique to decrease lung density (when patients performed DIBH, it increased the air volume in the lungs while simultaneously reducing lung density, which therefore reduced the volume of irradiated normal tissues) and to immobilise the tumour during treatment, again reducing the respiratory margin and allowing an increase in the prescribed dose to lung tumours. The study examined five NSCLC patients at stages IIA to IIIB,

Karnofsky performance status 70-90, with tumours located in the right middle lobe, right middle/lower lobe and left lower lobe. The patients, who were required to hold their breath for 12 and 16 seconds, had training sessions before the treatment and simulation, and so were coached in how to perform a reproducible DIBH. The coaching session began with quiet tidal breathing, followed by slow deep inspiration, a maximum inspiration, then a breath hold. A spirometer was used to help the patients hold their breath and to measure the inhaled and exhaled air volume.

Each patient underwent four CT scans in different respiratory conditions: FB, DIBH, shallow inspiration BH and shallow expiration BH. The PTV for the DIBH scan included a margin for setup uncertainty of 0.75 cm; however, the margin for respiratory motion was reduced from 1-2 cm to 0.2-0.5 cm. 3-DCRT planning was used in order to delineate the GTVs in all the different CT scans, which were taken during the different breathing manoeuvres, and three different treatment plans were produced with the same treatment parameters. The first plan was produced from the FB scan with normal lung density, the second from FB with normal lung density, although the margin for PTV was reduced to estimate the benefit of gated radiotherapy, and the final plan was produced by using DIBH CT scans to establish the effects of immobilising the tumour and the reduction of lung density. The results showed that using DIBH would reduce the normal tissue complications of the lungs and would then facilitate dose escalation. Lung density was significantly reduced by 28% and 37% in two patients respectively, and one patient with a very small tumour motion had his lung density decreased by 43%, while the other two patients' lung density decreased by 16% and 4% respectively. The mean reduction in lung density for all five patients was 0.26 g/cc.

These results indicate that there are three advantages to using DIBH over the other breath-holding techniques: first, this method provided a powerful tool for immobilising the tumour if the patient could hold his/her breath for 12 to 16 seconds; second, since the intra-fraction motion was controlled, it reduced the normal lung volume in the area of high dose by 18%, which subsequently reduced the NTCP and could aid in escalating the dose; finally, it reduced the lung density and decreased the mass of irradiated lung, which also allowed the escalation of the dose (Hanley *et al.*, 1999). However, the study is considered to be limited, since it was carried out on only five patients, as there were only five who were able to control their breathing and hold their breath for the required amount of time. In addition, the patients had been verbally coached and forced to hold their breath by using a spirometer, which added stress and increased the likelihood that patients would be distressed by the

combination of radiation treatment, DIBH and the spirometer. All of these factors could ultimately increase the treatment time and the workload of staff.

Rosenzweig *et al*. (2000) investigated the benefits of using 3-DCRT with DIBH in order to treat NSCLC, aiming to immobilise the tumour and then decrease the PTV margin, which would lead to less normal tissues toxicity. Their study involved seven patients with NSCLC, all of whom had been trained to perform DIBH before the simulation session. The training session started with quiet tidal breathing, then verbal coaching to perform deep inspiration, followed by deep expiration, then deep inspiration and finally breath-hold. The patients followed this sequence of breathing with the aim of producing approximately 100% vital capacity during breath hold. A differential pressure pneumotachograph spirometer (a device placed directly in the airway to measure the air-flow velocity during inspiration and expiration (Bronzino, 2000)) was also used to monitor patients' lung inflation levels and to control the reproducibility of deep inspiration.

After the training session, the patients underwent a simulation where sets of CT scans were taken at different levels of breathing (FB, deep inspiration, shallow inspiration and shallow expiration). All of the treatment plans were carried out using a 3-DCRT planning system and PT volumes were generated by adding margins of 10-15 mm to CTV. There were four treatment fields using a 10 MV photon beam and a total dose of 81 Gy. During treatment, the patients were monitored by the radiation therapist and had verbal coaching over an intercom system; breathing traces were followed by the therapist. The result was similar to those of other studies: DIBH was able to limit the intra-fraction motion so that the PTV could be reduced and the dose to the tumour could be increased from 69.4 Gy to 87.9 Gy. The study also showed that despite the increased dose, the NTCP decreased and did not exceed 25% when DIBH was used. Furthermore, the study recommended that the DIBH techniques should be used with all thoracic patients with the benefit of dose escalation in the treatment of lung tumours (≥ 81 Gy), aiding improvement of the local control of NSCLC primary lesions (Rosenzweig *et al*., 2000).

However, there are some limitations concerning patients' tolerance of the technique, which means that this method can be applied only to cooperative patients who are able to perform it reproducibly for the duration of their treatment. Another problem is that DIBH will increase the treatment time compared to free breathing; in the study, the FB simulation time was 110 minutes, compared with 211 minutes for

DIBH, with an average treatment time for DIBH of 27 minutes (Rosenzweig *et al*., 2000). Since radiation therapy departments are very busy, using such a technique would therefore increase the pressure on the staff and reduce the number of patients being treated each day.

Mah *et al*. (2000) studied the implementation of the DIBH technique in relation to the treatment of seven NSCLC patients, selected to join the study because they were able to perform certain breathing manoeuvres sufficiently well. During the coaching session, the patients' breathing was monitored with the use of a spirometer, its output being displayed and recorded as a function of time. In addition, a fluoroscopy unit was used in order to ensure inter- and intra-breath-hold reproducibility for each patient. The system required the use of a mouthpiece with a pressure sensor, with the objective of converting air pressure into digital signals, which were representative of the lung air volume. By adopting this method, the researchers were able to monitor the patients' breathing patterns and their regularity. The DIBH technique involves verbal coaching of patients to perform vital slow capacity and then to reproduce deep inhalation breath-hold during simulation (fluoroscopy, CT) and treatment sessions. The goals of DIBH in this study were first to immobilise the tumour and secondly to expand the lung tissues; therefore, it would be away from the area of high dose within the treatment field. During DIBH and FB, sets of CT scans were taken in order to estimate the tumour position during the quiet breathing cycle. PTV was created from GTV by adding a 1 cm margin, the 3-DCRT system was used for planning and the treatment was limited to 3-4 treatment fields.

The study concluded that using DIBH reduced tumour motion when compared to free breathing, thus allowing dose escalation. However, the PTV margin reduction was not mentioned, since it was considered to be beyond the scope of the study. In addition, the study warned that using DIBH would increase the treatment time and staff numbers, but with limited costs and increased patient compliance (Mah *et al*., 2000). Although the study suggested the use of DIBH with the intention of reducing respiratory motion in comparison with free breathing, it was limited by studying only seven patients. Another limitation was that these seven were not randomly chosen but were instead selected as being able to perform DIBH for the time required. Finally, the patients were required to use a spirometer, which added to the stress of routine treatment. Again, the results of this study cannot be generalised to every patient, since not all NSCLC patients are able to perform the technique or to hold their breath for the time required. It has the same drawback as the studies discussed

above, in that both treatment time and simulation time are increased, since the DIBH technique requires a training session plus the use of a spirometer.

3.3 BREATH HOLD AND BREAST CANCER TREATMENT

Other studies concerned with the effectiveness of breath-hold techniques have been performed in the closely-associated area of the treatment of breast cancer, where tangential radiation fields are often used. During the normal breathing cycle, the PTV — which may or may not be the whole breast and include the skin surface — moves, so the delivered dose is not as prescribed. Another major concern is the possible encroachment of the lungs and the heart (organs at risk) into the field during normal breathing; with this in mind, the deep inspiration breath hold technique is a valuable method of reducing tumour motion during radiation therapy in such cases, as it can reduce the cardiac and lung volume in the treatment field (Lu *et al*., 2000). For completeness, some of the relevant evidence is discussed below.

Lu *et al*. (2000) evaluated the potential benefits of DIBH in reducing cardiac volume during the typical tangent fields and the benefit of this breathing manoeuvre for breast cancer patients undergoing CT simulation for the left breast. This study used DIBH as a breathing pattern in 15 patients (46-72 years) with 0-3 positive nodes; all 15 patients had wide local excisions for their lesions. At CT simulation, patients had two sets of CTs: one was done during quiet normal breathing for the planning of the tangential field treatment of their left breast, while the second set was completed during the DIBH (20 s). The two sets of CT scans were used to compare the volume of cardiac tissue in the treatment field during normal breathing and DIBH. During DIBH, patients were instructed to hold their breath for 20 seconds, and their breathing cycles were monitored by a window and video system. At the moment when the chest reached maximum inhalation and stabilised, the scans would be initiated. In addition, during the different breathing patterns a set of scout scans (I-IV) were taken for the total target *a*rea and could then be used to define the tangential fields for actual treatment and for the breath-holding manoeuvres, and to calculate the cardiac volume and the difference in depth during DIBH (Lu *et al*., 2000). The planning of tangential fields was done using the two sets of CT scans. During CT simulation, radiopaque markers were placed on the patient's chest to mark the medial and lateral border of palpable breast tissue, scar area and the border of the right breast. A straight midline wire was placed longitudinally on the patient's skin and

used as a reference point for reproducibility during different breathing cycles, providing data concerning the correct volume of cardiac tissue in the treatment field.

The results showed that the majority of patients could tolerate DIBH for 20 seconds without complaint. In addition, for seven of the patients (47%) the use of DIBH during their CT scans allowed the cardiac volume to be totally eliminated from the treatment field. For another seven patients there was a reduction in cardiac tissue of 81% and the last patient had no cardiac tissue in the field, even during normal breathing. For all patients, the average reduction of cardiac tissue in the field was 84±24% (9.2 cc). The Maximum Heart Distance (MHD) was also reduced in 13 patients, due to the expansion of the lung during deep inspiration, which pushed the heart tissue away from the treatment field. The MHD was thus reduced from an average of 1 cm in normal breathing to 0.1 cm under DIBH. There was also an increase in lung volume during deep inspiration; this was still within the tolerance limit and did not produce any later lung complications (Lu *et al*., 2000).

These results show the benefit of using the DIBH technique. However, the study was done in breast cancer patients who had proper lung function and were able to hold their breath for the time required. Its results cannot therefore be applied to lung cancer patients suffering from reduced pulmonary function and breathing difficulty. In addition, the studies used CT scans to calculate the cardiac volume, which will have increased the radiation dose to the patient.

A study carried out by Remouchamps *et al*. (2003) evaluated ways of reducing the dose to breast cancer patients' OAR, such as lungs, heart, contralateral breast and coronary artery. This was done in order to ensure adequate dose coverage for the internal mammary lymph nodes. The study evaluated the use of moderate Deep Inspiration Breath Hold (mDIBH) with an ABC device and compared it with the free-breathing patterns during the radiation therapy session.

The study also used deep tangential fields with FB compared with IMRT and mDIBH; the results showed reductions in the heart and lung volume and in lung and heart mean dose, while also maintaining coverage of the CTV and PTV when using mDIBH with ABC and IMRT for breast treatment. The study limitation was limiting to breast cancer patients whom able to hold their breath and did not suffer from any lung problem. The study technique could not be used with every NSCLC patient whom suffers with breathing and pulmonary problems. In addition to that the study used ABC device to control the breathing of patient and to help them produce a

stable breathing patterns, which then added more panicking and stressing to the patients and overall increasing the treatment time.

Korreman *et al*. (2005) investigated the dosimetric benefits of Free-Breathing and compared them with the voluntary breath-hold technique by conducting a study of seventeen patients, each with breast cancer and who underwent CT scans during various breathing manoeuvres: Non-coached breathing (which included Free-Breathing), end-of-inspiration gating and deep inspiration/end-expiration breath hold. The study concluded that the use of the end-inspiration breath hold technique combined with DIBH reduced the cardiac dose and spared the normal lung tissue. The study was limited in the way that it been done in breast cancer patients, thus whatever result would be can not apply to NSCLC patients since patients with NSCLC would have a problem with breathing and could produce unstable breathing patterns. Another limitation for the study that each patient went through different type of breathing manoeuvres which is harshly difficult to be perform by patients with lung cancer.

3.4 ACTIVE BREATHING CONTROL

Active breathing control is another method which is able to limit respiratory motion when the patient holds his/her breath at a predefined air volume for temporary immobilisation of respiratory motion by valve occlusion (Wong *et al*., 1999). The ABC method is interventional in that the patient's airflow is temporarily blocked by a valve to achieve immobilisation. The system consists of an airflow meter and a valve which is able to stop the breathing cycle at a certain lung volume; by means of implication, the results should be consistent with those of the patient-controlled breath-hold techniques.

Wong *et al*. (1999) studied the use of ABC in the thoracic and abdominal areas with the aim of reducing the respiratory margin in the PTV. The investigation covered 12 patients: Four with Hodgkin's disease, four with lung cancer, and four with liver cancer. The results showed that the use of the ABC device was well accepted by all patients, including those with lung cancer; they were able to hold their breath for about 15-20 seconds, and there was subsequently a noticeable reduction in the breathing motion of about 3 mm. This study showed that ABC could be used by means of limiting intra-fraction motion for patients with thoracic and abdominal

tumours; however, for lung patients it was unclear as to what effect the histology and the stage of the lung cancer would have, since each stage of lung cancer will differentially affect the patient's breathing and the length of time he can hold his breath. Although the result sounded promising for reducing the PTV margins, however, the lung cancer patients number was limited it was only four patients with lung cancer. In addition using ABC with breath hold added another stressing to patients.

3.5 SELF-BREATH-HOLD

During this technique the patient voluntarily holds his/her breath for a certain time and to a certain point of his/her breathing cycle. During treatment, the patient partially controls the radiation beam with the use of a hand-held switch, having the ability to switch the beam off, while only the therapist can switch it on. Barnes *et al*. (2001) investigated the dosimetric benefit of the voluntary Breath Hold at Deep Inspiration (DIBH) for ten patients with Stage I–IIIB NSCLC without using any extra external monitor. CT scans were also used for Free-Breathing sessions and DIBH where fluoroscopy was used for reproducing the tumour position and to set the upper and lower limits of tumour movement. Eight of the ten patients completed the study, while the other two could not cope with the DIBH technique. The authors subsequently concluded that voluntary breath hold for NSCLC patients could reduce the lung volume receiving ≥ 20 Gy from 12.8% during Free-Breathing to 11.0% with voluntary DIBH. The reduction of lung volume is due to the stabilising of the tumour during the treatment by the breath hold.

Kimura *et al*. (2004) investigated the use of a voluntary breath-hold technique accompanied by spirometer-based monitoring in order to control organ motion and increase the level of reproducibility — especially with elderly patients and those with lung dysfunction — and then to implement this technique for extracranial stereotactic radiotherapy for lung or liver. Five healthy volunteers were trained to hold their breath before each CT session, learning to perform a deep inspiration and a deep expiration under a spirometer-monitor which could display a real-time breathing curve showing the state of inspiration, expiration and breath-hold. The training sessions were repeated three to four times until the patients became familiar with the method and were able to stabilise their breathing. CT-simulation scans were completed with the use of fluoroscopy and a spirometer-monitor, and were taken at the end of the

inspiration phase and of the expiration phase in order to estimate diaphragm movement. 3-DCRT planning and DRR were used for verification purposes and for evaluation of intra-fraction and inter-fraction reproducibility. In addition, the study evaluated systematic errors in the 3-DCRT treatment plan system and in CT.

The authors concluded that a voluntary breath-hold technique was better than various others, such as ABC or DIBH, since patients adopting these were forced to hold their breath and there was a need for extra apparatus, such as EPID (Kimura *et al*., 2004); furthermore, the costs of these other techniques fell within the upper range. They claimed that their approach had relatively good reproducibility, with a mean setup error of 3 mm in all directions, while diaphragm movement was significantly reduced to a range of 7.1-19 mm (with a mean of 13.4 mm), especially at end-expiration; thus they recommended its use with extra-cranial stereotactic radiotherapy (Kimura *et al*., 2004).

The study by Kimura *et al*. (2004) was limited in generalisability, particularly as it was carried out only on five healthy volunteers. Its aim was to help elderly patients and those with pulmonary problems to produce stable breathing in order to control organ motion; however, the results cannot be generalised for use with all patients with lung cancer, as its subjects were healthy and able to perform stable breathing patterns without the use of ABS or DIBH. Another issue is that four training sessions were needed to produce stable breathing patterns, which would increase treatment time, reduce patient throughput and adversely affect the functioning of the radiotherapy department if there were not enough staff to cope with the extra time needed. On the other hand, the study succeeded in limiting treatment costs by minimising the use of extra devices, such as ABC and EPID, since some radiation therapy departments would not be able to meet extra costs.

In another investigation, Kim *et al*. (2001) examined the benefits of the Held-Breath Self-Gating (HBSG) technique in the treatment of lung cancer. The study was carried out on 16 different patients, each of whom had been undergoing radiation therapy for NSCLC and was able to hold his or her breath for 10 or more seconds. They were aged between 48 and 71 years, and had NSCLC stage I, IIIA, IIIB and IV. The histology of the disease included adenosquamous cell carcinoma, squamous cell carcinoma, adenocarcinoma, large cell carcinoma and bronchio-alveolar carcinoma. The tumour locations were in the right upper lobe, the right middle lobe, the right lower lobe, the left upper lobe and the left lower lobe. All patients were coached in

how to control their breathing and perform the breath-hold technique at four different points — maximal and end tidal, inspiration and expiration — and were asked to hold it for as long as they could and repeat this six times for each phase. The breathing cycles were monitored with the use of a video fluoroscopy unit for visualisation at the simulator. Diaphragm movement reproducibility was measured at each phase. The study concluded that the method was tolerated well by all patients and that maximum inspiration and expiration produced the best positional consistency. In addition, the HBSG technique showed a reduction of diaphragmatic motion, with an average of 11.9 mm and a range of 4.4 to 21.5 mm compared with tidal breathing (Kim *et al*., 2001). The study recommended the use of HBSG in the treatment of lung cancer with the intention of immobilising the tumour and thus ultimately reducing the PTV margin, sparing the normal tissue and allowing for dose escalation (Kim *et al*., 2001).

The study of Kim *et al*. (2001) approached the stability of breathing by the HBSG technique to eliminate intra-fraction motion and reduce the PTV margin. However, the patients were selected according to their ability to hold their breath, which thus eliminated all patients who had experienced difficulties in breathing control and who were considered unable to hold their breath for a certain length of time. The procedure of the study was complicated in that the patients first had to go through a training session and then had to control their breathing at different points in their breathing cycles. Finally, they were exposed to more radiation, since the technique required the use of video fluoroscopy.

3.6 FORCED SHALLOW BREATHING WITH ABDOMINAL COMPRESSION

The forced shallow breathing technique with abdominal compression was originally used for the stereotactic treatment of small lesions in the lung and liver (Wulf *et al*., 2000). It consists of a Stereotactic Body Frame (SBF) and an attached plate which presses on the abdominal area. The goal is to reduce diaphragm movement while permitting the patient to breathe normally (Wulf *et al*., 2000; Keall *et al*., 2006). Simulator fluoroscopy is used during some days of the treatment in order to verify the reproducibility of diaphragm motion (Keall *et al*., 2006).

Negoro *et al*. (2001) evaluated the reproducibility of the daily setup and the reduction of respiratory tumour movement using a body frame in 3-DCRT for lung cancer. The SBF, which was shaped according to the patient's body contours, had

three parts: the body shell, the laser markers and a small abdominal pressing plate. Laser marks and skin marks were used in order to align the patient during treatment and simulation. The study was carried out on 18 lung cancer patients, 16 of whom had unresectable peripheral lung tumours and poor pulmonary function, while the other two had refused surgery for their tumour. The mean age was 65.2 years and tumour size ranged from 0.5 to 33 cc. SBF was used to immobilise patients from the thorax area to the pelvis area. Fluoroscopy of the X-ray simulator was used in order to estimate the tumour movement due to respiration, while daily orthogonal-view portal imaging was used for daily setup errors and alignment. Using the body frame and abdominal compression reduced the range of movement from 8-20 mm with a mean of 12.3 mm to 2-11 mm with a mean of 7.0 mm (p = 0.0002). The absolute setup errors were 8 mm in all directions (anterior-posterior, craniocaudal and left-right) and less than 5 mm in all verifications of all directions: 90% (L-R), 100% (A-P) and 93% (C-C) (Negoro *et al.*, 2001).

The study concluded that implementing this technique reduced respiratory tumour movement; however, daily setup verification was required for hypo-fractionated conformal therapy. Furthermore, the use of SBF was not suited to every patient; the study found difficulty in aligning a patient's rotation with the body axis, as this would increase the variation in daily setup errors. Another consideration is the body weight of the patient, with particular reference to obese patients; this can be seen as a limiting factor in reducing daily setup errors. The study emphasised that verification for daily treatment had to be done on a daily basis in order to avoid any significant decrease of target volume, especially when applying hypo-fractionated treatment. In addition, the PTV margin could not be reduced unless the daily setup verification was carried out in the same position and in the same treatment room for each patient; they recommended a PTV margin of 5 mm in the A-P and L-R directions and 8-10 mm in the C-C direction (Negoro *et al.*, 2001).

A very recent study of this method was carried out by Heinzerling *et al.* (2008), which investigated the different levels of abdominal compression force — Medium Compression (MC) and High Compression (HC) — and organ motion during stereotactic body radiotherapy for lung tumours using four-dimensional (4D)-CT scan analysis. Three 4D-CT scans were taken for each of ten patients diagnosed with lung cancer in the lower lobe of the lung, and different levels of abdominal compression were then applied. The maximum position of the tumour was limited to the peak of inspiration and expiration phases. The study found that using 4D-CT scans with

abdominal compression — especially with HC force — reduced the motion of lung tumours, especially in the superior-inferior direction. The mean (±SD) MC force was 47.6±16.0 N, while HC was 90.7±27.1 N; the mean overall reduction in tumour motion was 13.6 mm for MC and 8.3 mm for HC. However, regarding the direction of tumour movement.

Although the study examined ten lung cancer patients with tumours at varying sites and locations, using different levels of abdominal compression would ultimately not be a successful technique to adopt with all lung cancer patients, for various reasons. At any level, abdominal compression could cause breathing problems in some patients, considering the fact that they have lung problems and will be lying on the treatment coach while trying to hold their position for the treatment time. Furthermore, the study used stereotactic body radiotherapy with 4-DCT scans, which are very costly; such expensive treatment would not be available in every radiation therapy department. In addition, stereotactic body radiotherapy cannot be applied to all lung cancer patients, since it does not incorporate the normal number of treatment sessions and the standard dose; a total dose of 48-50 Gy is usually delivered in five or fewer fractions to small lung lesions of early stage NSCLC (Vassiliev *et al*., 2009). Finally, this technique would require more time than the usual treatments, as well as staff training, which would add to the cost of the treatment itself.

3.7 REAL-TIME TUMOUR TRACKING SYSTEMS

Another technique for tracking intra-fraction motion and for accommodating respiratory motion is the real-time tumour-tracking system, which is based on repositioning the radiation beam dynamically so as to follow the tumour's changing position (Keall *et al*., 2006). The main goal of such a system is to reduce the respiratory margin around the PTV. This is more complicated and more invasive for patients than other methods, since a radio-opaque marker and fiducial seeds — usually gold particles of specific size — have to be implanted in or near the tumour (Figure 8) (Shirato *et al*., 2000). The positions of the fiducial seeds are tracked using a pair of stereotactic kilovoltage X-ray imaging devices, and radiation is delivered only when the fiducial seeds are in their proper place (Shirato et al., 2000; Seppenwoolde, 2002).

Shirato *et al*. (2000) developed a linear accelerator synchronised with a fluoroscopic real-time tumour tracking system, which increased the accuracy of 3D conformal radiotherapy for mobile tumours in the lung (3 patients), rectum, prostate, and bladder. A 2 mm gold marker (99.9% Au) was inserted into the tumours of 14 patients with different types of mobile tumour, so that the motion could be detected by a CT scan. CT scans were taken at three different respiratory phases — inhalation, exhalation, and average respiratory — in a way which allowed an estimate of the relationship between the tumour and the surrounding normal tissues during each phase. During the scan, patients were asked to hold their breath during either the inhalation or exhalation phase. The PTV was formed by taking the average GTV in the different CT scans; in addition, a 10 mm margin was added to PTV. PTV reduction was carried out using four-dimensional treatment planning and by taking the average of the tumour motions in all directions. It was found that the tracking system could reduce unwanted radiation to the patient, thus reducing the margin around the PTV to less than 10 mm. Furthermore, it increased the accuracy of the treatment by ± 1 mm every 0.033 seconds during radiotherapy (Shirato *et al*., 2000). However, the authors suggest that more studies need to be carried out in order to avoid the invasive procedure of inserting the marker, and the treatment time would be three to five times longer than for conventional treatment.

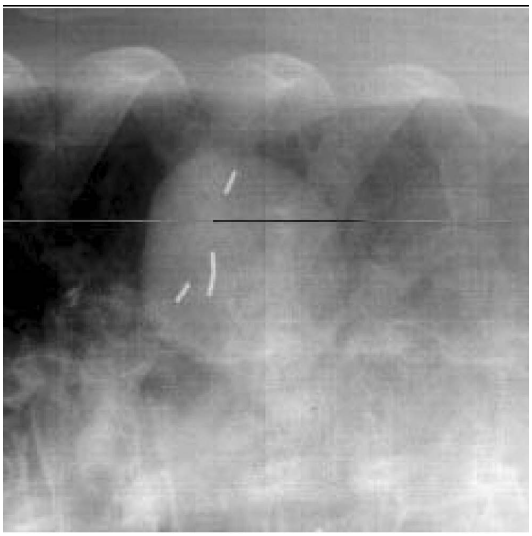

Fig. 8: Radio-opaque fiducial seeds (the white worm-like structures) in a lung.

With kind permission of Keall et al*. (2006)*

Similarly, Shimizu *et al*. (2001) used a real-time tumour tracking system to investigate the 3D movement of lung tumours in four patients. Again, a 2 mm gold

marker was inserted into the tumour. The study found that the range of motion while the beam was on was reduced to 5.3 mm in all directions for all four patients. The study concluded that the real tumour tracking system is useful for radiotherapy.

There are, however, some major issues in relation to real-time tumour tracking, such as that it is costly and involves many techniques which require high staffing levels. Although using real-time tracking with a seed implant will ultimately enhance the radiation treatment by reducing the effects of tumour motion, it also potentially causes more complications for the patient; the seed implant could cause pneumothorax or interstitial emphysema, which is the accumulation of air around the lung. Pneumothorax occurs in 3.3% to 15% of all patients, and may cause long-term pulmonary complications, such as asthma and, in severe cases, can ultimately lead to death, especially in patients with compromised lung function (Laurent *et al.*, 2000).

3.8 FLUOROSCOPY IMAGING

Fluoroscopy imaging can be used to track the radio-opaque markers for the measuring of tumour motion during the respiratory cycle, and can also serve as a tool for directly tracking tumour motion during treatment. The problem with X-ray fluoroscopy, however, is that the patient is subjected to more radiation (Keall, 2006). A study by Chen et al. (2001) found that the extra skin dose due to fluoroscopic tracking of diaphragm motion varied from 1.25 cGy to 9.82 cGy for a one-minute fluoroscopic examination; bearing in mind that the system is used daily, the total exposure would be considerable (Tasunashima et al., 2004). This is considered as a major problem to the patients since an extra radiation dose will be delivered in daily bases which then could increase chance of developing extra complication.

3.9 RESPIRATORY GATING RADIOTHERAPY

Most of the above-mentioned studies into breath control were carried out using patients with suitable lung function; in other words, they were selected as they were considered able to control their breathing for a certain amount of time, whereas breath-hold techniques are often poorly tolerated by patients with lung cancer (Underberg et al., 2005). In addition, most of the above-mentioned methods and

techniques increased the treatment times, as reported in studies by Hanley *et al*. (1999), Mah *et al*. (2000), Rosenzweig *et al*. (2000) and Remouchamps *et al*. (2003).

NSCLC patients tend to suffer from shortness of breath and irregular breathing patterns, which consequently makes it difficult and uncomfortable for them to control their breathing during their treatment to limit intra-fraction motion, whether by DIBH or by any other breathing manoeuvre. Furthermore, using respiratory manoeuvre techniques requires time for the patients to become trained for simulation and treatment and, therefore, it is ultimately considered more beneficial to allow such patients to breathe normally while their breathing is monitored by a respiratory gating system.

Respiratory gating has been used for some time in medical imaging, such as with the use of CT and MRI, and with the objective of reducing artefacts and blurring (Lui et al., 1993; Mori, 1994). This is a method of treating a tumour whereby the radiation beam is turned on only when the tumour is within a narrow range of positions, which is referred to as the gating window. The radiation beam is active only when the tumour 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 most popular commercially available respiratory gating system is the Real-Time Position Management (RPM) (Varian Medical Systems), which uses markers on the body's surface (usually the abdomen or chest wall) in order to monitor external body motion, which is assumed to correlate with the tumour motion. As mentioned above, the beam is switched on only when the markers are within a certain well-defined position window, with the assumption being made that the tumour is also within a defined position window.

Various authors have investigated the benefits of using respiratory gating radiotherapy in lung tumour treatment. A study carried out in Japan by Ohara et al. (1989) investigated the benefit of using respiratory gating in the treatment of lung cancer. Ohara and his group used a phantom integrated into the linac control systems; the phantom simulated the lung motion due to breathing, and directly switched the microwave oscillator of the linac on and off according to preset positions of the phantom tumour. Seven patients were studied; their breathing cycles (chest

wall movement) were programmed into the phantom, and the position of the phantom tumour was monitored. A series of control positions were defined for each simulated tumour, and the process was then applied to the treatment with the radiation beam being turned on and off according to pre-set points in the simulated respiratory cycle. The study concluded that using such a gating method could be beneficial in the treatment of lung cancer, especially if the tumour is located close to the diaphragm. However, the study was vague in the diagnoses of the patients plans that been simulated . Even though the study suggested the use of respiratory gating with lung patients but this assumption was only based on the phantom study not in actual patients.

Ford *et al*. (2002) investigated and evaluated the use of a commercial gating system (RPM) in radiotherapy treatment delivery with the objective of minimising and reducing intra-fraction motion due to breathing. The study was carried out on a total of 8 patients, 4 of whom were diagnosed with liver cancer and 4 with lung cancer. Patients were selected according to the size and location of the tumour. The criteria were that the tumours had to be mobile, small and located near structures or organs at risk.

The patients performed breathing control at the end of expiration and at the end of inspiration. CT scan and fluoroscopy images were used during the treatment and simulations in order to verify the position of the diaphragm and variation in soft tissues. During the treatment with gating, the patients had audio coaching sessions in order to increase reproducibility. The study found that the mean variability of soft tissue movement which was observed in portal films during gated treatments was between 2.6 and 5.7 mm, while it reduced the intra-fraction motion due to respiration between 0.6 mm and 1.4 mm. It was concluded that most of the treatment variability was due to patient setup errors rather than respiratory motion. The suggested use of EPI and gated localised film during the treatment twice a week would increase the patient total dose in the early days of treatment (Ford *et al*., 2002); however, in later fractions a correction for this is usually made.

The study did have some limitations: first, it investigated the use of a commercial gating system (RPM) with electronic portal imaging, which could bias results in favour of the system; second, its only aim was to investigate the use of a commercial system in reducing respiratory motion, although it was diverted into studying the patients' coaching and inter-fraction motion, and comparing gating with other

methods for reducing this motion; third, the study used lung cancer and liver cancer patients without giving any details relating to the stage, histology or pathology of their cancer. Diaphragm movement was taken as a surrogate for tumour motion in both groups of patients, assuming that their breathing was of the same pattern; however, this was not true, as each patient's breathing was different and they showed unique breathing patterns, with the variation changing and becoming irregular, depending on the tumour location and size. Another limitation was the number of patients, which is considered too small for investigating the effectiveness of RPM in treating either lung or liver cancer. The selection of patients for this study was based on tumour size and location, so the results cannot be applied to patients with large tumours located in the centre of lung lobes. Finally, using EPI as the basis to check the patients' position twice a week would increase the treatment time, as suggested in reference to other studies.

3.9.1 BREATH-HOLD WITH RESPIRATORY GATING

The use of respiratory-gated radiotherapy systems is considered to be more precise and the reproducibility of breathing cycle will increase if patient breathing manoeuvres are applied, providing that patients can tolerate it for the duration of the treatment, (Spoelstra et al., 2008). Nevertheless, the ability of patients to perform the Breath-Hold for certain time is considered as a limiting factor as mention in studies above, since not every patient would be able to hold his breath, could increase the patients complains and the treatment time, Hanley et al. (1999), Barnes et al. (2001).

Kini *et al*. (2003) investigated the effects of intra-fraction motion on a daily basis and monitored patient respiratory patterns using the respiratory-gated radiotherapy (RPM) system. The goal was to discover whether the use of respiratory manoeuvres — such as free breathing and the monitoring of the breathing cycle audibly or visually by the patient — would increase the precision of respiratory-gating radiotherapy. The study was carried out on five patients with no reference to their stage of cancer, nor their cancer specification. During the study, the selected patients had training sessions in free breathing, audio prompting and video feedback. The study showed that free-breathing would be the worse option to use with gated radiotherapy in producing unstable breathing patterns, since patients had no control over their breathing. Audio prompting produced a more stable frequency of the breathing cycle; however, it provided unstable amplitude (which plays a major role in gated

radiotherapy, since the gated window is set according to the amplitude). Video feedback produced a more stable breathing cycle in regard to the amplitude.

The study suggested that using audio prompting and video feedback would be beneficial during gated radiotherapy, and even suggested the use of breath-hold to increasing the precision of the treatment (Kini *et al*., 2003). It had some limitations and there was some lack of clarity as to what it was trying to establish; the entire study appears to have been completed in a short time just to give an idea concerning the use of the RPM system with different coaching methods. The first limitation was the selection of subjects; the study was carried out only on five patients with tumours in the chest and without any specification of what 'chest malignancies' referred to; the authors give more information about the RPM system than about the patients. The second limitation of the study is the fact that the duration of coaching for patients is not specified; no information is given concerning the length of each session, as all that is mentioned is that the patients were coached and a few breathing cycles were recorded. Finally, the study does not reveal when the training sessions took place — was it before simulation, during simulation or immediately before the treatment?

The concept behind the Kini *et al*. (2003) study appears generally similar to that of the research reported in this thesis, but there are major differences between the two studies. First, Kini *et al* (2003) investigated the use of patient training in order to improve treatment with gated radiotherapy, whereas in the present study the main reason to coach patients was to eliminate the need for any high specification machines such as RPM. The second difference is that a number of breathing cycles were recorded by Kini *et al*. (2003), whereas in the present study only four minutes were recorded. Third, all of the equipment used by Kini *et al*. (2003) was related to the RPM system, so that they used audio prompts based on the system, the camera which came with the system and even an LCD screen which was part of the RPM facility, whereas the device and the system used in the new work reported here are totally independent of any other machine. The final difference between the two investigations is that Kini *et al*. (2003) made the assumption that abdominal marker motion was correlated to tumour motion, whereas we make no such assumption here but are focused only on studying the expansion of the chest, with the aim of helping patients to control their breathing during treatment and so to produce more stable breathing patterns.

Butler *et al*. (2004) studied the amount of lung tissue which could be saved when using respiratory gating radiotherapy by comparing the masses of lung tissue receiving at least 20 Gy, which is used as indicator of probable lung toxicity to the average of the gated GTV volumes at different locations, with all characteristics related to the disease, such as pulmonary function and lung density. Gating was done during different phases of the respiratory cycle, either by inspiration or expiration. Ten patients with primary lung cancer were the subjects of this study. CT scans were taken for each patient during different phases of the respiratory cycle: FB, inspiration and expiration using the assisted breath-hold technique based on a spirometer. The Varian RPM system was used for gating. CTV was created by adding 1.8 mm to GTV for FB and 0.8 mm for gated treatment. The PTV for the gating treatment was calculated without any respiratory motion margin; only a setup error margin was permitted.

The results showed no difference between inspiration and expiration phases in sparing more lung tissue; however, respiratory gating was shown to save 43% more normal lung tissue if either phase was applied. Despite the fact that the study was sponsored by Varian Medical Systems, Inc., Palo Alto, CA, the result was considered impartial, since the study concluded that using respiratory gating as a treatment option would increase the treatment time, the total cost and the overall number of staff required.

A study carried out by Berson *et al*. (2004) investigated the use of the Varian RPM gating system with the aim of reducing respiratory motion during treatment sessions, and also attempted to establish which types of patient would benefit the most from using this particular treatment system. The study was conducted on 108 patients, each of whom had been diagnosed with different cancer at different sites, such as the lung, breast, and the upper abdominal and mediastinal areas. Different treatment techniques, such as 3-DCRT, IMRT and stereotactic radiotherapy, were used. During the simulation and the treatment, patients' breathing patterns were either FB or DIBH with gating. The results showed that gating could be used by all patients during simulation and treatment. The study recommended the use of DIBH techniques with gating over Free-Breathing, since there was no tumour motion during DIBH, the treatment time was shorter and, finally, DIBH was totally reproducible. However, the study also found that using DIBH with gating depended on the patient's ability to perform such a technique, Berson et al. (2004). The study was comprehensive one in including 108 patients for this investigation, in addition patients

diagnoses were different among patients, which make the study as full study .Another good point for the study was investigation the used of different treatment modalities such as 3-DCRT , IMRT and etc. However, this study was the same as the above mentions study by Kini et al. (2003) and Ford et al. (2002) in the way that it investigated the use of RPM system and how it could improve the accurate of respiratory gated treatment.

As mentioned above, respiratory gating radiotherapy is one of the most effective techniques for treating mobile lesions, such as lung and abdominal tumours. It has been proven to be very well tolerated by most patients — regardless of their stage or their histology — since it does not require any respiratory manoeuvres and patients are able to breathe freely , Ohara et al. (1989) , Ford et al. (2002), Butler et al. (2004) While some authors, such as Berson et al. (2004), have suggested that the use of the DIBH with respiratory gating radiotherapy delivers a more precise dose to the PTV, the patients' ability to perform DIBH and the time taken for training sessions nevertheless remain limiting factors. Respiratory gating radiotherapy also aids in limiting the margin of respiratory motion from the PTV; however, this effect is still under investigation, and there is so far no clear data on how much is safe for elimination or reduction of the margin without affecting the total dose coverage to the PTV.

3.9.2 RESPIRATORY GATING RADIOTHERAPY AND IMRT

Using respiratory gating radiotherapy and the modality of IMRT will provide two benefits to the patients during the treatment: First, respiratory gating will eliminate or at least limit respiratory motion and hence reduce normal toxicity; second, an increase in tumour dose homogeneity will be experienced. Therefore, respiratory gating with IMRT reduces the dose to normal tissue and Organs at Risk, such as lungs, oesophagus and heart (Keall et al., 2006), while still allowing for a more uniformed tumour dose and possible dose escalation.

Keall *et al*. (2006) investigated the implementation of respiratory gated intensity-modulated radiotherapy for the treatment of NSCLC, aiming to improve the coverage of the planning target, reduce normal tissue dose and improve the survival rate of lung cancer patients. The study used the commercial RPM system with external respiration signal markers; patients selected had to have suitable lung function so

that they were able to produce stable respiratory patterns. In addition, age, tumour position and overall health condition were well specified.

During the study, the patients had respiratory coaching using audio prompts and visual biofeedback. The report covers each modality in full detail used in the study; for instance, the use of fluoroscopy, the respiratory-gated IMRT planning procedure, portal imaging, respiratory-gated CT imaging and dosimetric quality assurance. However, regarding the breathing coaching, it refers to the method used in an earlier study by Kini *et al*. (2003). The study concluded that using IMRT with gated radiotherapy was a very complicated technique and in addition it could increase the treatment time by 2 minutes. The study suggested the use of highly dosimetric quality assurance whenever this technique is used.

The study was mainly intended to provide guidelines for the implementation of respiratory gated IMRT at Virginia Commonwealth University, USA, with no indication of the number of patients used and it based it training session in Kini et al. (2003). It concludes that if respiratory gated IMRT is implemented carefully, it will ultimately improve the outcome of radiation treatment.

3.9.3 SYNCHRONISING RESPIRATORY GATING AND ADAPTIVE RADIOTHERAPY

Kubo *et al*. (2000) studied the technical aspects of synchronising the radiotherapy beam with respiration using the gating system (BSRT). The study was an inclusive description and comprehensive in investigating different methods of breathing monitoring such as voluntary breath-hold, forced breath-hold, or breathing gating , the effects of gating on machine output, the extent of organ displacement due to respiration motion and, finally, the use of different types of sensors, such as thermistors, thermocouples, pneumotachography and strain gauges. It recommends fluoroscopic imaging as a successful tool for indicating the movement and the direction of the tumour, and the use of temperature sensors and strain gauges to produce the most desirable signal in addition to accuracy, reproducibility and the comfort of the patient. Finally, the authors suggest that using gating radiotherapy with breath hold will reduce the treatment volume. There was no change in machine output or beam characteristics when using the gating system (Kubo et al., 2000). The study covered every technical aspect of BSRT and it could be useful to be used as a guideline for such a modalities.

The core aim of adaptive radiation therapy is to acquire data on patient geometry and organ motion which was previously obtained from images during the treatment and adapted or aligned to the treatment parameters; such alignment is based on soft-tissue and bony contrast. This is done on a day-to-day basis using EPID in order to measure setup errors (Perez and Brady, 2008). It leads to reduced treatment set-up uncertainty and provides information concerning daily organ motion and variations in anatomy (Wittmer *et al*., 2009). It also requires the use of a suitable treatment machine (LINAC equipped with MLC) and on-line imaging devices. Adaptive radiotherapy requires many steps: first, the acquisition of everyday images is necessary in order to ensure a complete record of patients' changes and deformation during treatment; second, the dose needs to be recalculated for every image; finally, assembling all dosimetric information in common images is required with the use of a deformable image registration algorithm (Ramsay, 2006). The advantage of adaptive radiotherapy is in improving clinical outcomes and treatment efficiency for lung cancer patients, which leads to dose escalation. Seibert *et al*. (2007) found that using adaptive radiotherapy for NSCLC could reduce the V_{20} of the lung by 21% and that with online information obtained during treatment the radiation oncologist could develop a model to predict changes in the tumour and so optimize the treatment. However, this system is not available to every clinic, it increases the treatment time, exposes patients to extra radiation doses (which must be corrected for) and, most importantly, increases the workload of the staff, so that staffing levels need to be increased appropriately to cope with this complex treatment (Barrett *et al.*, 2005).

A drawback common to all of the above studies is that the methods used require control of the breathing cycle to limit tumour motionm, so patients have to perform manoeuvres such as DIBH in order to control their breathing. While this is mostly (but not always) well accepted by healthy volunteers or patients without significant respiratory dysfunction, it is apparently not so well tolerated by those with some form of respiratory impairment. Another disadvantage of these methods is that they require the use of highly sophisticated systems which are directly integrated with the treatment machine. This significantly increases the risk of machine-dependant failure, the requirements for sophisticated quality assurance and the overall treatment cost and time. Furthermore, techniques which require the implantation of fiducial markers together with extensive gated CT scans are invasive, place the patient under additional stress. The additional steps involved increase the treatment cost and overall treatment time as much as threefold (Kubo et al., 2000).

The above drawbacks have led to the assumption that allowing a patient to breathe freely or asking him/her to follow some pre-designed breathing pattern following coaching may provide a more comfortable and more widely accepted method of breath control than DIBH, chest restrictors, etc. The following section reviews the available literature on patient breath coaching methods and devices.

3.10 PATIENT COACHING METHODS AND DEVICES

The coaching method and device will depend mostly on the biofeedback of the patients' breathing patterns. Biofeedback techniques have long been used in the treatment of bronchial asthma and pulmonary disease (Vachon, 1976; Ritz, 2004). A review by Ritz et al. (2004) of earlier studies investigating the efficacy of biofeedback in asthma management concluded that biofeedback using spirometric feedback, video display and coaching patients to follow certain patterns were beneficial for asthmatic patients; however, it also found that using these techniques would make no difference to lung function.

Another study was carried out by Spoelstra *et al*. (2008) with the aim of investigating the use of a smaller treatment field in order to reduce toxicity when concurrent chemo-radiotherapy and respiration-gated radiotherapy with time-integrated electronic portal images were used for the treatment of locally advanced NSCLC. Eleven patients with lung cancer and TNM-stage III, IIIA and IIIB were treated and audio-coached using respiration-gated radiotherapy at end-inspiration. PTV was generated by adding 5 mm in all directions in order to account for treatment setup errors, while another margin of 5 mm was added to the cranial-caudal direction for respiratory motion. The study concluded that using gating radiotherapy with patient audio-coaching would increase the reproducibility of internal organs and would subsequently improve the dosimetry of the treatment by increasing the total lung volume by 17% compared with the same method without coaching. During end-inspiration, the lung is expanded with air, which increases lung volume and reduces the fractional amount of normal tissue being irradiated, thus potentially reducing NTCP, which could then lead to a decrease in the margin for PTV (Spoelstra *et al*., 2008).

The most frequently cited study which discusses the benefits of training patients to control their breathing is by Kini *et al*. (2003), who investigated the use of audio

prompting and visual feedback in mind of training patients during treatment. The study was carried out on patients with chest tumours, and their treatment included respiratory gated radiotherapy using RPM. Patient training tools included audio prompting and the use of a computer system with a recorded message instructing patients to breathe in and out at periodic intervals. Another tool was visual feedback, which depended on using a monitor in order to show the patients their breathing patterns and to further help them to maintain the same pattern by watching the image Kini *et al*. (2003) concluded that patient training and coaching during treatment would ultimately increase the reproducibility of the breathing pattern; specifically, they recommend the use of visual feedback over audio prompting.

Neicu *et al*. (2006) investigated the effectiveness of combining breathing coaching with a dynamic radiotherapy method, called Synchronised Moving Aperture Radiation Therapy (SMART) in the treatment of lung cancer patients. The method used a radiation beam to track tumour motion using a dynamic multi-leaf collimator. The study, of five healthy volunteers and 33 lung patients, used respiratory coaching techniques in order to control their breathing and to improve reproducibility. The coaching was carried out using audio prompts and video biofeedback via the RPM respiratory gating system for less than four minutes (200 s); however, the total training session took an hour to complete. The training and coaching techniques were the same as those developed by Kini *et al*. (2003). The five healthy subjects had no problem with the breathing coaching, while six lung cancer patients produced stable breathing patterns and were excluded from the breathing coaching. Four other patients could not cope with the coaching due to their health and lung problems, and thirteen more could not attend the video session and could be coached only by audio instructions. This left only ten of the 33 patients who were able to complete the audio and video breathing coaching. The results showed an improvement in treatment with the SMART technique when using respiratory coaching, but coaching using the RPM respiratory gating system was limited and needed to be improved in order to be tolerated by all patients. The study started with 33 patients but was completed in only ten patients, which limits the generalisability of the results to lung cancer patients. Furthermore, the study did not mention the stage or the diagnosis of the patients beyond stating that all 33 had lung cancer. The study recommended that the use of the SMART technique with breathing training would be more efficient than using free breathing, but this was tested in only ten patients. Finally, the training session took an hour, which is another limiting factor for this technique, since time is considered critical in any radiation therapy department.

Coaching patients to breathe in certain patterns will improve the outcome of radiation therapy treatment, as mentioned in all of the above studies; however, not all patients could cope with it, and another way of coaching or training needs to be developed to help patients to produce stable breathing patterns without the need for complicated machines or techniques and without forcing patients to perform the desired patterns.

In another study, George et al. (2006) investigated the causes of residual motion during respiratory gating. Residual motion is defined as an uncontrolled motion which cannot be completely eliminated due to the unpredictable movement of the tumour or an organ; it is now an important part of the advanced techniques of radiotherapy, such as IMRT, 3-DCRT and respiratory gating, and requires the allowance of a small margin (Saw et al., 2006). George and colleagues studied twenty-four SCLC and NSCLC patients aged from 36-82 years. The breathing techniques used were the same as those adopted by Kini *et al.* (2003). The coaching sessions were divided into three segments of 4 minutes each; there were five sessions for each patient with a week between sessions.

The study used the RPM respiratory gating system. During the first (FB) session, the patient was asked to breathe normally with no instructions or protocol, and the session was recorded. Next, the audio instructions session was recorded for four minutes, followed by the Audio-Visual (AV) biofeedback session; four of the twenty-four patients were unable to complete the study due to complications or death. The study concluded that there was no change in residual motion during the training sessions. Additionally, patients were able to produce stable breathing patterns in the first four minutes. Finally, respiratory training could produce more respiratory reproducibility, thus increasing the outcome of respiratory-gated radiotherapy (George *et al*., 2006).

The study was based on using patient coaching methods in conjunction with the commercially available RPM gated system, as were most of the investigations reviewed above. Kini *et al.* (2003) used this technique to train subjects while using and investigating the RPM system. Although the results of the study were promising, showing that coaching could increase breathing reproducibility, which thus increased the accuracy of gated radiotherapy, it is nevertheless based on the use of a more sophisticated machine and system, such as RPM. The methods of patient training using audio prompting and video feedback have not so far been investigated without

the use of such systems, but the need for lower cost treatment and to reduce the likelihood of stress or the potential for panicking by patients during the treatment leads us to consider using Kini's method of training subjects to stabilise their breathing without the need for machines such as RPM.

Another study was recently conducted by Keall et al. (2006), who investigated the impact of audio-video feedback used with the commercial RPM gating system to increase the efficiency of gating and improve respiratory reproducibility by reducing residual motion. A total of 331 minutes of breathing traces were recorded over five sessions for each of twenty-four lung patients. Those selected for this study were over 18 years old, had no discomfort or pain in supine position, were not oxygen dependent and were receiving external radiotherapy. One patient withdrew from the study, three others could not complete the full five sessions, another died during the study, and two more finally withdrew due to back pain. The study used the same protocol as the study above, and the same (RPM) gating system.

This time, there were four parts to each session, the first being FB, which was recorded for four minutes. The second was an audio prompting part which was based on the frequency and the amplitude produced during the Free-Breathing session. The patients were instructed to breathe in and out, and the data was again recorded for four minutes. The third part was for visual biofeedback, where the patients were shown their breathing trace on an LCD monitor, and subsequently asked to follow it. Finally, there was a combined AV biofeedback part, where the breathing cycles were again recorded for four minutes.

The study concluded that the audio instructions tended to increase the amplitude when compared with the FB and visual sessions, thus reducing treatment precision. However, by using audio-visual biofeedback, there was a significant increase in the reproducibility of gating radiotherapy and reducing the residual motion than compared with Free-Breathing and audio instruction alone. In addition, the study concluded that the patients felt more comfortable with the visual biofeedback.

As the study concluded that using audio prompting and video biofeedback could improve the outcome and precision of treatment with gating radiotherapy, but more investigation needed to be done to allow patients to breathe freely while performing stable breathing patterns. Further studies were also required to discover how patients could perform stable breathing patterns without the need for extra machines or complicated procedures.

3.11 SUMMARY

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. This obvious difficulty has led to the development of techniques which have attempted to capitalise on the patient's free breathing. However, it seems that the search for a technological solution has, to some extent, outstripped the evidence as to the best way to train a patient to breathe in a regular and controlled fashion, thus missing the potential for a simple solution to the problem of monitoring chest wall motion. While this clearly ignores the potential weakness of the assumption that tumour motion and chest wall motion are indeed correlated, this is nevertheless considered to be beyond the scope of the current study.

As suggested above, the research and literature on breathing manoeuvres are quite limited, and there has been no rigorous analysis of the best method(s) of patient coaching (i.e. pure free breathing, visual feedback, audio feedback or audio-visual feedback) for use with the aim of promoting a stable and controlled breathing pattern. Furthermore, most of the above studies investigated the use of audio instruction and video biofeedback with a commercial gating system (RPM), and it was mostly based on the same technique and the same number of patients, such as the studies by George *et al.* (2006) and Keall *et al.* (2006), thus limiting the sources of information for the investigation and providing a limited analysis of performance. The choice of using the gating system is not open to every facility, since it is costly and requires complicated planning and the use of CT scans etc., thus increasing the total absorbed dose above that which is used in the diagnostic and curative phases of the treatment. Finally, the RPM system significantly increases the treatment and setup time — and thus the distress for the patient — and the treatment costs are also increased.

Table 4 summarises all the literature review results, in addition to detailing the advantages and disadvantages of each breathing method.

Breathing Manoeuvres	Authors and Dates	Results Summarised	Limitations
Breath-hold	Rosenzweig, 2000; Barnes, 2001; Hanley, 1999; Mah, 2000; Lu, 2000; Remouchamps, 2003; Korreman, 2005.	Immobilises the tumour, reduces NTCP, leads to dose escalation and improves patient treatment outcomes.	Not all patients could perform BH. Increased the treatment time.
Active Breathing Control	Wong, 1999.	Limits intra-fraction motion	Based on use of extra device for controlling breathing. Not suitable for all patients
Self-Breath Hold	Barnes, 2001; Kimura, 2004; Kim, 2001.	Immobilises the tumour, reduces the PTV margin, leads to dose escalation	Requires the use of fluoroscopy, EPID, extra dose to patients and not all patients could perform it.
Forced Shallow Breathing	Wulf, 2000; Keall, 2006; Negoro, 2001; Heinzerling, 2008.	Reduces respiratory motion, increases daily setup accuracy	Needs daily verifications, inability to detect patient's rotation along the body axis. Needs the use of CT and fluoroscopy for every treatment
Real Time Tumour Tracking	Shirato, 2000; Shimizu, 2001.	Patient breathes freely, reduces PTV margin and increases the accuracy of the treatment, reducing the effects of tumour motion	Invasive; increases treatment time 3-5 times; costly; risk of pneumothorax, emphysema and long-term pulmonary complications
Fluoroscopy Imaging	Chen, 2001.	Increases the accuracy of treatment	Extra skin dose, requires radio-opaque markers
Respiratory Gating With BH, Synchronising and IMRT	Ohara, 1989; Ford, 2002; Soelstra, 2008; Kini, 2003; Butler, 2004; Berson, 2004; Keall, 2006; Kubo, 2000.	Patient breathes freely, decreases respiratory motion, decreases NTCP and increases TCP	Increased treatment time and cost, and requires more staff.

Adaptive Radiotherapy	Perez and Brady, 2008; Seibert *et al*., 2007	Improves the clinical outcomes of lung cancer, could reduce V_{20} and leads to dose escalation	Not available to every clinic. Extra radiation dose. Costly and increases both treatment time and staff workload.
Patient Coaching	Spoelstra, 2008; Kini, 2003; Neicu, 2006; George, 2006; Keall, 2006.	Increases the reproducibility of internal organs, decreases NTCP, eliminates the unpredictable movement of the tumour or an organ. If used with gating it would increase the outcome of respiratory-gated radiotherapy	Never used alone. Still needs more investigation in order to be used widely in treatment for every lung cancer patient.

Table 4: Summary of the literature review results

3.13 RESEARCH AIM

The aim of this project is restated here for completeness: The work is primarily aimed at the improvement of our knowledge of a patient's response to and tolerance of 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. In general, this also means developing methods of monitoring the chest wall motion as well as developing a robust method of analysing the data. As a subsidiary aim, it is hoped that the project 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 such as those which are used in other hospitals.

CHAPTER 4: DESIGN AND TESTING OF A RESPIRATORY MONITORING SYSTEM

4.0 INTRODUCTION

This chapter discusses the design and testing of a system focused with monitoring and controlling the breathing patterns of patients undergoing radiotherapy. The reasoning behind the chosen approach is discussed. A system (Figure 9) has been adopted in the design and prototyping phase; this means that system specifications were first devised and the hardware and software then designed by means of facilitating the requirements within the specification. Once the system had been built, a testing phase was undertaken and the results were then used to modify the design with the aim of improving overall functionality and usability. The hardware and software were then modified and the testing phase revisited. This iterative process was continued until the system could be produced in such a way that it satisfied the constraints and requirements of the specification, and was ultimately deemed to be usable and robust.

Fig. 9: InRad device

4.1 SYSTEM DESIGN

The assumption that regulating the breathing pattern improves the ability to treat patients with NSCLC is well documented and has been discussed in the previous chapters. While the correlation between the chest wall and tumour motion has not been totally proved, the evidence demonstrates that controlling the breathing reduces the amount of tumour motion in and out of the beam.

The objective of this thesis, as stated in Chapter 1, was to design and manufacture a system to monitor a patient's breathing cycle in order to assess methods of assisting the patient in adopting a suitable breathing pattern, and to also identify the best of these methods. The reasons for modifying the breathing pattern of a patient undergoing thoracic radiotherapy have already been discussed in Chapters 2 and 3. A further goal was to design a system which was considered to be inexpensive, easy to use and could also be adopted by any radiotherapy treatment centre without the need for interconnections to the radiotherapy treatment machine.

The work was predicated on the ubiquitously held assumption that there is a correlation between chest-wall movement and tumour movement, which this project did not set out to investigate. Table 5 summarises the main investigator and the management of this project, in addition to the company building and providing support for the device and software.

Project Management	**Device Concept / block design**	**Device Build**	**Device testing**	**Software conceptual design**	**Software build**	**Software testing**
Al-Mohammed / Supervisor	Al-Mohammed	RM Cybernetics	Al-Mohammed	Al-Mohammed	Al-Mohammed	Al-Mohammed

Table 5: Device Design and Build

4.2 SYSTEM REQUIREMENTS

The following functional specifications and system requirements were based on the aims and objectives of the project, and the limitations perceived to be present in devices discussed in the literature:

- It should be non-invasive and comfortable for the subject;
- It should be passive and not use restrictive methods to modify the breathing (e.g. no chest-press or breathing restraints);
- It should be USB or battery powered so as not to expose the subject or user to harmful voltages or currents;
- It should be portable in size and weight;
- It should work independently of any radiotherapy equipment, without the need of support from fluoroscopic equipment, linear accelerator or video camera systems that are integrated into a radiotherapy equipment room;
- It should have the ability to record the subject's respiratory cycle for up to 5 minutes;
- It must be computer-driven with a software package which can analyse the recorded data in real-time, and provide audio and visual feedback information that can be presented to the subject;
- Its function controls must be PC-based and driven from a single screen software console (or at most two);
- It should provide training patterns composed of pure waveforms and waveforms derived from the patient's own free breathing pattern;
- It should provide an overlay of the training waveform and the subject's real-time breathing pattern in different display formats for presentation to the subject during training and analysis phases (display formats should be continuous graphs, sliding bars, modulated tones, or composites of these);
- It should provide an output which can be read directly into a spreadsheet for offline analysis;
- Data should be recordable in anonymous subject-specific data files;
- Construction cost must be less than £3,000.

4.3 POSSIBLE TECHNIQUES AND SENSORS

The problem of designing the sensing system was broken down into two parts: Choosing the most appropriate method to monitor the breathing cycle, and deciding on the most appropriate sensor. Based on the criteria outlined above and the review of methods currently used (Chapter 3), the following possible combinations of methods and sensors were identified.

4.3.1 Methods

- (M1) Monitor the influx and efflux of air from the nose / mouth;
- (M2) Monitor the rise and fall of the chest wall;
- (M3) Monitor the expansion / contraction of the chest volume.

4.3.2 Sensors

M1:

a) Mechanical flow sensors
b) Hot-wire flow sensors
c) Pressure-change sensors (piezoelectric, semiconductor, membrane)

M2:

a) Reflective laser systems (laser displacement)
b) Capacitive systems and magneto-resistive
c) Three-axis accelerometers
d) Global positioning systems (GPS)

M3:

a) Strain-gauges
b) Resistive elements – linear variable resistors, liquid metal.

4.3.3 M1 – Monitoring Air Flow from the Nose or Mouth

Mechanical flow sensors are often used to monitor the flow of gas in machinery as well as in hospital (patient-based) systems. Unfortunately, an exhaustive search and testing of commercial sensors failed to identify a device which was small in size and weight, but which also provided an output signal allowing a differentiation between inhaling and exhaling, and which was easy to integrate into a device suitable for placing close to a subject's nose/mouth without interfering with normal breathing. A further complication with these devices was that if the subject stops breathing — even momentarily — the signal will fall to zero, mimicking a change in direction of breathing and destroy any correlation between the signal and depth of inhalation or exhalation.

Medical sensors in the M1 group were extremely expensive; as already noted, the cheaper commercial sensors provided a signal which was independent of the direction of air flow and ultimately not usable for this project. One commercial system used in the analysis of sleep disorders did seem to offer the possibility of an 'off-the-shelf' solution; this was the Stardust device (Starduste-Respironics Inc, Murrayville, USA) (Figure 10 and Figure 11), which uses a 7-channel recording equipment in order to monitor breathing during sleep (Ferguson et al., 2002) in individuals suffering from obstructive sleep-disordered breathing or sleep apnoea.

Fig. 10: Stardust kit

Fig. 11: Use of the Stardust device by a sleep-related breathing disorder patient (http://www.cpap-europe.com/stardust-home-screening-rental-o-50.html)

The Stardust device is portable, weighing less than 250g, and can be used at home. It has three sensors and can record data for up to 8.5 hours using a 9V battery. It records nasal airflow, breathing effort, heart rate, oxygen saturation, and body position (supine or prone). It measures respiratory effort via a respiratory effort belt, heart rate via a finger pulse oximeter and airflow via a nasal cannula/pressure transducer system (Figure 11) (Deldin *et al*., 2006). The data is then recorded and stored in the system, and can be loaded onto a laptop computer via a serial connection. Figure 12 showing the out put of Stardust device.

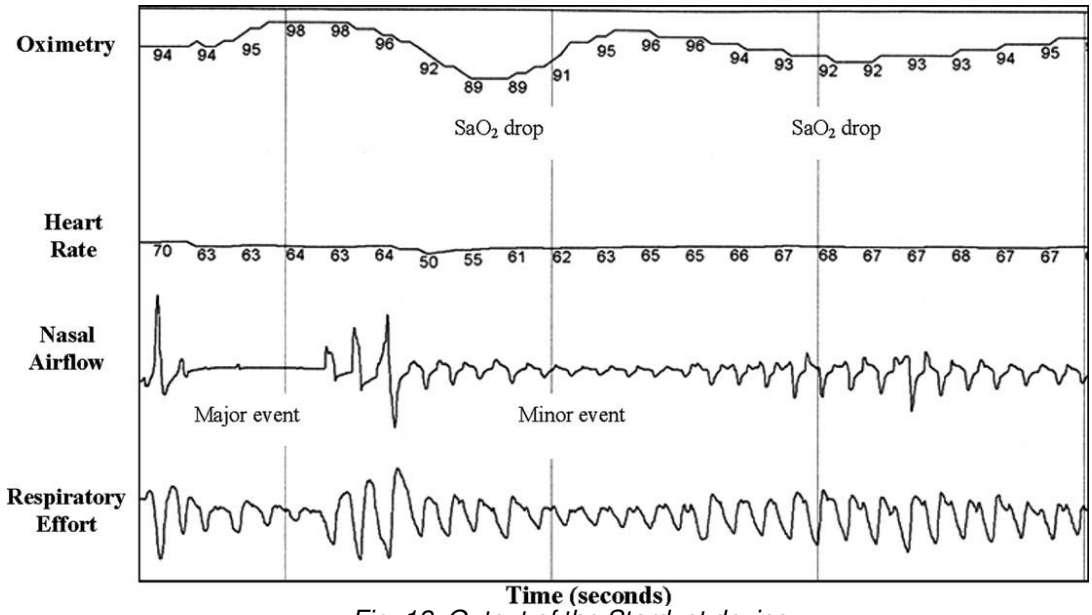

Fig. 12: Output of the Stardust device

4.3.4 M2 – Monitoring the Rise-Fall of the Chest Wall

Laser-based position detection is currently the method most often used in radiotherapy treatment rooms, usually in the form of the RPM gating system, which uses laser position detection. The system was considered inappropriate for our use, as it requires a direct connection to a linear accelerator. In principle, a simpler system could be built but this would still nevertheless require the use of laser tracking devices and software, which would be ultimately too expensive and outside the scope of this research to design.

Capacitive and electrostatic methods do, however, offer a possible way of monitoring chest movement, but these would require some form of reference framework to be placed over the subject; this would be impractically slow and cumbersome to use in any real setting — or even in a controlled environment.

A three-axis accelerometer system would seem to be the most appropriate solution for M2-type measurements; such a system would consist of an accelerometer pack (typically a cube with a side length of about 3 cm) placed on the subject's chest wall, which has an output which would provide a time-varying signal which could be integrated via hardware or software in order to produce the displacement. The disadvantage is the time taken to prototype the electronics and software needed to perform the mathematical integration operations and the time

needed to quality assure the output signals. Such a device would, however, certainly satisfy the above design criteria.

Finally, GPS systems — which are currently not used in such applications as far as the author is aware — would be extremely expensive and outside the scope of this work to design.

4.3.5 M3 – Monitoring the Expansion / Contraction of the Chest Volume

Both strain gauges and resistive elements lend themselves to integration in a simple chest belt; they are cheap, easily maintained, and robust. The electronics and mechanics needed to monitor the output of such devices, and are relatively simple to realise. A chest belt method for monitoring chest expansion would consist of a simple non-compliant belt attached to either side of the sensor, which would then simply need to be buckled around the subject's chest. The tension in the belt — which could initially be easily adjusted for the subject's comfort — would vary in response to the subject's breathing, increasing with inhalation, and decreasing with exhalation. Strain gauges and resistive elements (including liquid metal) would be sensitive to temperature, and so would consequently require temperature compensation. They are also passive devices, and so a system based on them might well be limited in terms of its sensitivity. However, their simplicity and low cost — in comparison to all the other methods reviewed — make them very appealing.

4.4 SYSTEMS CHOSEN FOR FURTHER INVESTIGATION

Due to the expense and complications associated with systems based on M2, these were rejected for further investigation.

The commercial system (M1) used for analysis of sleep disorders looked very promising and it was decided that this would be investigated further. An ex-demonstration system was purchased at a significantly reduced cost; however, an analysis of its functionality revealed that, while it apparently provided differentiation between inhalation and exhalation, this was not sufficiently robust or responsive for our needs. Furthermore, the system in question was rather cumbersome in terms of applying the sensors to the subject. Subsequently, some time was spent

investigating whether the individual sensors could be used in a homemade device, but this turned out to be rather difficult due to its construction. Modification of the software and electronics similarly proved to be too difficult. And, finally, although the ex-demonstration model was purchased quite inexpensively, a fully-calibrated virgin system would have been extremely expensive. For these reasons, the system was rejected.

A measurement system based on M3 therefore seemed to be the most promising, and a simple proof of principle system (POPS) was built.

4.5 PROOF OF PRINCIPLE (POPS) SYSTEM

The POPS device consisted of a simple belt and a variable resistive element constructed from a rubber capillary tube and a liquid metal filling, and an operational amplifier (Figure 13). No software was used and the signal was not digitised. The POPS was built and the dynamic range of the output, its stability, and its usefulness were investigated using an oscilloscope. The POPS clearly demonstrated that it was practical to place a sensor on a belt and use simple electronics in order to monitor chest expansion.

Fig. 13: PoPS

4.6 *FIRST PROTOTYPE DESIGN*

Following the PoPS experiments, a simple system was designed without specifying the exact sensor type; it consisted of a belt with integrated sensor, as shown in Figure 14.

Fig. 14: The belt positioned on the subject's chest

A Wheatstone bridge arrangement (conditioning unit) was specified to enable temperature compensation for all sensor types and to correctly bias the strain gauge sensor. The output of the sensor was directly fed into a simple amplification circuit using an operational amplifier prior to Analogue-to-Digital Conversion (ADC); the output from all possible sensor types was analogue, and this needed to be converted to a digital signal for interpretation at the computer level.

A Personal Computer (PC) was used to control the whole system with the use of a custom-built software package. The required specifications of the hardware were as follows:

- Semi-elastic chest belt with buckle
- Belt width approx 4 cm for comfort

- Length suitable for chest sizes up to 70 cm
- Sensor placed in line or on the chest belt
- Sensor power drawn from computer USB
- Sensor to be small – no more than 10 cm x 3 cm including any integrated hardware such as pre-amplification stage
- Sensor and hardware to be light – no more than 100 g
- Sensor to be connected to external electronics via simple light coaxial cable (2 mm diameter max)
- Facility to monitor and control two independent (and possibly different) sensors simultaneously
- Main conditioning ADC control box to be a stand-alone adjustable gain system, offset for both sensors (independently) using linear potentiometers.
- Sensor ID check signal buttons – simple button-operated signal that marks the signal graph to identify which signal belongs to which graph.
- Output via USB to PC.
- Output signal (displacement) should be reproducible to within 2 mm.

4.6.1 Software Design

The following specification was used as a first approach to the software design:

- Written for PC using widows XP
- Communication via USB port
- Single screen system with all controls and output
- Second screen for displaying sensor / simulated output or graphical data online or offline
- Control of input, output, file generation and save features
- Save features to include output formatted directly into MS excel and direct access ASCII formatted text file
- Each file to be subject-specific with numerical identifier
- Instant display function for online checking
- No additional communication cards or graphics cards.

The software should provide:

- Input for record identification and data
- Start / stop data record button

- Open / close file button
- Indication of data from sensor (live) or simulated data
- Input screen for data record identification
- Simulated data facility (sine wave, square wave and triangular wave)
- Amplitude and period adjustment (slider bars) for simulated wave form
- Separate window for displaying the output graphs
- Radio buttons to switch from bar graph to line graph output
- Upper and lower marker line switches to produce guide lines on the active graph – these lines indicate a breathing depth that the subject is attempting to match. Switches allow indicator lines to be made visible / invisible.

When in the active graph mode, i.e. displaying the sensor output in real time, the system should:

- Display a displacement time graph (line graph) with the ability to present either the subject's breathing pattern only, or that pattern overlaid with the control pattern, or the control pattern only, or neither.
- Display a chart with two bars side-by-side, one showing the desired breathing pattern, the other the subject's actual pattern. This should show either subject's breathing, or both subject and control, or just control, or neither.
- Be able to show output from either one or both of the sensors
- Be able to allow the graph to continuously scroll in time or become stationary
- Allow the upper and lower markers to be switched off or on independently.

RM Cybernetics was approached to build the entire system — including software implementation — based on the abovementioned design criteria. As the project was experimental, a flexible contract was agreed to include small redesigns without additional cost, while major changes/additions would incur a cost. The first prototype system was delivered 6 weeks after the contract was agreed upon.

Figure 15 shows the components of the system: an elastic belt was used to hold the sensor in place, and was designed to fit round the subject's chest or abdomen. The output from the sensor was connected to the electronics (in the black box) via a thin flexible data cable. The box containing the conditioning circuit, together with the amplifier and ADC, had two outlets for two sensors to be used (A and B).

A USB lead was connected the electronics to the PC. A separate video monitor was used in order to display the breathing traces to the subject. Figure 15 shows the belt attached to a subject who is positioned for monitoring.

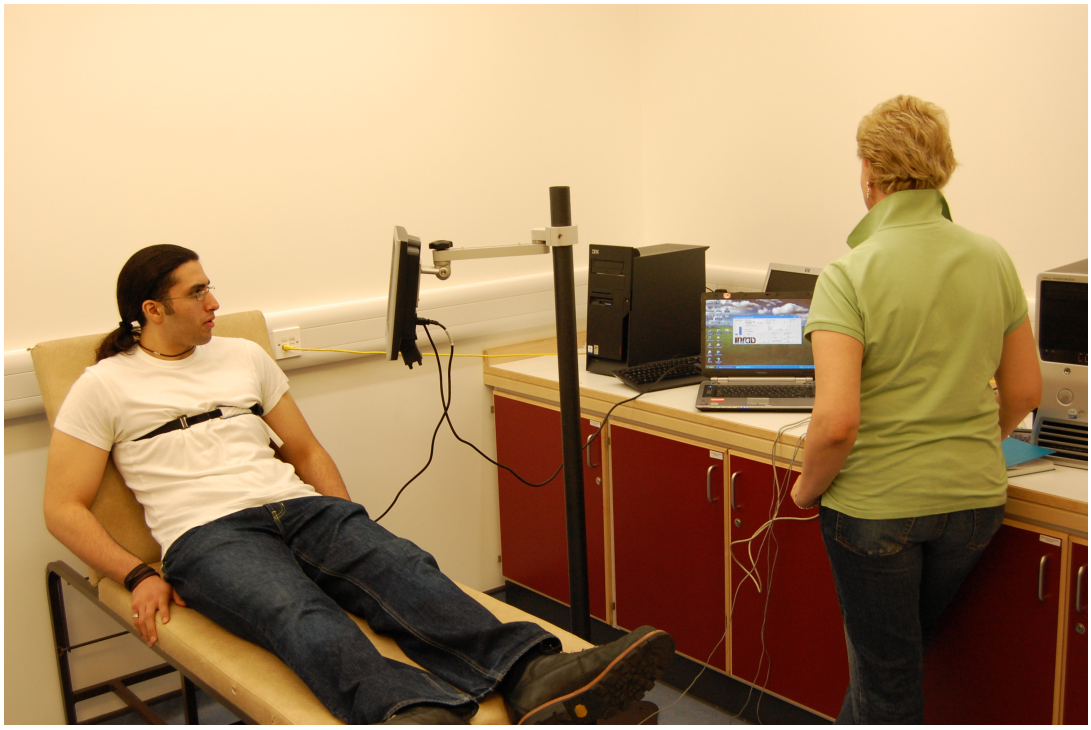

Fig. 15: Components of the whole system.
The belt (with its integral sensor) is seen across the subject's chest with the USB connection to a laptop running the dedicated software. The monitor displays the feedback information to the subject.

4.7 PRINCIPLES OF OPERATION

This section provides a brief overview of the operation of the device. During the in-breathing phase, the expansion of the chest caused a change in strain across the chest belt. In the cases of the liquid metal sensor, the chest expansion changed the cross-sectional area of the tube holding the liquid metal and then a change in the resistance of the liquid metal column. This change in resistance was measured with the Wheatstone bridge circuit, the output being a voltage change, which was approximately linear over a sensible range of strain (or chest expansion). The

change in voltage across the bridge amounted to a few millivolts for a full chest expansion. This voltage change was analogue, and had to be converted to a digital signal; it was conditioned, amplified and digitised electronically, and then passed to the PC.

During exhalation, the strain in the belt — and hence the sensor — was reduced, and the voltage signal returned towards its base reading. The time progression of the voltage signal followed that of the chest wall expansion and contraction during breathing. The software displayed this in one of three ways:

i) A continuous moving line graph (the amplitude indicating the depth of breathing, the period indicating the frequency of breathing and the phase indicating the phase of breathing;
ii) A continuous moving bar chart (the height of the bar indicating the depth of breathing) or a sound with increasing/decreasing pitch.

4.8 SHAKEDOWN TESTS

Initial tests on the prototype system were divided into three sections:

I. Functionality and performance of the software subsystems;
II. Functionality and performance of the hardware when used on a subject;
III. Reproducibility and quality assurance studies.

Tests were designed in order to evaluate several factors, such as the compliance of the system with the design criteria, the usability of the software, the ease of use of the system when monitoring a live subject, the reproducibility and accuracy with which the chest expansion and contraction was measurable and the robustness of the belt and sensor system. In all, the software and hardware went through three incarnations before being used to collect data from research subjects.

4.8.1 Software

Tests conducted on the software revealed several minor problems which limited the system's functionality and ease of use. The initial and final versions of the opening

screen are shown in Figures 16 and 17. The problems identified in the shakedown tests are discussed below.

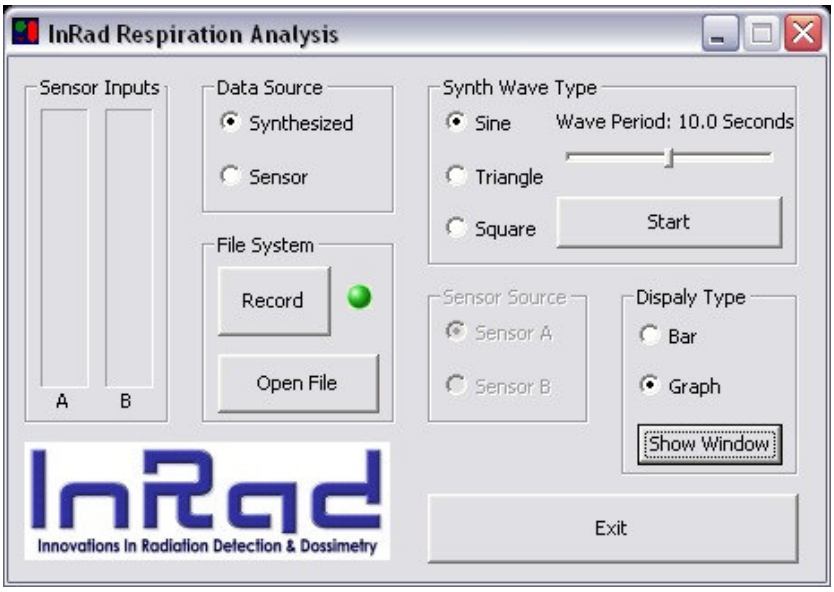

Fig. 16: The first InRad breathing system starting screen

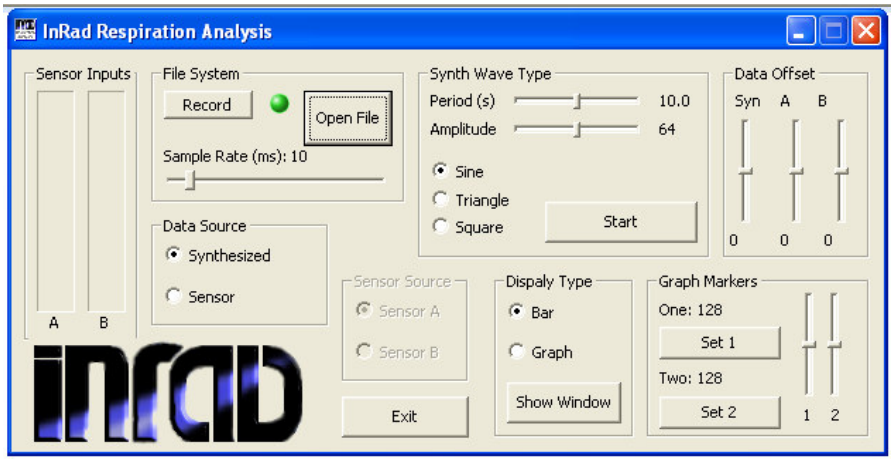

Fig. 17: The modified InRad breathing system starting screen
Note the addition of synthetic wave amplitude slider bar, data off-set slider bars and a sample rate slider bar (see text).

4.8.1.1 Graph offset – data offset slider bars

The vertical position of the subject's breathing pattern depended on the measured output voltage from the sensors, which had two components: the time varying signal, seen as the breathing pattern, and a static offset, which was dependent upon the tightness of the belt around the subject, etc. The latter differed from subject to subject and measurement to measurement. In some cases, it was observed that this offset placed the graph on the extreme upper/lower portion of the screen. In order to compensate for this, a simple offset slider was added — in fact, there were three data offset sliders; one each for the two possible sensors and one for the synthetic or simulated waveform. These were designed purely to alter the way in which the graph was displayed and did not alter the recorded data in any way.

4.8.1.2 Data sampling rate

The data sampling rate was initially a fixed value, which resulted in an excessively large data file and incompatibility errors with the Excel spreadsheet (a Microsoft error which was outside the control of this project). A control variable was then added in order to allow the sample rate to be varied; in practice, this was always set at 10 ms.

4.8.1.3 Waveform period control

The waveform period control indicated seconds but did not function correctly. This was changed in later versions to ensure provision of true values in seconds, thus allowing the period of the simulated training waveform to be accurately set to the natural mean free-breathing period of the subject, as determined from short FB tests.

4.8.1.4 Marker lines

Upper and lower marker lines indicated the maximum extent to which the subject should breathe in and out; in other words, they provided the subject with a controlled breathing envelope. Clearly, different subjects would feel most comfortable with different depths of breathing, so the extremes of the envelope indicated by the upper

and lower guidelines had to be altered to suit each subject. In V1.0 of the software, the position of these lines was alterable only through the use of two slider bars which had no relationship to the actual amplitude of the breathing cycle. This was corrected by adding the ability to position the marker lines by setting absolute values for the amplitude and offset; this allowed the guide envelope to be easily set to the subject's natural mean free-breathing amplitude as determined by a short FB experiment. The natural breathing amplitude determined could then be used in subsequent training episodes as the target amplitude to which the subject should match his/her breathing depth.

4.8.1.5 Coordinate scaling

During subject-based tests, it was observed that no coordinate scaling was provided for the graphs displayed. Effectively, the subject's breathing pattern needed to be displayed in a way that would allow the patients to follow it visually; in other words, a function needed to be included in order to permit the time and amplitude scales to be altered. Furthermore, scaling changes needed to be consistently applied to both the subject's measured breathing pattern and any simulated patterns; this was ultimately achieved by adding time and amplitude sliders, which permitted visual scaling.

4.8.1.6 Time axis looping

Initially, the time progression behaviour of the waveform was such that once the trace had reached the end of the data screen, the plot would reset and start again at a time of zero. This was both confusing and resulted in a discontinuity in the real-time plot, caused by a short time-latency in the reset phase. This was corrected by allowing the time axis to scroll continuously. The non-scrolling option was retained.

4.8.2 Hardware

Tests on the hardware revealed several problems associated with the belt and with system noise which made the initial system rather delicate and difficult to use; these are outlined below. There were also several minor problems in relation to plugs and

sockets, etc., which had no significant effect on performance but were nevertheless corrected; it is felt there is no need to discuss these here.

4.8.2.1 Sensitivity

The output of the system was found to be rather sensitive to the positioning of the belt on the subject's chest, to chest motion during the breathing cycle and to the tension of the belt. This was an issue associated with the absolute sensitivity of the system which, in turn, was related to the system gain. In certain situations, it was found that the amplitude of the signal was too small for any meaningful work; increasing the amplitude scaling had a limited usefulness, as this would effectively stretch any inherent noise, making the graph difficult to follow. Initially, the degree of amplification was preset, although it could be altered through a logarithmic inline pot. The ADC system had sufficient accuracy to allow an amplification phase to be added to the circuit. The circuit was altered to provide a fixed degree of pre-amplification followed by a linearly variable post-amplification stage, permitting variable gain control.

4.8.2.2 Noise

Adding a second amplification phase had the undesirable effect of increasing the signal noise, both due to small motion slippage of the belt during breathing and also from AC environmental signals. Additional filtration — predominantly 250 Hz — was added to the circuit and effectively solved this problem. Figures 18 and 19 show respectively a sample trace with excessive noise after the inclusion of the second amplification phase and reduced noise after the inclusion of a noise filtration circuit.

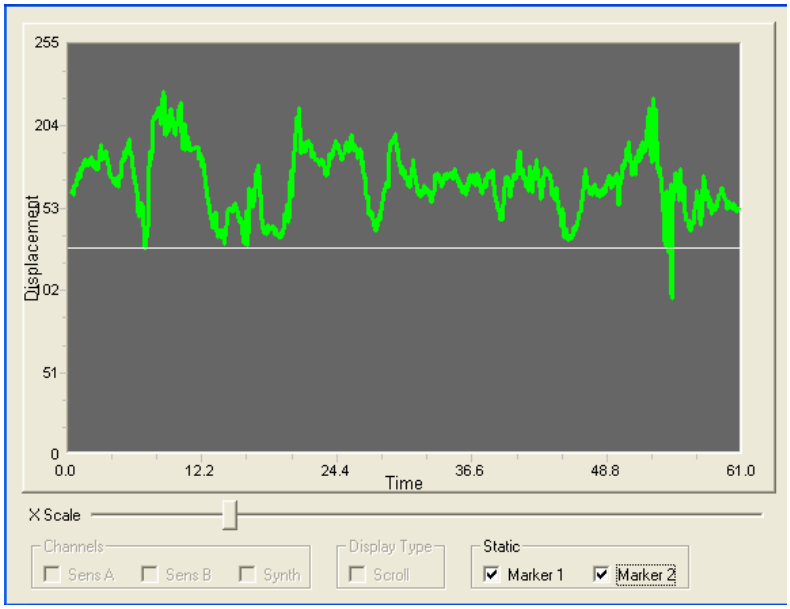

Fig. 18: The real-time breathing of subject with excessive noise following the modification of the amplification circuit

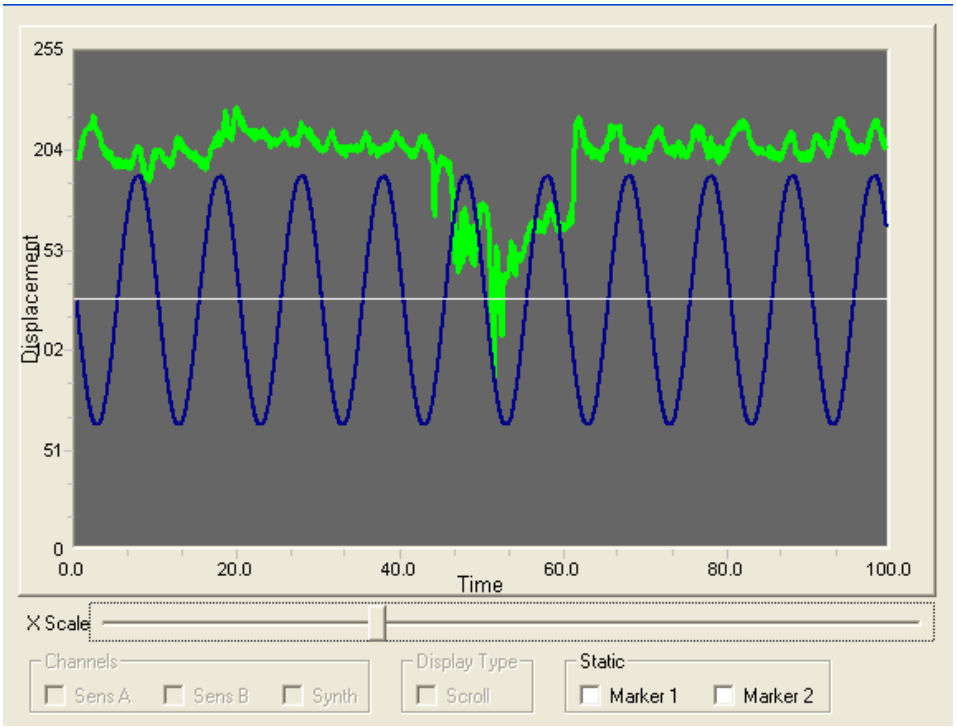

Fig. 19: Real-time breathing of subject with reduced noise following the addition of a noise filtration circuit

4.8.3 Reproducibility and quality assurance tests

It was clearly important that sensitivity and time-based drift should be insignificant over the measurement period. To this end, a simple test was devised in order to attempt to evaluate the extent of such drift. The belt was attached to two spindles, ensuring it was kept under tension, and simulated by being placed around the subject's chest. One spindle sat in a groove on a base-plate and could be driven in such a way as to alter the gap between the spindles periodically, simulating simple chest expansion/contraction. The test consisted of driving the spindle in a periodic (sinusoidal) motion for several minutes and then recording the output waveform from the sensors; this could then be compared with the driving signal which moved the spindle.

The experiment was repeated several times, disconnecting the belt between experiments and reassembling. Repeatability across all measurements (amplitude and frequency) was within 5% and there was no observable drift in period or amplitude when measuring for prolonged periods (over 10 minutes). The system followed the driving signal with no significant time delay. This last point is quite important, as a time delay in the monitoring system would introduce a feedback delay for subjects, who would then see what they were doing some time after they did it, making the task of following a time-varying waveform rather difficult (Appendix A).

4.9 TRAINING (SYNTHETIC) WAVEFORM GENERATION

Figures 20, 21 and 22 show the results of setting up sine wave, triangular wave and square wave training patterns respectively. A series of such patterns were initiated and the data recorded using the 'record data' button. Following the record sequence, two functions were tested, which were concerned with the display of the data using the InRad breathing monitor software regarding retrieval and display of the data using MS excel. The InRad software provided a function to write the data to a formatted Excel spreadsheet.

The period and amplitude of the saved data was then checked against the parameters set on the InRad setup screen. In all cases, the waveform, its period and its amplitude precisely matched the parameter settings, confirming that the waveform generator and save functions were operating correctly.

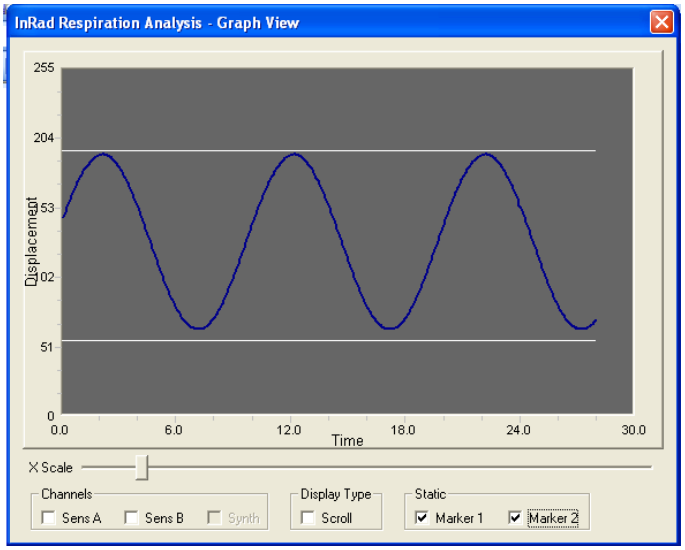

Fig. 20: InRad software displaying synthetic sine-wave data
The figure is a post-generation plot using saved data.

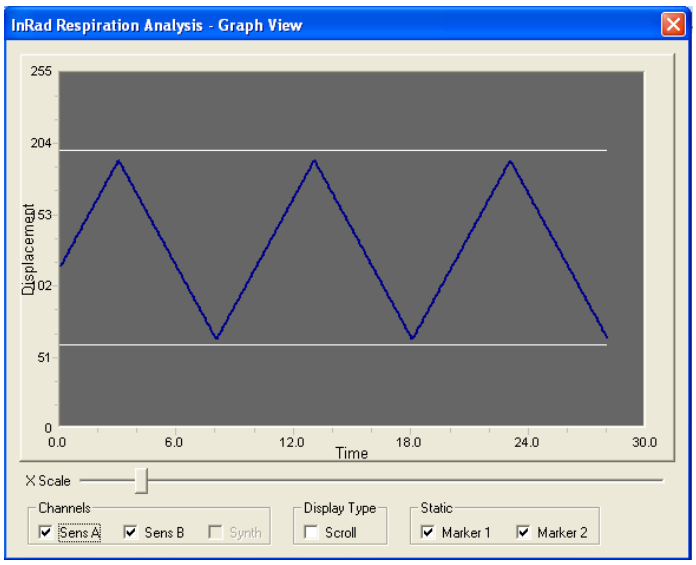

Fig. 21: InRad software displaying synthetic triangular-wave data
The figure is a post-generation plot using saved data.

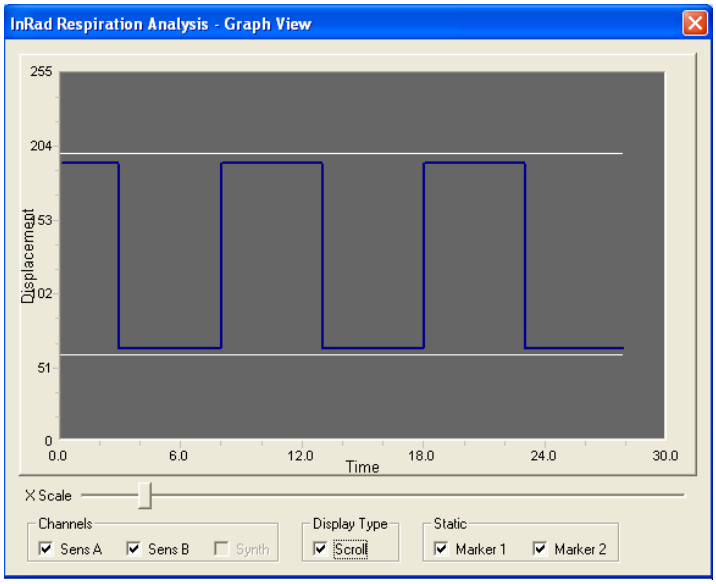

Fig. 22: InRad software displaying synthetic square-wave data
The figure is a post-generation plot using saved data.

The layout of the V 1.0 screen is shown in Figure 23, while Figure 24 shows the final version and the alternative bar-chart presentation: a moving column graph in which the height represents the y-axis displacement.

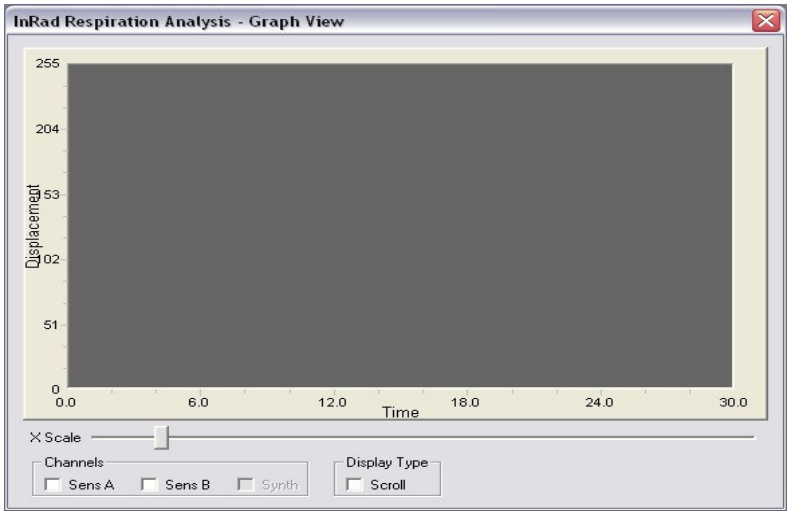

Fig. 23: Layout and functionality of the V1.0 graph screen
Note that the time axis has arbitrary units.

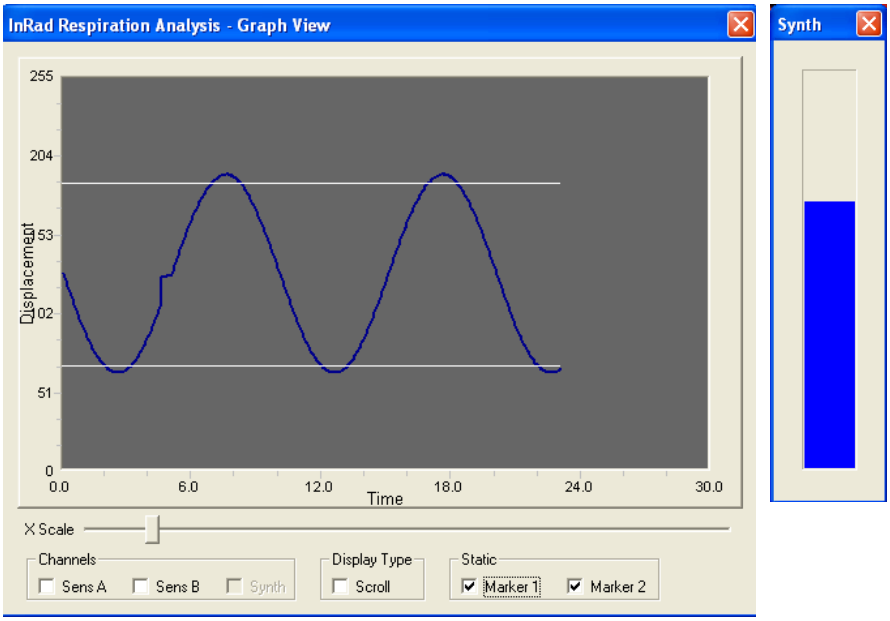

Fig. 24: Layout and functionality of final version of the graph screen (left-hand image)

Notice the addition of the static marker tick-boxes, which allows the two marker lines to be switched on or off. Also, the time axis now has the units of seconds. The position of the upper and lower markers is controlled from the initial screen by graph marker buttons and sliders. The bar graph on the right shows the alternative presentation. The blue column moves up and down in time following the displacement and frequency of the sine-wave. Frequency is indicated by the rate of the rise and fall of the bar.

The result of the system test is shown in Appendix A, which presents the actual data produced.

4.10 BELT POSITIONING

To evaluate the system in its entirety, a series of measurements were taken using two healthy volunteers. Various belt tightness settings and belt positions were investigated for both comfort and device functionality. The optimum position for the belt and sensor was found to be with the buckle placed on the subject's back and the

sensor was with the belt positioned laterally; this provided good sensitivity with little tendency for the belt to slip over clothing. The positioning is shown in Figure 15 above.

4.11 SUMMARY

The InRad breathing device used a belt with integral sensor to monitor the subject's breathing patterns. It was fully computer controlled using USB power and data transfer. The system permitted the use of one or two individually-configured sensors. Only two screens were needed for the setup and operation of the hardware and software.

The opening screen permitted the sensor type and number to be configured, as well as the data sample rate and record status. It provided controls for the generation of synthetic data (its type, period and amplitude) as well as data offset controls, which ultimately allowed the graph plotting to be controlled. These controls were placed on this page so that the graph screen could be presented as simply as possible in relation to the subject; any adjustments to be made during a monitoring session were not seen by subjects, and so would not disturb their attempts to following the training instructions, etc. The type of graph shown to the subjects during a measurement could also be chosen from this parameter setup screen (the opening screen).

Finally, the parameter screen allowed the positioning of the upper and lower depths of breathing marks to be placed on the graph. These appeared as static lines and acted as upper and lower boundaries to the patient's breathing envelope.

Basic shakedown tests were performed on the software and hardware in both subject measurement and passive modes. These highlighted failures and weaknesses of both hardware and software, prompting successive redesigns prior to the taking of full data measurements from subjects.

The second screen was the display screen, which had a minimum number of parameter controls and simply displayed the graphs in real time to the subject.

CHAPTER 5: EXPERIMENTAL DESIGN AND METHOD

5.1 INTRODUCTION

This chapter presents the methodological considerations and the decision-making choices used to conduct this study.

The research categories used in this project were analytical and experimental. The goal of the project was to develop a non-invasive device which could monitor the breathing of subjects during radiation therapy treatment and to use this to investigate different methods by which subjects could be helped to perform regulated breathing. The experimental component of the research was thus divided into two distinct parts: phase 1 was the development and testing of the device and phase 2 was the investigation of the different methods of regulating breathing patterns. The development of the device and its testing are discussed in Chapter 4, while the current chapter relates only to phase 2, in which the device was then used with volunteer subjects to monitor their breathing patterns.

5.2 EXPERIMENTAL DESIGN

The research methodology used during phase 2 is now outlined. Table 6 summarizes the main aspects of experimental design.

Ethics Application	**Consent for Design**	**Information on Design**	**Device Testing**	**Subject Recruitment**	**Experimental Design**	**Measurements**
Al-Mohammed / Supervisor	Al-Mohammed	Al-Mohammed	Al-Mohammed	Al-Mohammed	Al-Mohammed	Al-Mohammed and Supervisor (3 subjects)

Table 6: Experimental Design

5.2.1 *Research Question*

The research question to be answered can be expressed as: Which breathing technique produces the most stable breathing pattern: free breathing (FB), audio prompting (AP) or video feedback (VF)?

5.2.2 CONTROL

In order to answer the research question and identify the best technique, FB, AP and VF were compared to a control breathing pattern. Under the assumption that we wished to regulate as much as possible the period, amplitude and phase of a subject's breathing, a control pattern was defined as a clean (ideal) sinusoidal trace, having constant period and amplitude. This control was derived from the subject's natural free breathing, the amplitude of the control being set as the mean amplitude of measured FB and the period of the control being set as the mean period of the same measured FB; thus, as required, the control had a constant period ($T_{Control}$) and constant amplitude ($A_{Control}$). In this way, the control was closely related to the subject's natural breathing rhythm and avoided any form of unnatural forced breathing, i.e. at an uncomfortable frequency or amplitude.

5.2.3 DECISION PARAMETERS

The main parameters were:

- the difference between the control amplitude and that of the breathing patterns created using FB, AP and VF; and
- the difference between the control phase and that of the breathing patterns created using FB, AP and VF.

A good breathing pattern is here defined as one that minimises the above differences. Clearly, a single measure of these differences is insufficient here, so the observable parameters are statistical estimates of the underlying mean difference and the standard deviation of the difference, the objective being to establish which, if any, of the FB, AP or VF methods has the smallest values of these statistical parameters. There are two cases to consider – averages over the number of cycles for a single subject and averages over all subjects. The analysis used is developed in chapter 6.

5.2.4 SAMPLE SIZE CONSIDERATIONS

a. Averaging over subjects

The number of subjects chosen was based on time constraints and the requirements of statistical significance. Estimates of the time needed to perform a complete measurement set on one subject obtained was limited to fifty. The counting error with fifty samples provides an uncertainty at one standard deviation (68% confidence) of approximately 14%. Clearly it would be better to have a lower standard uncertainty, but there was a limited timeframe for this project to be undertaken and based on the time needed to asses one subject, the limitations of subject availability and on the time available for use of the SAAD centre etc, it was decided that fifty subjects were as many as could be sensibly accommodated.

b. Averaging over cycles

The measurement protocol was set to approximate a typical timeframe as seen in a radiotherapy treatment but avoiding the risk of induced fatigue, which would otherwise bias the results. A measurement period of 4 minutes was chosen, typically providing 70 cycles. The uncertainty associated with this on a simple counting process is approximately 12%. It was felt that this was the best that could be achieved for this experiment.

The total uncertainty, based on assuming that the above factors are uncorrelated, independent and can be combined in quadrate, is approximately 17% at 68% confidence.

5.2.5 EXTERNAL BIAS

The external bias for this project could include any fault in the device or the belt, any distraction during the measurements and finally any problem with the subject. To limit any external bias the device was fully tested before each measurement, access to the measurement room was limited to the subject and experimenters during the time of measuring and finally, the subject was fully informed about the procedure and the time that it was likely to take.

5.2.6 INTERNAL BIAS

The internal bias includes the influence of any form of training, relaxation and fatigue of the subjects over the measurement period and specifically between measurement procedures (FB, AP, VF). Such learning or relaxation might potentially influence the results – presumably showing improvement as the session progressed (in the case of learning / relaxation) and presumably a worsening of results in the case of fatigue. However, the sequence of the measurements had to start with FB, to provide a trace on which to establish baseline control. Audio prompting was then placed before visual feedback so that the easier method came before the more complex procedure. In addition, visual feedback took time to set up; adjusting the monitor according to subject preference could cause changes in belt position, which would affect the AP reading later. It was felt that ordering the session in this way reduced the possibility of fatigue. Considering the learning effect, each method required a different physical response from the subject and so learning should not be an issue. Furthermore, prior to commencing measurements, the subjects were given some time to become familiar with the equipment and setup, and any questions were dealt with. In this respect the initial steep learning phase would apply to all three methods. This initial learning was supported by the initial one-minute session in which the subject was simply asked to breathe so that the system could be set up and tested. It is recognised that learning was not completely eliminated from this work, but its effects are seen as limited and the real possibility of fatigue if a different order had been chosen is seen to outweigh this potential bias. Due to time constraints, further random sequence tests could not be performed.

5.2.7 EXPERIMENTAL ENDPOINTS/OUTCOMES

The endpoints for this project were set as follows:

1. to produce a simple, portable, basic device
2. to produce software that could be used with the device
3. to implement the device to be used in clinical facilities
4. to establish if one of the training methods (FB, AP or VF) was best.

5.2.8 RECRUITMENT METHOD

The recruitment methods for this project included:

1. A flyer at the university hall inviting students and staff to join the study. It gave details of the time the measurements would take, the investigator's name, the contact person's telephone number and email address (Appendix E);
2. Asking people at work, family members and acquaintances if they would participate.

5.2.9 INCLUSION CRITERIA

The minimum inclusion criteria for volunteer enrolment in this project were the following:

a) Healthy, male or female subjects aged 18-70 years;
b) Unspecified pulmonary function;
c) Subject has provided written consent;
d) The ability to understand and discuss his/her participation;
e) Does not require oxygen or any other form of breathing aid; and
f) Is able to lie or sit in the supine position for approximately one hour.

5.2.10 EXCLUSION CRITERIA

Exclusion criteria for all subjects were:

a) Any breathing problems which require breathing support, such as oxygen;
b) Pain or discomfort when lying down or sitting up for the measurement time;
c) Mental disorder; or
d) Health problems, such as heart problem or back pain.

5.2.11 NON-CONFORMANCE TO PROTOCOL AND NON-SPECIFIC WAVEFORMS

It seemed clear that better results in training would be obtained if a target were selected with a breathing pattern which was close to the natural pattern of the subject. This hypothesis was tested in a separate set of training exercises whereby we deliberately chose waveforms with parameters different from those of the natural breathing patterns of the subjects. The results (as discussed in Chapter 6) confirmed our hypothesis and so all our training sessions used data collected from the free-breathing sessions.

5.2.12 TRIAL MANAGEMENT

The trial management of this project included all aspects of the processing of data recording, all subjects involved in the measurement, analysis of the measuring data, the quality plan of day-to-day measurement and the timeframe for the project. The supervisor was informed on all occasions of any changes to protocol and of any testing. The trial was seen as the initial basis for further study.

5.3 ETHICAL CONSIDERATIONS AND CONSENT PROCEDURE

The University's full ethical consent procedure (under City University Guidelines) was followed (Approval of Experiment and Investigation Involving Human Subjects (Appendix D)) and ethical consent granted through the Ethics Committee. The signed ethical approval letter is shown in Appendix B and the completed ethical application form in appendix D. Some of the ethical considerations are detailed below.

a. Confidentiality and Anonymity

All data was anonymous and no personal information was stored under the subject's name. Each subject was assigned a number in order to protect the privacy of the information. The data results were protected from unlawful detection or use under any circumstances by being stored in a laptop to which only the principal investigator had the right of access. All ethical considerations of protecting subjects' privacy were taken to avoid any instance where data or information could be published or used by any unauthorised person.

b. Payment, recruitment and characteristics of subjects

This investigation involved no payment or inducement for the volunteers to participate in the study; there was therefore no ethical consideration regarding payments to subjects. The study took into consideration that all the subjects had to be physically healthy volunteers without disorientation or poor mental health. Children and young people were excluded by the criterion that subjects had to be fully competent adults aged 18 or above.

c. The Device, Duration of Measurement and Safety of Subjects

The device was considered safe, consisting of a flexible belt carrying a strain gauge sensor (as described in Chapter 4). The device was not mains powered and had no direct contact to high voltage equipment. Participants were subjected to no risk of harm. Measurements took from 40 to 60 minutes to complete, including explanation and three sessions of different breathing patterns. The procedure was not invasive and was considered safe for all subjects, who were not restrained during the measurement. The safety of the subjects and their awareness of safety were fully considered.

d. Written Informed Consent

Prior to the measurement the subjects were informed about the procedure, its duration and the device. They were then asked to sign a written consent form (Appendix C).

e. Withdraw from the study

All subjects had the right to withdraw from the study at any time and not to complete a full session.

5.4 EXPERIMENTAL METHODS AND PROCEDURE

Fifty 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. No pre-selection was made except for the ethically approved inclusion criteria stated above.

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. Each subject was assigned a randomly generated number that was used on all subsequent data files. It is important to note that only the principal investigators had access to any of the volunteers' information, as required by the ethical approval obtained from City University Senate Research Ethics Committee for Approval of Experiment and Investigation Involving Human Subjects (Appendix E).

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, 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 custom-made belt and strain gauge 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. Generally, only two such adjustment sessions were needed before the optimum settings were determined. The subject was not shown any breathing data, nor was the subject 'trained' in any way during this initial setup phase.

As previously mentioned, each data collection session lasted 4 minutes. There was an interval of 10 minutes between sessions for the subject to rest.

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.

The subjects of this study, who were divided into two groups, all had to be aged at least 18 years, be able to understand and discuss their participation, 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. Figure 14 in Chapter 4 shows a typical setup, where the subject is in a recumbent position for ease of photography (allowing the belt, waveform monitor and subject to be seen), while Figure 15 shows a demonstration of a typical attempt to follow a breathing trace, in this case a triangular wave (as with figure 14, the subject has not been placed in the treatment position).

For each subject, a series of 4-minute 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, audio prompting (therapist's voice providing prompt commands to breathe in and out) and visual feedback. Originally, it was also planned to include audio-visual feedback, but initial investigations showed that this was problematic and caused confusion, so this suggestion was excluded.

The data collection was organised in the above way in order to facilitate the most natural free-breathing response, i.e. one that was not influenced by any form of training or relaxation. Certainly, it was recognised that relaxation and/or fatigue could influence the later collections in the sequence, but analysis of the data showed no such effects. Audio prompting was placed before visual feedback so that the easier method came before the more complex procedure. In addition, visual feedback took time to set up; adjusting the monitor according to the subject's preference could cause the belt position to vary, and thus would affect the AP reading later on.

The data collected in all sessions were recorded and each recording contained the numerical data to enable the full 4-minute 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 analysed against the different prompt or feedback waveforms. The data was exported directly to Excel spreadsheets, as discussed in Chapter 4.

5.5 PROCEDURE DURING THE BREATHING SESSIONS

5.5.1 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 InRad 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.

As will be seen in the results section, the amplitude and period of participants' breathing varied with time over the 4-minute 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 sessions, time-averaged data from the FB pattern were used in order to establish the parameters of a regular training pattern.

5.5.2 AUDIO PROMPTING SESSION

For the audio prompting session, the breathing belt was left on the patient from the FB session and the monitor software was set to produce a sine wave with a frequency and period determined as above. 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.

After completing this session, the subject took a break for approximately ten minutes, then the video feedback session started.

5.5.3 VISUAL FEEDBACK

For visual feedback, the subject was presented with exactly the same training signal as had been presented to the researcher during the audio session, except that presented on the same rolling graph was the subject's real-time breathing pattern. The subject was able to follow his/her real breathing and to try to match it with the ideal breathing. The real breathing was shown to the subject on a flat screen monitor which had been fitted to a medical stand and which the subject was able to adjust according to his/her position and vision, so that he or she could see the breathing trace very clearly; the idea behind this was that the subject should attempt to make his/her pattern follow as closely as possible the guiding (or synthetic) waveform, which took the form of a sine wave.

Upper and lower guidelines were also placed on the rolling graph (just above and below the maximum inhalation and minimum exhalation phases of the synthetic waveform) in such a way as to act as an envelope within which the subjects were asked to keep their breathing amplitude. They were asked to try to follow the synthetic sinusoid for four minutes.

5.6 PILOT STUDY

A pilot study was conduct on two subjects in order to determine whether all operational parameters of the device, belt and software were as expected, so that the full procedure could be applied to all fifty subjects. Problems were found relating to the positioning of the monitor (used by the subject in the VF experiment), room lighting / noise and methodology for transferring data in an efficient way. All of these issues were corrected prior to the full testing of subjects.

CHAPTER 6: RESULTS AND DISCUSSION

6.1 INTRODUCTION

As previously discussed, the success of advanced radiotherapy treatment modalities, — such as IMRT or very small field treatments — crucially depends on the ability to control (conform) the tumouricidal dose to the Planning Treatment Volume (PTV) while also sparing the healthy tissue and organs at risk. This is limited in turn by our ability to control how the treatment is delivered during the natural movement of the tumour, and currently depends on the stability and reproducibility of the patient's breathing pattern.

A portable monitoring system was designed, built and tested, as discussed previously. The device allows the patient's breathing to be monitored, displayed and analysed in real time, and further permits various training techniques to be investigated via the presentation of a training or feedback waveform (visual or audible). The system does not rely on integration with the treatment machine, but is wholly independent of it, so it can, in principle, be used both inside the treatment room during treatment (following a training session), allowing patients to actively control their breathing in accordance with some agreed optimum feedback signal, and as a training aid prior to treatment so that patients can control their breathing in a passive way, without the use of the device.

This chapter examines the relative appropriateness of the methods of providing the feedback signal to ensure that the subject's breathing is repeatable. Such a signal would act as the guide-signal in the event that the device was used inside the treatment room during treatment, or simply as the training signal if the system was used purely outside the treatment room as an aid to passive breathing during treatment.

6.2 SUBJECTS' CHARACTERISTICS

During this study, all fifty-one subjects were unpaid volunteers, divided into two groups. The first group consisted of healthy volunteers, each of whom was aged between 18 and 48 years old and had no health condition or smoking history; thirty-eight were students or staff of City University or their family members. All of the

participants joined the project either after reading the flyer or because they worked in the same office or had otherwise received a personal invitation to join. All were considered to be physically active, practicing sport and exercising as a regular routine in their daily lives.

This group was investigated in a simulated room within the SAAD Centre at City University, London. This was a fully equipped diagnostic room used in the training of therapy and diagnostic radiographers. It mimicked, as closely as possible, the treatment room within a radiotherapy department. The subject was placed on a medical couch in a position typically adopted for radiotherapy treatment.

The second group of four subjects comprised elderly relatives and friends in a nursing home, whose ages ranged from 56 years to 70 years. Each of them was very well mentally oriented, able to discuss and sign the consent forms, and experienced no problems with vision or hearing. The subjects there had a full introduction session concerning the device and the purpose of the study, and had the right to ask any questions. Three of the volunteers within this group had been smokers for a long time before quitting, while the remaining member still smoked. There were no health conditions of which we should have been aware besides coughing and mild rheumatism; none of the participants had cancer or severe pulmonary dysfunction. These subjects were measured in the nursing home, since they could not visit the SAAD Centre. Analysis was undertaken with the subject recumbent in a quiet room. The subjects had no problem with measurement and could cope with the duration of the sessions; there was minimum distraction caused by coughing or having to ask questions.

The study was conducted over a period of several months. The data from one subject was rejected as it was later discovered that the subject had only one lung – but this had not been revealed to the researcher before testing. Thus 50 subjects in total were included in the analysis.

Access to the nursing home proved to be time-restrictive, which imposed a further significant restriction on the total number of subjects who could be investigated. Typically, a single investigation would take approximately one hour.

The experimental procedure adopted for all measurements on all subjects is fully discussed in Chapter 5.

6.3 *FREE-BREATHING, UBIQUITOUS SINE-WAVE FORMULATION AND AMPLITUDE GATING*

For several years it has been 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. Figures 25 and 26 are examples of free-breathing patterns from two subjects measured during this work. The individual traces correspond to isolated inhale-exhale cycles (of which only seven are shown in each plot for brevity). These figures have been created by chopping individual cycles out of the subject's wave form and laying them on top of each other. What is evident from this is that the amplitude and position of maximal inhalation (corresponding to the phase) and the period vary from cycle to cycle. The effect is subject-dependent, as can be seen by comparing Figures 25 and 26. For example, in Figure 25 the variation in all parameters is quite pronounced, while subject B, as shown in Figure 26, had a more tightly controlled breathing pattern. He had the ability to produce a more stable breathing pattern, which has limiting effects on the period and amplitude in his breathing cycle. Looking at Figure 26 on the time axis, we can see that the subject was limiting his breathing period between 30.75 and 34 seconds, whereas Figure 25 shows that for subject A, the period shifted in every cycle. The variation in period, amplitude and phase shown in Figures 25 and 26 were all replicated for all subjects studied in this work; clearly then, it is inappropriate to attempt to gate a treatment under the assumptions of consistency in amplitude, period or phase for free-breathing.

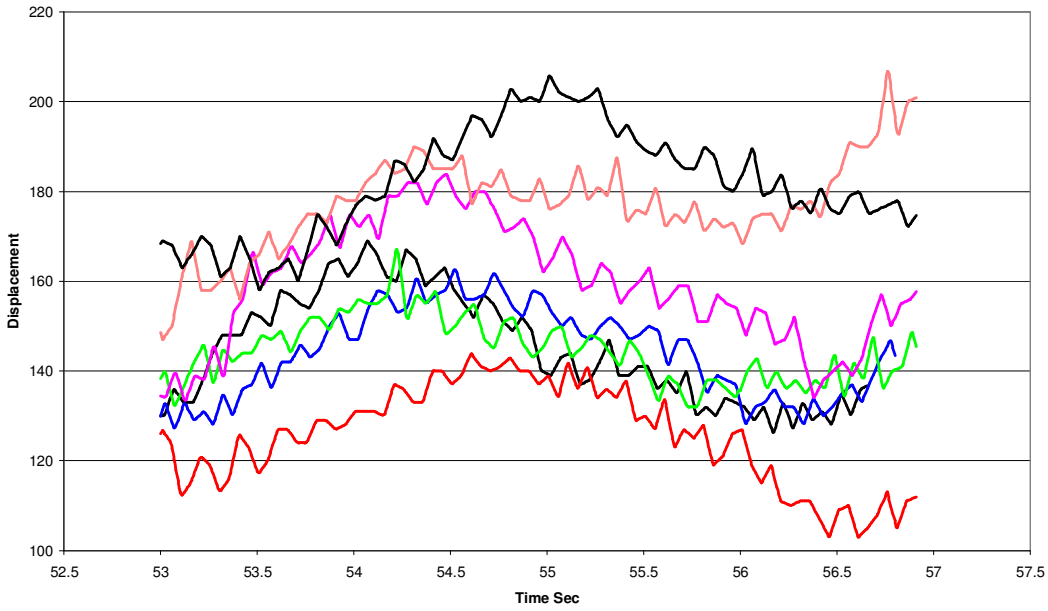

Fig. 25: Variation in free-breathing pattern for subject A.

Each curve represents a measured inhalation-exhalation cycle. Seven cycles are shown, superimposed in the time domain. Clearly, the shape, period and location of maximum change from cycle to cycle, as does the baseline level.

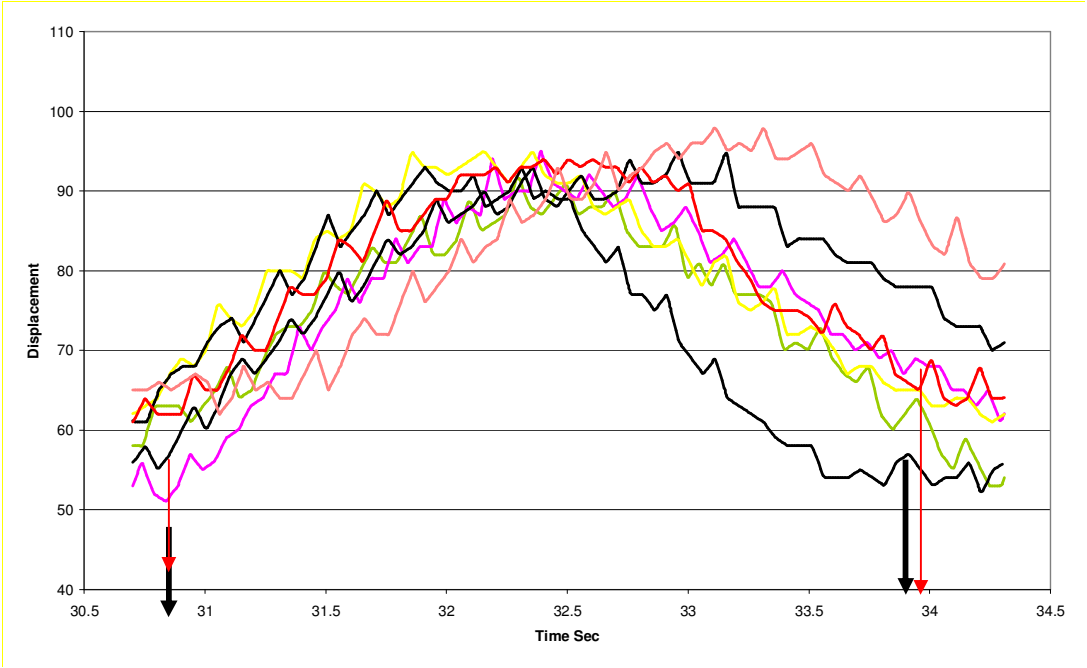

Fig. 26: Variation in free-breathing pattern for subject B.
Each curve represents a measured inhalation-exhalation cycle. Seven cycles are shown. Here the location of the maxima, the baseline level and the period are more consistent from cycle to cycle than for subject A in Figure 25.

6.3.1 BASELINE SHIFT PHENOMENON

Figure 27 shows a trace from subject B; again, this is a free-breathing trace, so there was no feedback or breath training. The trace shows a characteristic changing baseline, which corresponds to the subject slowly changing the style of breathing by not completely emptying the lungs during the exhale portion of the cycle. It demonstrates quite graphically an interesting problem which can arise 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 tumour is within the treatment beam. This effect is shown in Figure 27, where an exhale amplitude window has been superimposed on the breathing pattern of Figure 28. During the real-time treatment with gating, the verification for tumour position would be checked using EPI, portal film or by tracking, as explained earlier in Chapter three, where 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 exhale amplitude maximum or the inhale amplitude maximum.

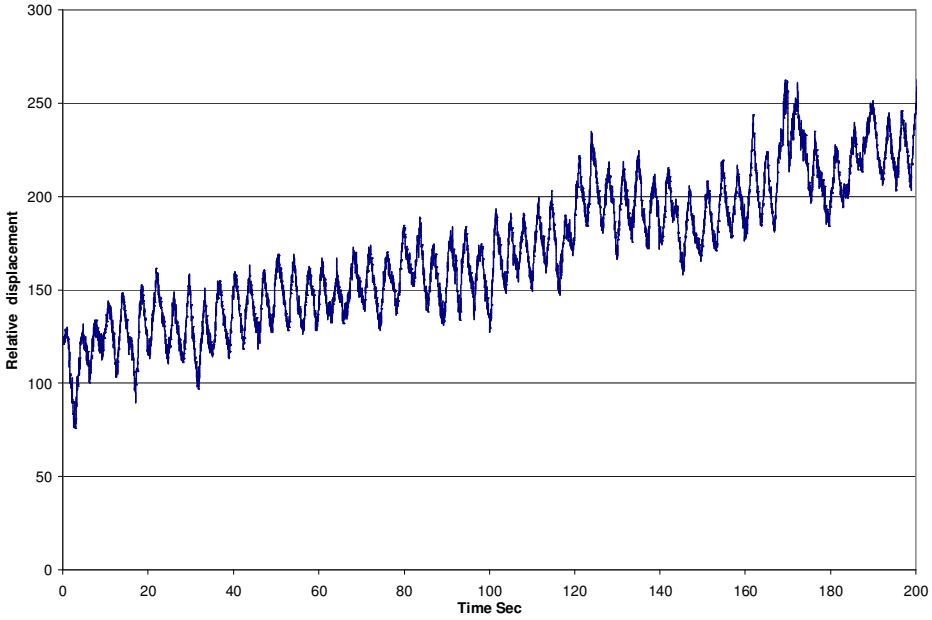

Fig 27: Free breathing trace for subject B.

The subject had no training: note the irregularity in breathing pattern and the changing baseline (corresponding to a change in the subject's mean chest position at exhale).

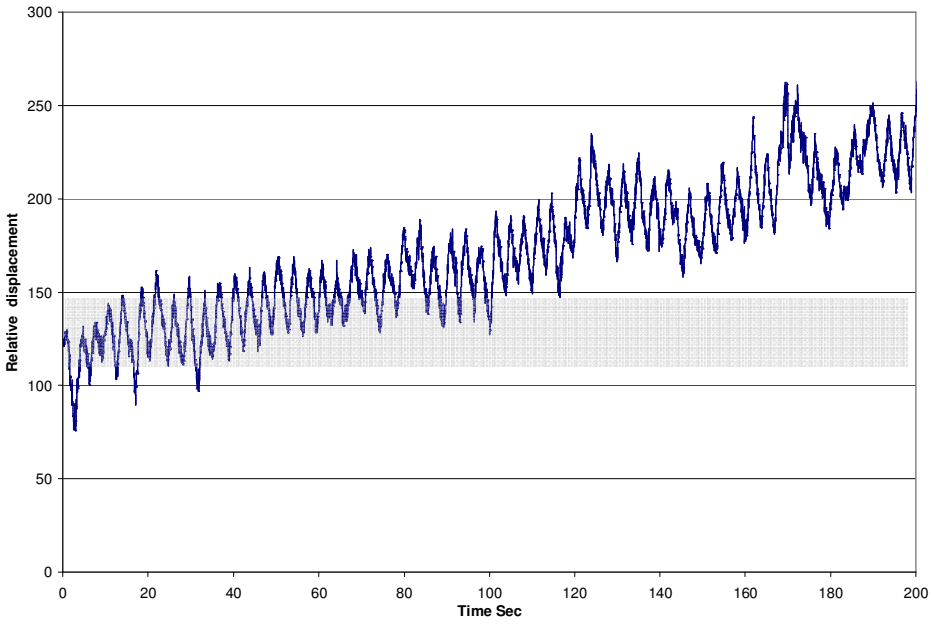

Fig 28: Exhale amplitude window.

This shows difficulties which can arise in setting a treatment (beam-on) window based simply on the free-breathing pattern when, in this case, using the exhale portion of the cycle. The beam is switched on only when the exhale maximum (positions of minimum displacement on this graph) falls within the shaded trigger region. Beyond about 60 seconds, the machine will be turned off even if the phase (local position in time) of the breathing is correct.

The opposite effect would occur in this case if gating were to be set on the inhale amplitude. This is shown in Figure 29, where the machine would switch on between 20 seconds and 100 seconds, irrespective of the phase.

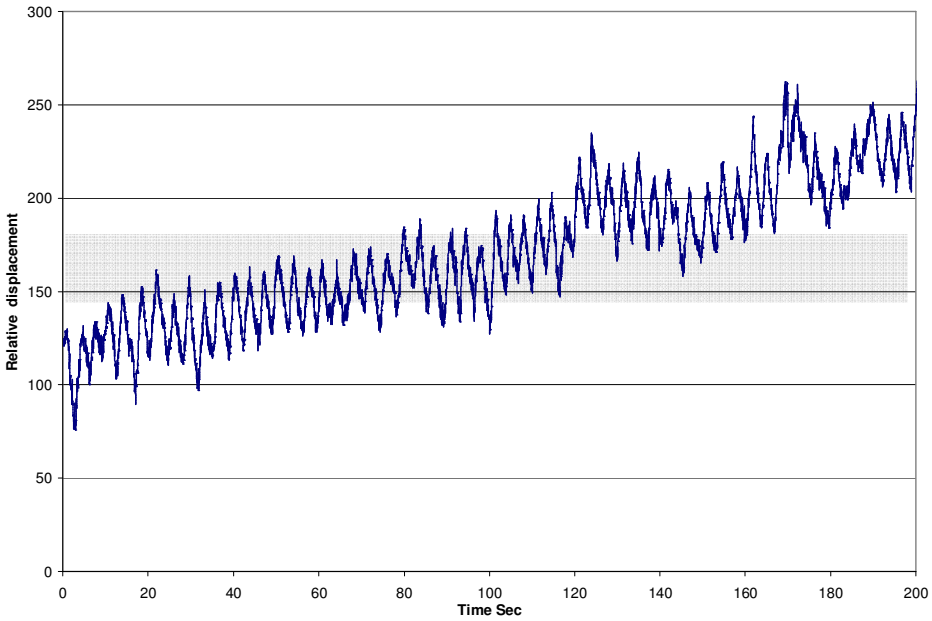

Fig 29: Inhale amplitude window.

When the window is based on the inhale portion of the subject's breathing, the opposite effect to that shown in Figure 27 occurs. From about 20 seconds to 100 seconds, the beam will trigger irrespective of the phase (time position of the maximum). In other words, even if the tumour is in a position which is diametrically opposed to its required position, the beam will nevertheless be switched on because the amplitude is within the window.

Figures 27 to 29 demonstrate the importance of controlling both the amplitude and the phase of the patient's breathing pattern, and of gating on phase (and possibly amplitude), rather than amplitude alone. All of the 50 subjects who were examined and measured produced the baseline shift, as explained above, due to the fact that they would not take a full inhalation as they were supposed to, or they did not totally exhale and empty their lungs. This phenomenon of baseline shifting was even worse with elderly subjects and smokers.

6.3.2 BREATHING WITH FEEDBACK – SIMPLE COMPARISON

Figures 30 to 32 demonstrate the effects of feedback on a subject's breathing pattern. Again, subject B is presented, and so Figure 30 should be compared directly with Figure 28 for a simple comparison of Free-Breathing and breathing with feedback. Using video feedback where the subject's real-time breathing trace is presented to the subject overlaying a 'desired' breathing waveform, the subject is able to remove the baseline drift in his or her breathing, and ensure that the amplitude remains reasonably constant, as seen in Figure 30, with the peaks and troughs staying mostly between approximately 150 and 110 units respectively. In Figure 30 the training signal has been removed for clarity; however, this can be seen in Figures 31 and 32, where it is clear that the phase of the subject's breathing (the relative positions of the peaks and troughs with respect to the guiding signal) does not change significantly.

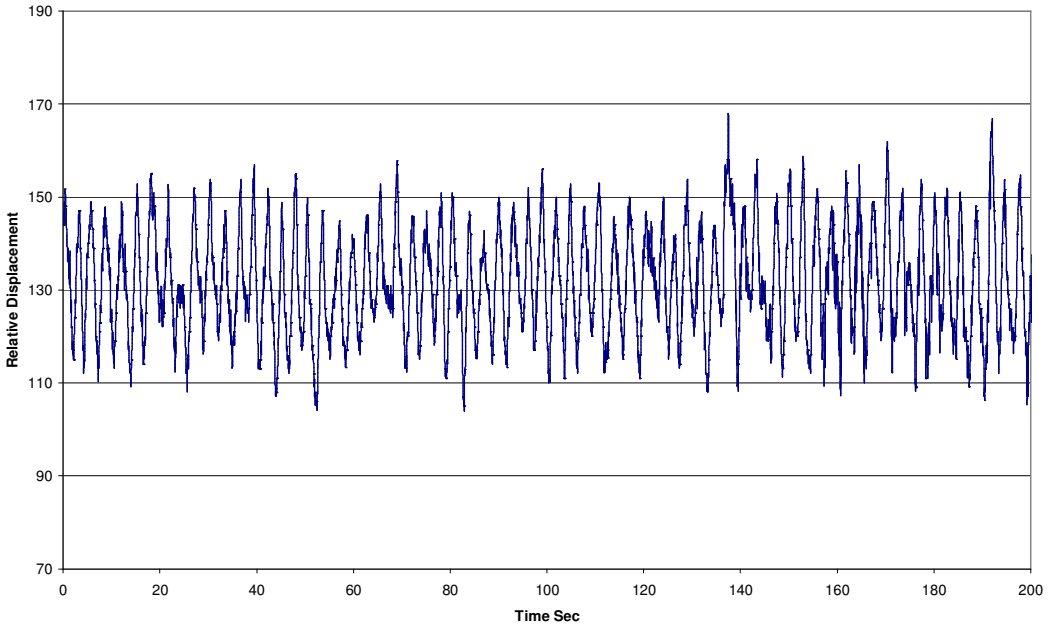

Fig 30: Video-trained breathing trace for subject B
The training signal has been removed for clarity. Notice how the breathing pattern does not show the baseline drift present in the free breathing trace (Figure 27).

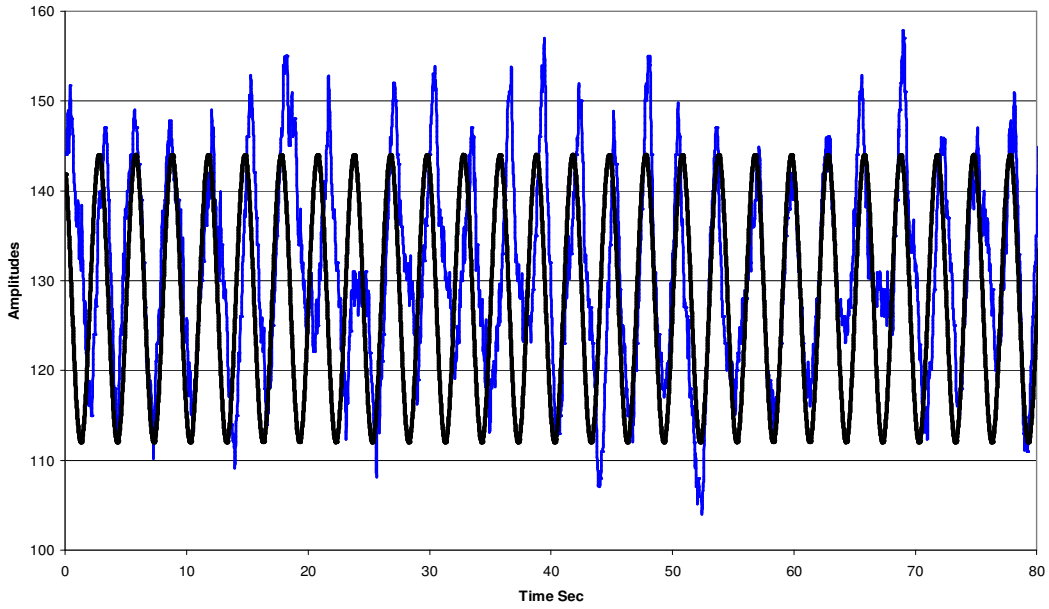

Fig. 31: Video-trained breathing trace (blue) for subject B & the training pattern (black)

For clarity we have limited the time axis to 80 seconds, but the pattern persists beyond this (see Figure 32). The subject is seen to match the peaks and troughs of the training signal (period and phase) very well, while the amplitude (depth of breathing) is relatively constant.

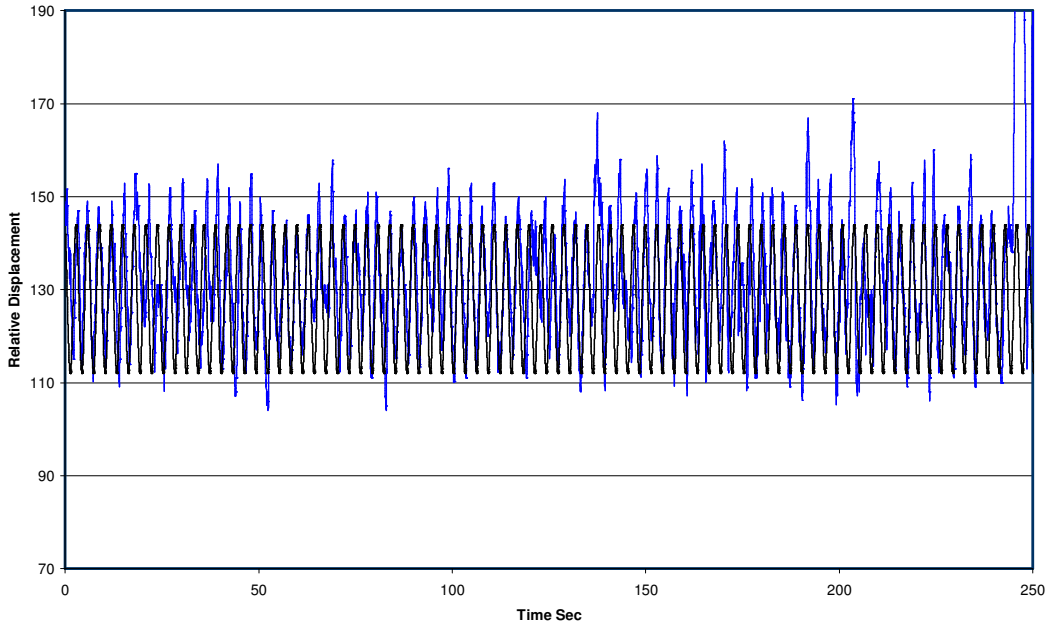

Fig. 32: Video-trained breathing trace (blue) for subject B & training pattern (black) for the whole measurement period.

Consistency is maintained throughout.

6.3.3 BREATHING WITH IN/OUT AUDIO PROMPTING – SIMPLE COMPARISON

Figure 33 shows the same subject (B) breathing under audio prompting (the researcher addressing the subject with in/out commands, but without the subject seeing either his/her own breathing signal or a guide signal). Here we are able to see the effect of the delayed feedback, as the researcher is responding to the position of the subject's trace relative to the guide signal and attempting to cause the subject to regulate his/her breathing by matching it to the 'ideal'. In comparison to Figures 27 and 30, it is evident that the average stability of the subject's breathing (amplitude, period and phase) varies less in the case of the video feedback session than for the audio prompting session which, in turn, is considered to be far more stable than the Free-Breathing session. This pattern was generally repeated throughout the studies reported within this thesis, as will be demonstrated in the remainder of this chapter.

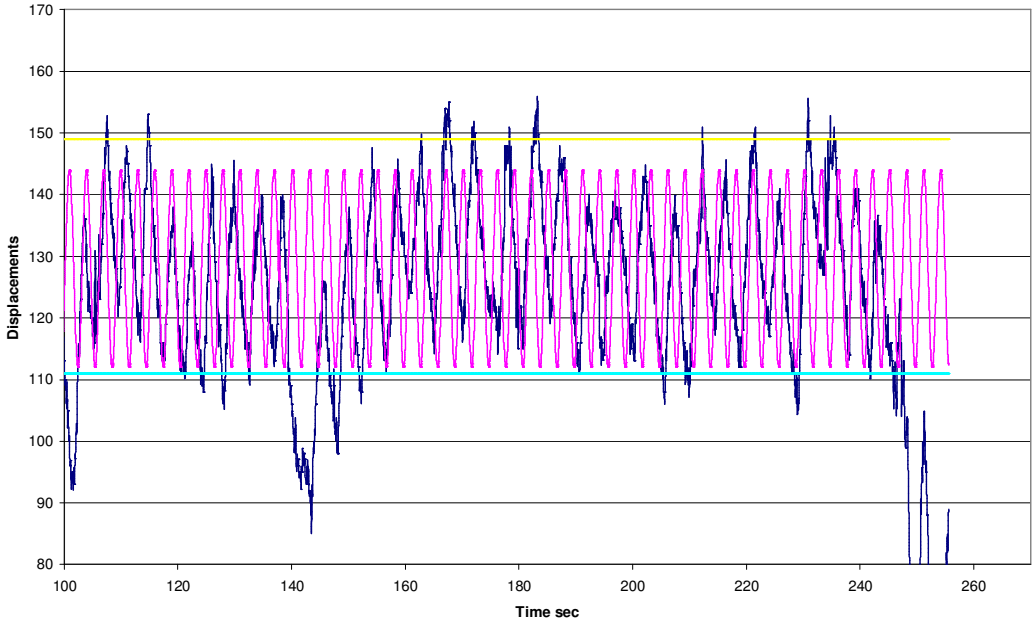

Fig. 33: Audio prompted breathing trace (blue) for subject B & the ideal pattern (pink) The researcher used in/out prompts to attempt to regulate the subject's breathing and to match it in amplitude and period to that of the ideal pattern. Shown here is a section from 100 to 260 seconds. Clearly, the match is less than good.

6.3.4 RANGE OF MOTION ANALYSIS

In this section, we are able to compare the variation in the inhalation and exhalation depth across all subjects for free-breathing, audio prompting and video feedback. Despite the fact that the breathing analysis system used in this work could be directly calibrated to provide an absolute measure of breathing depth (cm), this was not practical, as it would have required recalibration several times during a measurement. For example, the calibration would change if the belt were moved between measurements; instead, only relative measurements were taken, but these were normalised to the same baseline in order to allow a comparison between subjects.

Thus, if we denote the inhalation maxima by I^{max} and the exhalation maxima by E^{max}, then we define the mid-point of the tidal displacement for cycle i as:

$$\Delta_i = \frac{1}{2}\left(I_i^{\max} + E_i^{\max}\right) \qquad 1$$

We then define:

$$I_i^{\nu} = \frac{I_i^{\max}}{\Delta_i} \text{ and } E_i^{\nu} = \frac{E_i^{\max}}{\Delta_i} \qquad 2$$

to be the normalised maximum inhalation and normalised maximum exhalation for the i^{th} cycle. By doing this, we are effectively removing any necessity to calibrate the system, which ultimately allows all measurements to be simply compared. Notice that the normalised values are all dimensionless numbers.

In an obvious way, we define the averages over all cycles to be:

$$\left\langle I^{\max} \right\rangle = \frac{1}{N}\sum_i^N I_i^{\max} \text{ and } \left\langle E^{\max} \right\rangle = \frac{1}{N}\sum_i^N E_i^{\max} \qquad 3$$

Similarly, we define the second moment (variance) as:

$$S_{in}^2 = \frac{1}{N-1}\sum_i^N \left(I_i^{\nu} - \left\langle I^{\max} \right\rangle\right)^2 \text{ for inhalation and}$$

$$S_{ex}^2 = \frac{1}{N-1}\sum_i^N \left(E_i^{\nu} - \left\langle E^{\max} \right\rangle\right)^2 \text{ for exhalation} \qquad 4$$

The quantity $S_{(\bullet)}$ is the estimated standard deviation of the population for the variable x based on the values of x_i which were actually sampled. The estimated variance of $\langle x \rangle$ is given by $S^2_{\langle x \rangle} = \frac{S^2}{N}$, where x stands for either $\langle I^{\max} \rangle$ or $\langle E^{\max} \rangle$, depending on whether we are considering inhalation or exhalation respectively.

Notice that these expressions do not solely depend on any restriction on the distributions of x or $\langle x \rangle$, such as normality, beyond requiring the first moment (mean) and the second moment (variance) exist and are finite. However, it would have been difficult to test whether these last two conditions were true for the samples considered, and so we opted to test for normality of the data using the Kolmogorov-Smirnov test. As such, we therefore computed the means and standard variations, which are sufficient to fully characterising the underlying distributions, provided that trends have been removed (where appropriate) and the data passed the Kolmogorov-Smirnov test for normal distributions.

The range of motion (RoM) provides information on the maximum displacement of the abdomen and, thereby, under the overall assumption of correlation, on the maximum displacement of a lung tumour. We computed the average RoM and the standard deviation for all subjects for each of the different techniques: free-breathing, audio prompting and video feedback.

Figures 34 to 36 show the average RoM for all subjects as defined using Equation 3. Figures 37 to 39 show the corresponding standard deviation analysis using Equations 4. For all data, we used the null hypothesis of a normal distribution in the Kolmogorov-Smirnov test and accepted this for D values <0.08. All data — except for that corresponding to one subject — were accepted as approximately normal. Data for the apparently non-normal subject showed bi-modal behaviour; the subject had no defined respiratory illness specified at the time of testing, but later discussions revealed that the subject had only one lung; this data was therefore rejected from the current analysis.

When comparing Figures 34-36, it is clear that the RoM was generally largest in the case of AP, with more extreme inhalation/exhalation swings than for any other technique, while the range of motion was least for the video feedback technique, the excursions in inhalation/exhalation were slightly less than for FB and considerably less than for AP.

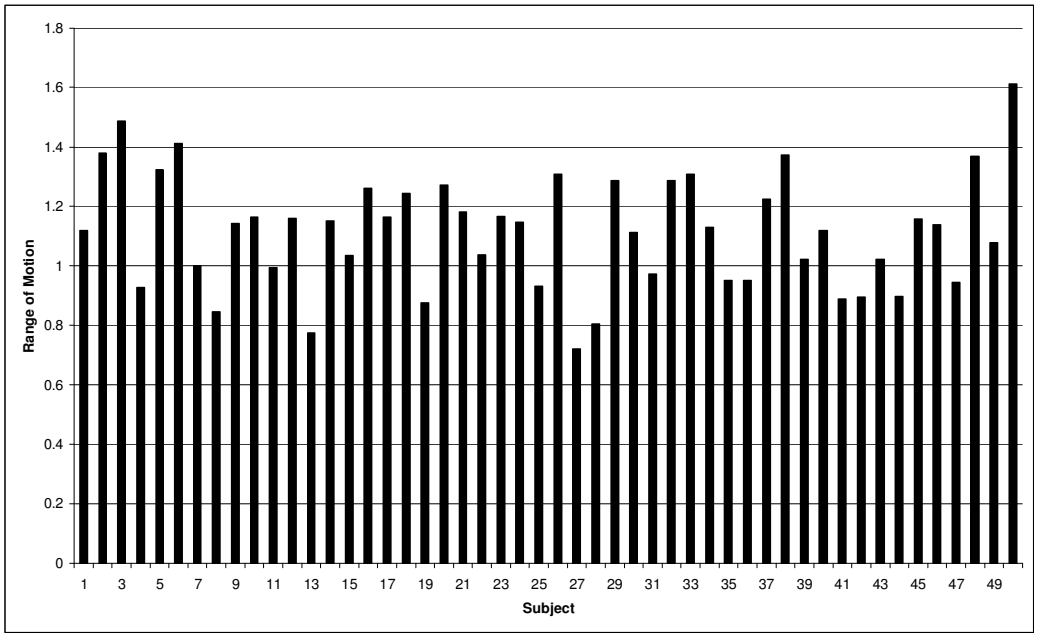

Fig. 34: Free breathing range of motion analysis for every subject
The RoM is defined by Equation 3 and represents the difference in the mean maximum inhalation and the mean maximum exhalation for a given subject.

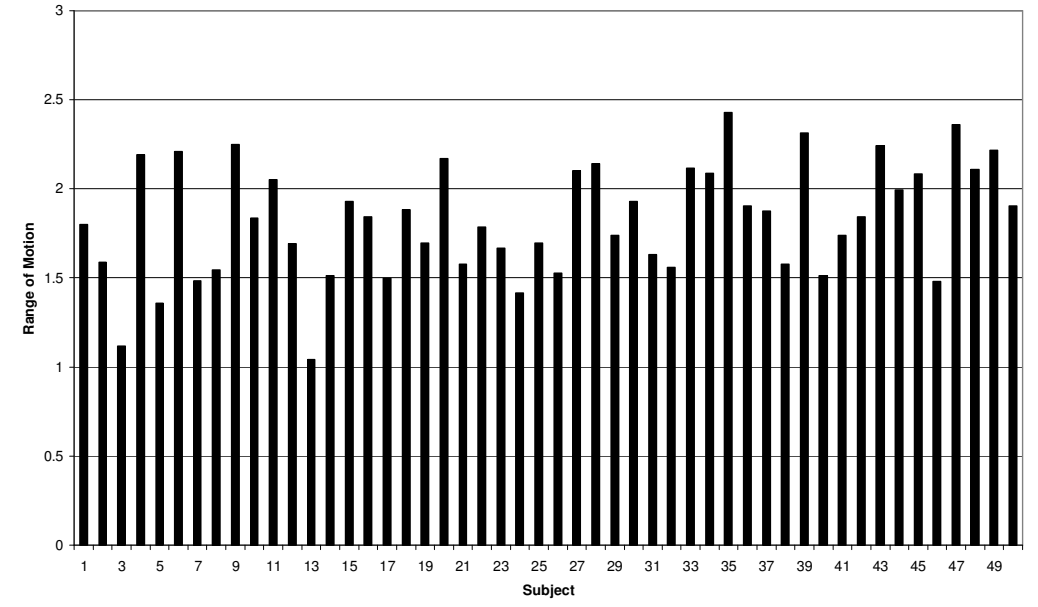

Fig. 35: Audio prompted breathing range of motion analysis for every subject
The RoM is defined by Equation 3 and represents the difference in the mean maximum inhalation and the mean maximum exhalation for a given subject.

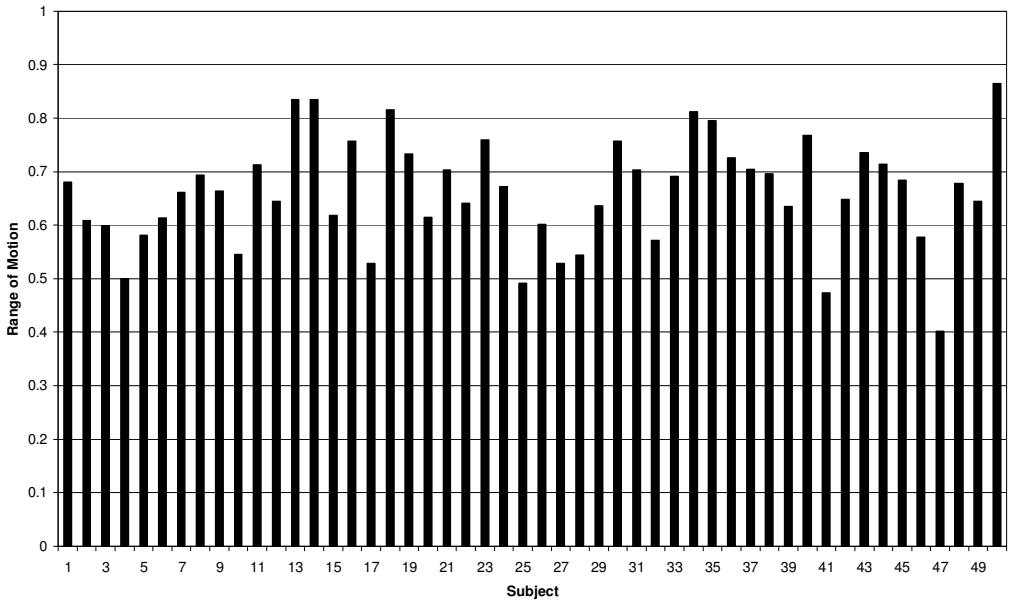

Fig. 36: Video feedback range of motion analysis for all subjects

The RoM is defined by Equation 3 and represents the difference in the mean maximum inhalation and the mean maximum exhalation for a given subject.

Figures 37-39 show the mean standard deviation (averaged over all cycles for a given subject) for each subject. It is clear from the comparison of these figures that VF reduced considerably the variation in breathing depth in comparison to free breathing, whilst AP increased the swings in inhalation and exhalation in comparison to free breathing.

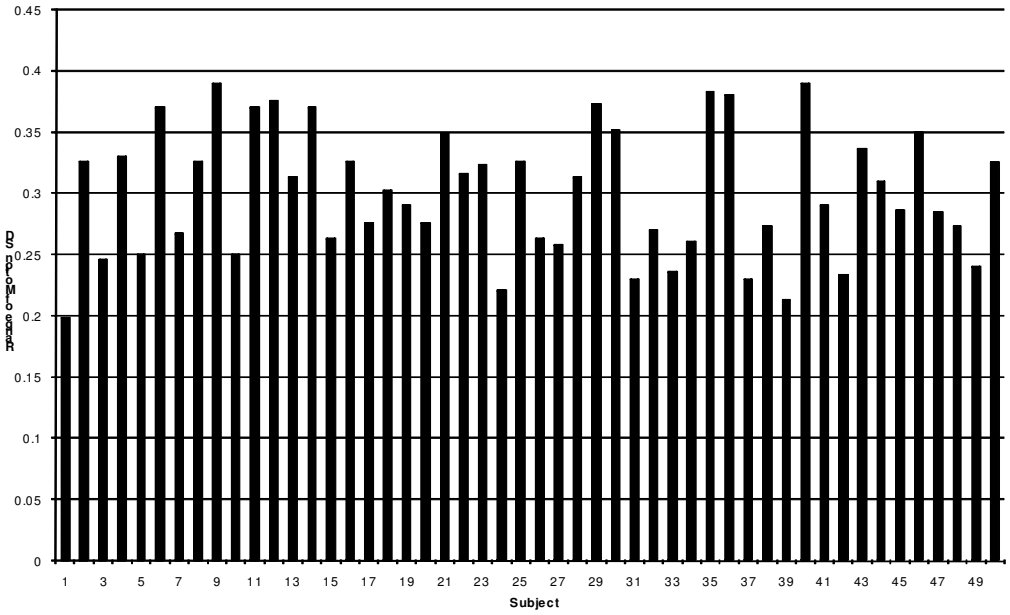

Fig. 37: Free-breathing standard deviation of range of motion analysis for every subject

The standard deviation is expressed in Equation 4 and represents the variation in the difference between maximum inhalation and maximum exhalation over all cycles for each subject.

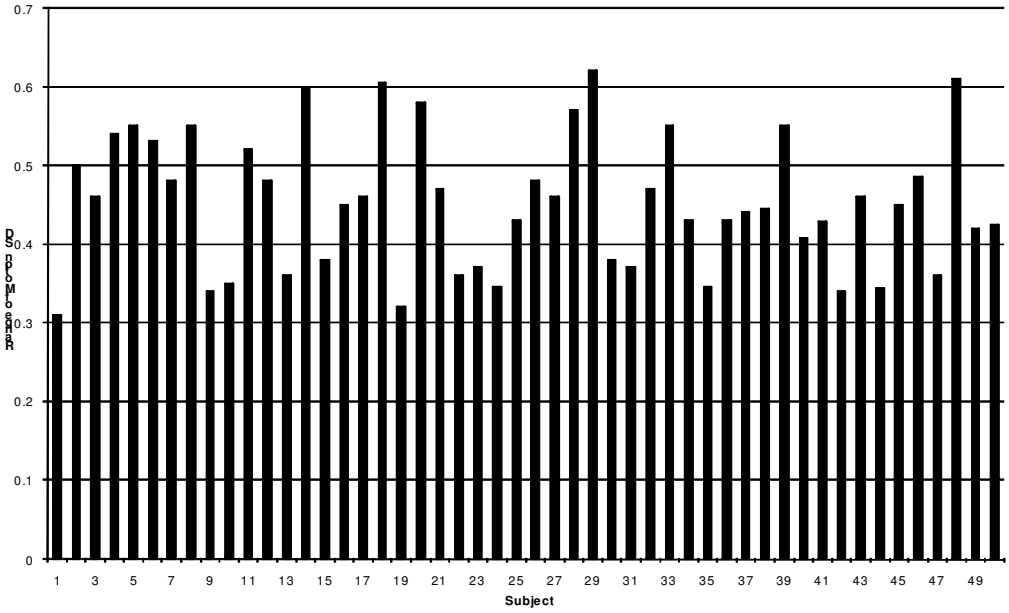

Fig. 38: Audio prompting standard deviation of range of motion analysis for all subjects

The standard deviation is expressed in Equation 4 and represents the variation in the difference between maximum inhalation and maximum exhalation over all cycles for each subject.

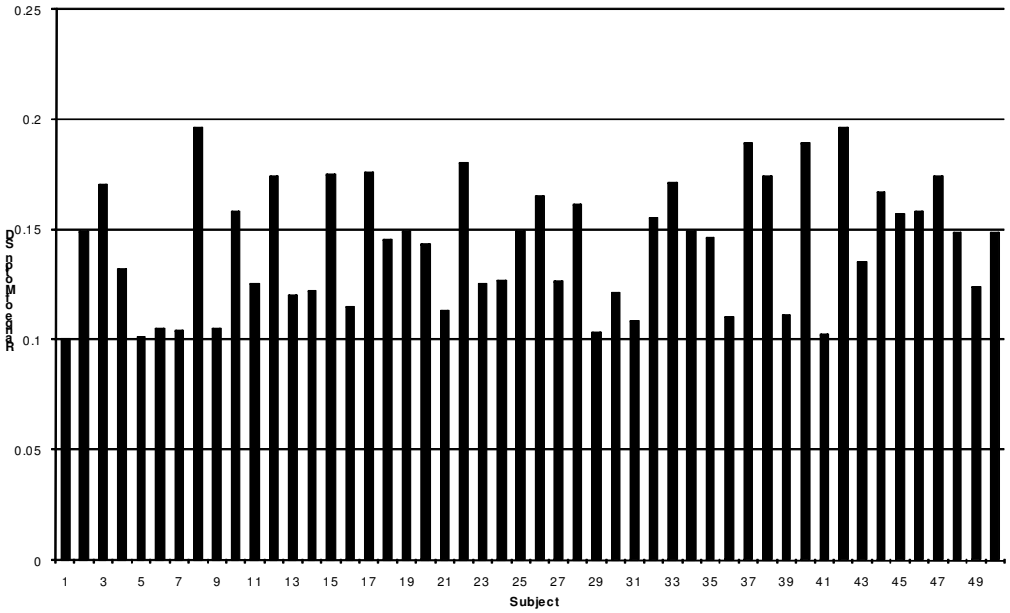

Fig. 39: Video feedback standard deviation of range of motion analysis for all subjects. The standard deviation is expressed in Equation 4 and represents the variation in the difference between maximum inhalation and maximum exhalation over all cycles for each subject.

Table 7 provides a summary of the statistical parameters (mean value $\langle x \rangle$), standard deviation (σ) and 68% confidence interval ($\langle x \rangle \pm \sigma$) for the range of motion, as described in Figures 34-39. What is now clear is that video feedback offers an improvement in the ability of subjects to regulate their breathing patterns (at the 68% level), ultimately allowing them to reduce the overall swing in the inhalation/exhalation pattern, and to further reduce the variation in these swings over the measured breathing time of 4 minuets. Furthermore, it is apparent that audio prompting disturbs the subjects' breathing (at the 68% level), causing more violent swings in inhalation and exhalation when compared to both Free-Breathing and video-feedback.

	Mean ($\langle x \rangle$)	**Standard deviation (σ)**	$\langle x \rangle \pm \sigma$
Free breathing	1.13	0.2	[0.93, 1.33]
Audio prompting	1.82	0.3	[1.52, 2.12]
Video-feedback	0.66	0.1	[0.56, 0.76]

Table 7: Summary of distribution statistics for each technique, with 68% confidence interval (column 4)

6.3.5 PHASE DRIFT CONTROL ANALYSIS

In this section we will investigate how well the subjects are able to control the phase of their breathing throughout the 4-minute measurement period: If the breathing phase changes in relation to the ideal waveform, the position of the maximum inhalation or maximum exhalation will then occur at a later or earlier time than expected; if this occurs during treatment, the tumour will be out of position and the dose distribution will be correspondingly wrong. Figure 40 is a graphical illustration of this; notice that, although the period and amplitude of the ideal waveform and the subject waveform are identical, the peaks and troughs occur at different times. If the treatment machine is being switched on at the time when the ideal signal is at a minimum (maximum exhalation), then due to the fact that there is a phase difference, the subject has gone beyond the maximum exhalation point and started to inhale, and so the tumour will not be in the expected position.

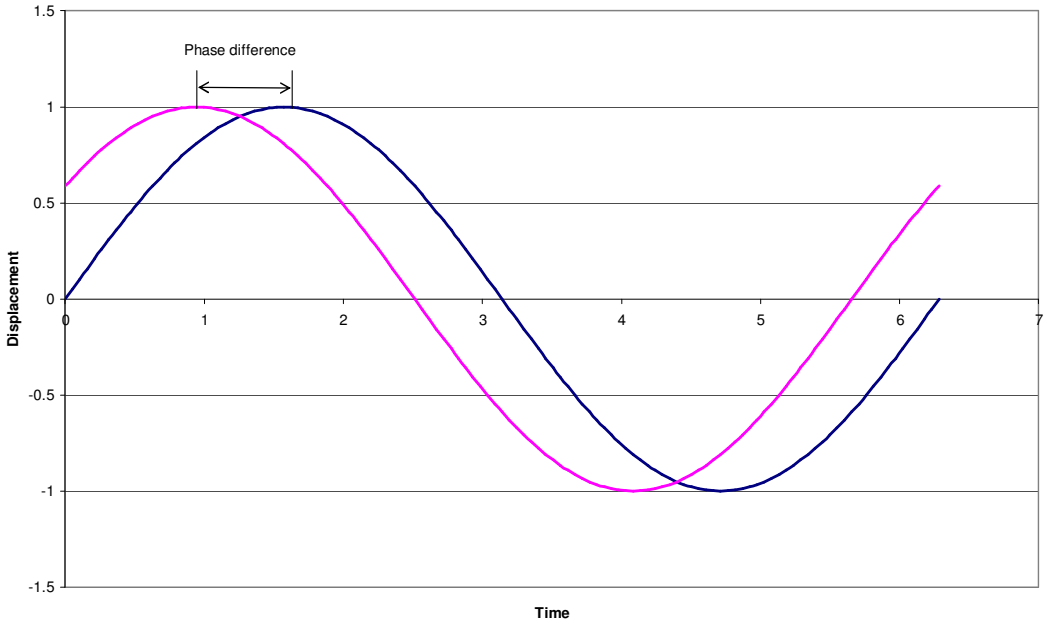

Fig 40: The concept and implication of differing phases.

The blue curve represents an ideal (expected) breathing pattern, whilst the pink curve shows a subject breathing slightly out of phase — i.e. peaks (and troughs) of the two curves occur at different times. Both curves have the same amplitude and period (distance between peaks). Clearly the trough (peak) of the ideal curve occurs after that of the subject, so that a beam switched on at this point will not have the subject at the maximum exhalation (inhalation) point.

For every subject, the position of every maximum inhalation and every maximum exhalation was determined for each 4-minute measurement period. This was done for all techniques: FB, AP and VF. For AP and VF, these positions (in time) were compared with the associated ideal curve which the subject was attempting to replicate; this was not applicable in the case of FB where the subject was simply Free-Breathing with no ideal curve. To the knowledge of the author, this is the first time such an analysis has been attempted.

Figure 41 shows a typical phase analysis for a subject during audio prompting. Figure 42 shows the corresponding plot for video feedback.

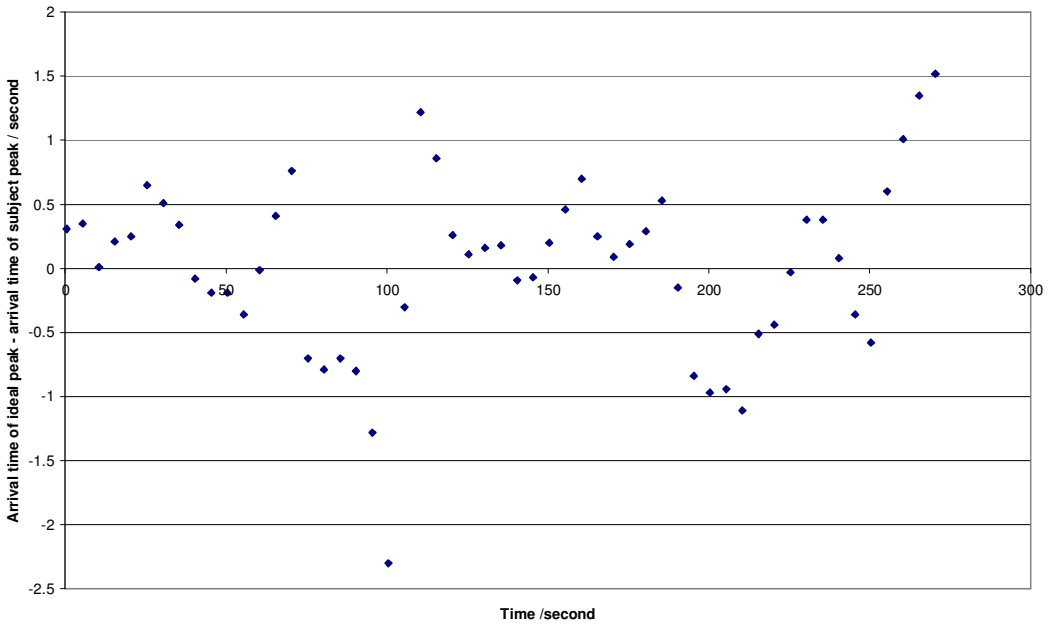

Fig 41: Difference in peak arrival-time between ideal waveform and subject's measured breathing pattern under audio prompting (Subject 2)

The vertical axis represents this difference; clearly there is a significant degree of variation in arrival time compared with the corresponding VF plot shown in Fig 42.

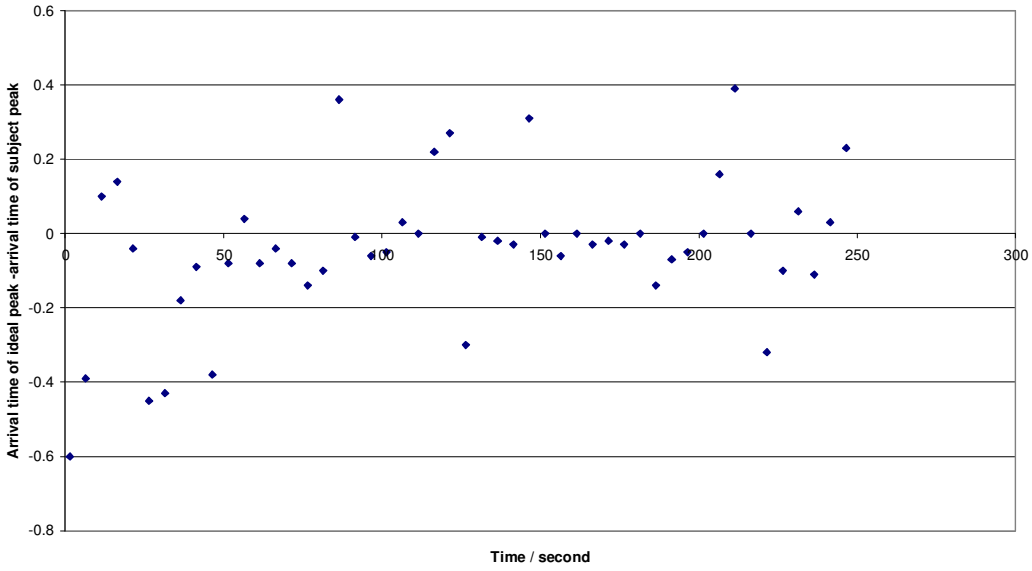

Fig 42: Difference in peak arrival time between ideal waveform and subject's measured breathing pattern under video feedback (Subject 2)

The vertical axis represents this difference; clearly, the degree of variation in arrival time is reduced compared to the corresponding AP plot shown in Figure 41.

Figure 43 shows a plot of the average time-of-arrival difference (averaged across all cycles) for each subject under the AP technique. The range of arrival time differences was approximately -2.2 seconds to +1.5 seconds; comparing this to the average period over all subjects and all cycles of approximately 4 seconds, we are able to determine that this corresponds to a large phase shift. The mean value of the time difference was approximately +0.6 seconds, with no indication of significant drift over the measurement period.

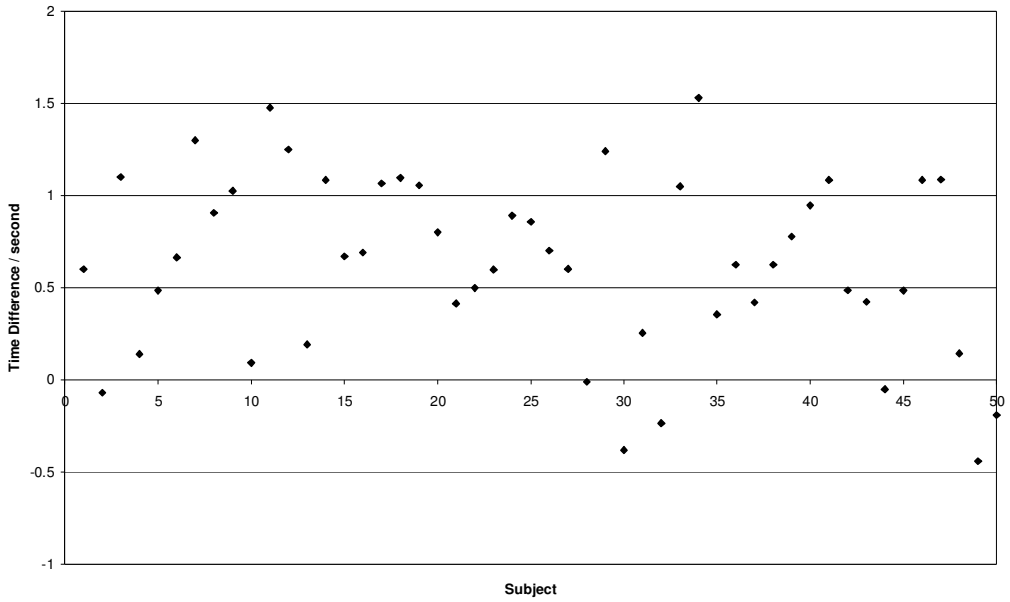

Fig 43: Difference in arrival time (averaged over cycles) between ideal waveform and subject's measured breathing pattern under audio prompting.

The ideal waveform for each subject is derived from the FB analysis prior to the AP measurement.

In comparison, Figure 44 shows the results for the VF technique. It can be immediately seen in this instance that the control of the breathing phase over all subjects was much improved when compared to AP breathing. The figures in this case ranged from approximately -0.25 seconds to +0.1 seconds, with the mean value being approximately -0.07 seconds, and there being no indication of drift over the measurement period.

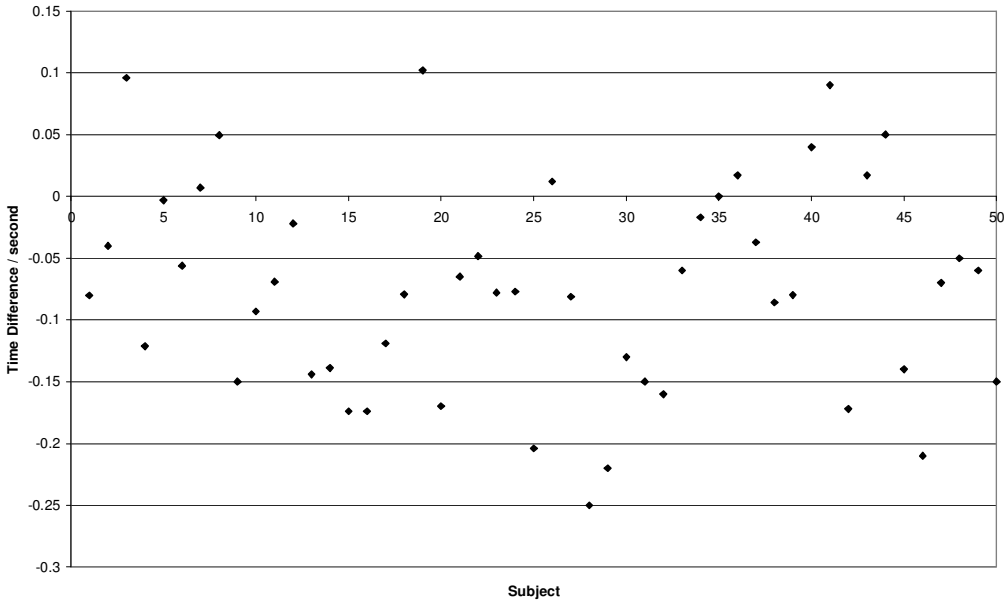

Fig 44: Difference in arrival time (averaged over cycles) between ideal waveform and subject's measured breathing pattern under video feedback

The ideal waveform for each subject is derived from the FB analysis prior to the VF measurement.

Table 8 summarises the statistical data. Again, as the data are approximately normal, the mean and standard deviation are sufficient to characterising the distributions.

	Mean ($\langle x \rangle$)	**Standard deviation (σ)**	$\langle x \rangle \pm \sigma$
AP	0.647	0.474	[+0.173, +1.12]
VF	-0.066	0.085	[-0.092, +0.019]

Table 8: Summary of means and standard deviations for mean difference in arrival times of peaks/troughs for each technique, with 68% confidence interval (column 4)

Table 8 shows that the VF procedure provides a much tighter control over the breathing phase than the AP technique does, with an SD of 0.09 for VF compared to 0.47 for AP. It can also be seen that, for VF, on average, the subjects' breathing showed little phase difference from the ideal wave form, while there was nevertheless a large phase difference in the case of AP: The mean differences were

0.65 seconds and -0.1 seconds for AP and VF respectively; the means come from different distributions and is significant at the 68% level with $p \leq 0.001$ from a t-test (in fact, it was also highly significant at the 99.98% level). Thus, we conclude that the difference in means is highly significant and VF provides a far better approach to regulating the phase than does AP.

6.3.6 PHASE-SHIFTING IN FREE BREATHING

It is instructive to consider how a subject's Free-Breathing changed over the course of a 4-minute measurement period; this was done by making an estimate of the initial breathing period for each subject by averaging the inter-peak and inter-trough times (periods) over 30 seconds, beginning at 15 seconds after the start of the measurement (subject-by-subject). In other words, the FB measurement was made over 4 minutes and recorded; post-analysis was performed in order to establish the inter-peak/-trough times from a point 15 seconds after the recording started. This 'shakedown' time allowed the subject to establish regular breathing, and ultimately avoided any initial disturbances.

For a single subject, from the derived average period (averaged over 30 seconds), a simulated cycle was generated which assumed, as before, a simple sine wave of single period (equal to the derived average). This was then compared with the recorded breathing wave, assuming that both started at time t=15 seconds and were initially in phase. From this, an analysis identical to that above was performed, i.e. the average difference in arrival time (over all cycles starting from t=15 seconds) was computed, together with the standard deviation. This was then repeated for all subjects; this approach is similar to a rather crude auto-correlation analysis.

Figure 45 shows the average time of arrival difference for each subject based on the assumptions previously discussed. A sensitivity analysis of the mean period showed that shifting, reducing or increasing the settling time resulted in less than 4% change in the calculated period.

The sensitivity in respect of the assumption that the ideal cycle and the measured cycle started in phase was approximately 10%. These sensitivities have been included in the calculation of the standard deviation, assuming Gaussian statistics. Thus, the standard deviation in this case is calculated as:

$$\frac{1}{(\sigma^{*})^2} = \frac{1}{(\sigma)^2} + \frac{1}{(\sigma^{V})^2} \qquad 5$$

where σ represents the purely statistical standard deviation from the random fluctuations in the data and (σ^{V}) represents the component of variation derived from perturbing the initial phase and assumed period. In fact, these were also combined assuming Gaussian statistics and no correlation, thus:

$$\frac{1}{(\sigma^{V})^2} = \frac{1}{(\sigma^{PS})^2} + \frac{1}{(\sigma^{TS})^2} \qquad 6$$

where $(\sigma^{PS})^2$ is the variance associated with shifting the phase and $(\sigma^{TS})^2$ is the variance associated with shifting the period.

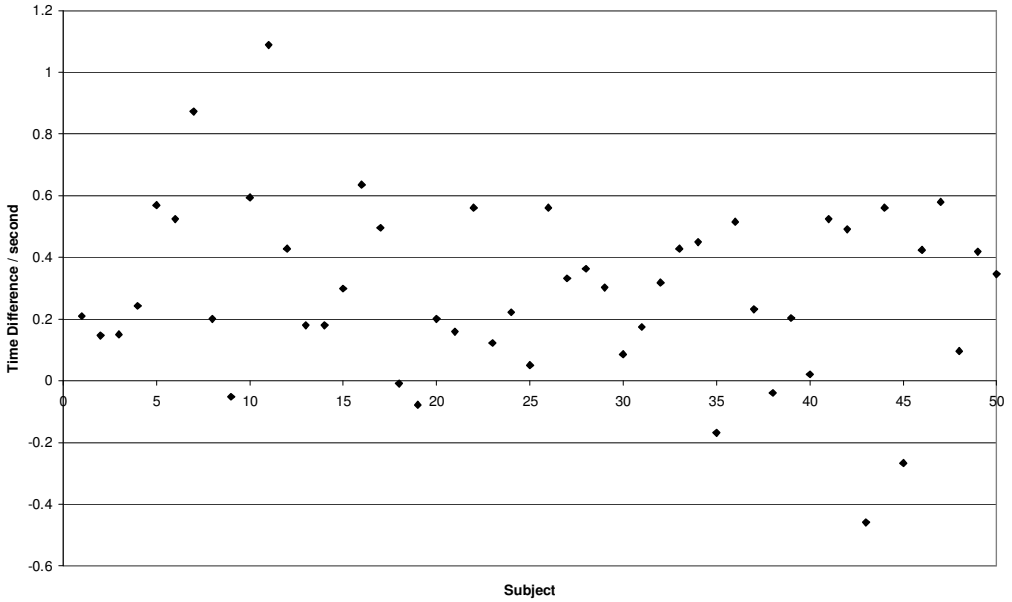

Fig 45: Difference in arrival time (averaged over cycles) between a waveform (based on the first 30-second average period derived from subject's free breathing) and subject's free breathing pattern

The graph suggests that FB is slightly worse than VF in controlling the phase (cf Figure 44) but apparently better than AP (cf Figure 43).

The mean difference in arrival time and associated standard deviation are shown in Table 9, together with the 68% confidence interval. Again, a simple t-test indicates that the means for FB and VF did not come from the same distribution ($p \leq 0.001$). Thus we conclude that VF provides a better phase control than FB.

	Mean ($\langle x \rangle$)	Standard deviation (σ*)	$\langle x \rangle \pm \sigma$*
FB	0.277	0.278	[-0.001, 0.555]

Table 9: Statistical parameters for phase control of free breathing

In all of the above we have used the usual definition for the t-statistic:

$$t = \frac{\langle x_1 \rangle - \langle x_2 \rangle}{k} \text{ ; with } k = \sqrt{\left(\frac{s_1^2}{N_1} + \frac{s_2^2}{N_2} \right)} \qquad 7$$

where $s_m \approx \sigma_m$ for manoeuvre *m* and N_m is the population size for manoeuvre *m*. The test was performed as a two-tailed test with one degree of freedom in each case.

6.3.7 FIGURE OF MERIT

Just as it was pointed out above that basing a gating system on the amplitude of breathing alone is not wise, it can also be argued that while, theoretically, it is far better to gate on phase, it is probably better still to do so, if possible, on both amplitude and phase. In this vein, a simple Figure of Merit (FoM) is here proposed in order to attempt to establish whether one technique is better than another; this FoM takes into consideration the ability to control both phase and amplitude, and is given by:

$$FoM = \left(\frac{1}{s} \frac{1}{|\langle \Delta t \rangle|} \right)_P^{\frac{1}{2}} \left(\frac{1}{s} \frac{1}{|\langle \Delta x \rangle|} \right)_A^{\frac{1}{2}} = \left(\frac{1}{s_A s_P |\langle \Delta x_A \rangle \langle \Delta t_P \rangle|} \right)^{\frac{1}{4}} \qquad 8$$

where the *A* and *P* represent amplitude and phase respectively, $\langle \Delta x \rangle$ is the mean difference between the desired amplitude and the subject's measured amplitude over all measurement cycles and all subjects, and $\langle \Delta t_p \rangle$ is the mean difference between the times of arrival of the desired breathing and the measured breathing over all cycles and all subjects. Notice that a modulus has been included in the denominator, as the difference in amplitude can be negative or positive, as defined earlier, but in reality, this is of no consequence here. Furthermore, for the FoM to be a real number,

the denominator of the final expression must be positive, so it is always true that FoM ≥ 0. Thus, as the standard deviation decreases, and so the FoM increases; similarly, as the amplitude increases further from the desired amplitude, so the FoM decreases.

The technique with the greatest FoM is thus best at controlling the overall breathing cycle, considering both the phase and amplitude together. For the techniques considered in this work, the composite FoMs are derived from Tables 7 to 9 and Equation 8, and summarised in Table 10. It should be noted that the FoM, as proposed here, is approximately linear with the combined variation in standard deviations and means, so that a doubling of the FoM implies, in some way, that the technique is twice as good.

Technique	FoM
FB	2.8 (3)
AP	1.6 (2)
VF	7.3 (7)

Table 10: Calculated values of the figure of merit
(as defined by Equation 8 and using the data presented in Tables 7, 8 and 9. The higher the FoM the better is the technique. The table shows that VF is better at controlling the breathing cycle than either FB or AP and that AP performs the worst)

Thus, we see that an advantage is gained in terms of using VF against either FB or AP, and that AP is the worst technique to use when attempting to control and regulate both the phase and amplitude of a subject's breathing.

6.4 SUMMARY

This chapter has reported the use of the breathing monitor whose design was discussed in previous chapters. The effects of different techniques designed to regulate a patient's breathing were also investigated in a population of some 50 subjects, each of whom were randomly chosen and ranging in age from 18 to 72 years. Three regulation techniques were investigated: Free-Breathing, visual feedback 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 — is not wise (see Figures 25-29). Figures 30-32 show how the FB for a given subject was modified by applying VF, while Figure 33 shows how using AP can have a worsening affect on the breathing pattern of a subject by producing exaggerated amplitude swings.

A range-of-motion analysis was performed for each technique and for every subject. Figures 34-39 show graphically how the mean RoM and its associated standard variation were affected by the different techniques. Table 7 summarises the results and suggests that VF allowed subjects to better control their breathing in terms of both the mean RoM and of the standard deviation. Although this is clearly significant from the table (the 68% confidence interval), a t-test was performed which rejected the null hypothesis that the means came from the same distribution (VF v AP, VF v FB and AP v FB); thus it was concluded that, in terms or RoM, the order of preference is VF first, followed by FB and by AP last.

The effects of the different techniques on the phase control of a subject's breathing were also analysed for AP and VF. Figures 41-44 demonstrate this graphically and Table 7 summarises the results. The order of preference (VF first, followed by AP) was found to be statistically significant.

An analysis of phase control, akin to a crude autocorrelation analysis, was conducted for the case of FB. A sine wave was derived from a 30-second average (period and amplitude) of the FB trace. The peak arrival times of the FB trace were then compared with the expected arrival times of the stationary simulation wave. A sensitivity study was conducted in order to investigate thoroughly how the arrival times varied as the assumed period and assumed epoch were varied, and this was built into the analysis of variance for the overall results. Figure 45 and Table 9 summarise these results.

In Figure 45, the time difference of each cycle arrived for each subject is shown; when we compared the real time of each FB cycle arriving with the ideal free-breathing that had been established and built into the model, the model then took account of the average of the thirty-second period and estimated the rest for the total measuring time (4 minutes); the mean and standard variation were then compared with those for AP and VF, allowing the conclusion that in terms of phase control, the statistically significant preference was VF, followed by FB and finally AP.

Finally, a figure of merit was proposed (Equation 8) which took into account the effects of phase and amplitude to rank the different techniques. Table 10 summarises the FoM for each of these, and allows us to conclude that VF is by far the most effective technique for regulating a patient's breathing in terms of both amplitude and phase, while the worst method is considered to be AP, which is, unfortunately, currently the most popular approach. If some form of breathing monitor and VF system is not available, then the best approach would be to leave the patient to breathe freely.

CHAPTER 7: CONCLUDING COMMENTS

This work has analysed the effectiveness of different breath control methods in establishing a regular respiratory pattern appropriate for subjects undergoing radiotherapy on mobile lung tumours. The aim of such breath control techniques is to increase the fidelity of the treatment; this is achieved through two complimentary effects:

- By reducing the frequency and extent to which the tumour moves out of the treatment beam; and
- By reducing the frequency and extent to which healthy tissue and organs at risk move into the treatment beam.

Although this work was based on a relatively small subject population size, it has nevertheless conclusively demonstrated that an approach based on visual feedback offers the greatest degree of control. It has also demonstrated that audio prompting (the method most commonly used today) is by far the least effective approach of the three considered.

Whilst 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 tumour out of the beam further than would occur in free-breathing and thereby destroying the desired uniform dose distribution over the tumour, reducing both the tumour dose and the TCP. Concomitantly, more healthy tissue would be driven into the beam, distorting the desired isodose distribution, increasing the non-tumour dose and thus the NTCP. Together, these would presumably reduce the efficacy of the treatment and the patient's survival probability.

In the above paragraph, I have used the term 'presumably', as there is currently no firm evidence which conclusively demonstrates the effects that breathing-induced tumour motion has on the dose-volume histogram and three-dimensional dose distribution for a prescribed treatment. However, a recent study by Britton (2009) investigated the effects of respiratory motion during the course of treatment of NSCLC internal anatomy, normal tissues and dose distributions, using weekly four-dimensional computed tomography scans. The study concluded that there was a small dosimetric variation (mean and SD differences between the prescribed dose to PTV and the internal target volume using 4-DCT were -11.9% ± 12.1% and -2.5% ± 3.9%, correspondingly, and -2.3% ± 4.1 for the ITV). The study recommended the

use of image-guided treatment for any locally advanced lung cancer patients for the duration of treatment.

Furthermore, the exact correlation between the tumour 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 tumour (as in the now routine use of IMRT), the greater the risk of the tumour partially moving out of the field during treatment, ultimately leading to underdosing and an inhomogeneous dose distribution; the consequence will be an increase in the probability of incomplete tumour kill and hence of tumour cell repopulation.

Video feedback showed a clear improvement in the phase control of the subject's breathing (as did audio prompting) and in amplitude control (unlike audio prompting). Together, such control results in a much closer match of the subject's breathing cycle to the desired periodic cycle. Using such a method allows for an accurate approach to administering gated radiotherapy, as it makes possible a more precise calculation of the correct times at which the beam can be switched on (when the tumour is in the correct place) and off (when the tumour has been forced out of position by the patient's breathing). Closely tuning the patient's breathing to the desired regular waveform will maximise the duty cycle, which is the ratio between the beam-on time (treating) and beam-off time (non-treating).

In the case of audio prompting, the duty cycle would decrease as the machine would switch off during the frequent amplitude excursions, and so the overall treatment time would increase; as a result, the patient might then be less tolerant of the treatment, as a consequence of having to remain lying for longer in what may be a slightly uncomfortable position. Furthermore, it would potentially reduce the throughput of patients within the hospital, and thereby increase the cost of treatment.

In this study, it was not possible to investigate the possibility of video training which involves using the video feedback system prior to treatment in order to train patients to breathe regularly. However, even if this method did work, it would significantly increase the resources needed for a given treatment, which goes rather against the spirit of quality control, as there would be no evidence of correct machine synchronisation during the treatment.

All subjects studied during this work tolerated the monitoring belt and feedback method well; the system was quick to position on the subject and is inexpensive. It therefore seems reasonable to draw the conclusion that there would be little or no advantage to using video training in most cases.

The project was mostly carried out in order to establish a way of helping patients with NSCLC to produce stable breathing patterns, which would then eliminate the extra advanced machines and radiation dose that might otherwise be required. During the time of this project, other devices — such as Stardust, as was explained in Chapter Four — were investigated for use; however, it was found that such methods required extra hardware and accessories to be employed during the measurement. Furthermore, the project was time- and budget-limited in such a way that we were unable to include a higher number of subjects or otherwise to spend time interviewing and collecting surveys. After a series of searching and reviewing the literature in this field, a device was built to our specifications and then tested in order to determine whether we could help to produce a stable breathing pattern.

Our results are similar to those obtained by Kini *et al*. (2003) and Keall *et al*. (2006), who found that patient coaching — using audio prompting or video feedback — would improve the breathing patterns and ultimately increase the reproducibility. However, these earlier studies were carried out with the objective of investigating the use of this coaching during respiratory gating radiotherapy, with the aim of improving the outcome of treatment, whereas the present study aimed to improve the breathing pattern first, so that it could then be incorporated in the radiation therapy treatment.

7.1. STUDY LIMITATIONS

During the project some limitations were experienced, the main ones being:

a) The timeframe — the project had to be completed within 3 years;
b) Cost — the project was budget-limited;
c) Device building and testing;
d) No access to a real treatment unit;
e) Subject recruitment and time spent with everyone.

Some more detailed limitations of the project were as follows:

- It took a full hour to measure each subject, which included explaining the procedure, setting up and measuring. In the early part of the study, we began each session with FB, then randomly progressed onto either audio-prompting measurement or video prompting feedback. At this point, we established that when the video was done before the audio, the belt had always moved and was never in the initial position. This was due to the fact that during VF, the subject had to move the monitor according to his or her preference, which then gave us a reading which was different to the reading we expected from the ideal patterns. In addition, the time of measurement would be longer, since the belt had to be restored to the correct position and the measurement started again from free-breathing. After a while, we decided to follow the order which had been adopted by Kini *et al.*, 2003, in which the free-breathing method is implemented first, followed by audio-prompting and finally video feedback.
- It was noted that during our measurements, six subjects did better with audio prompting and felt more satisfied when following the voice commands of 'breathe in' and 'breathe out', then following their own breathing patterns. However, investigating the difference between visual learners and audio learners is outside the scope of this thesis.
- No data was collected on how this measurement needed to improve and what the subjects' recommendations were. The aim at the beginning of the study was to interview each participant and ask them after the measurement to complete a questionnaire form concerning how the measurement could be improved. However, given the time restrictions and the subjects' desire to leave the measurement room, this stage was omitted.

7.2 FURTHER WORK AND RECOMMENDATIONS

There is still much further work to be completed in order for the device to be proven for clinical use. First, there is a need for the device to be made as rugged and durable as possible so that it would not be affected if accidently dropped; second, the sensor needs to be changed in such a way that it could be placed in the middle of the chest instead of at the left side of the subject; third, the device and the sensor should be wireless so that the patient would be able to use it in the treatment room while the

laptop or PC would be in the console area; fourth, the belt needs to be made of a suitable cloth material which would not irritate the patient's skin and the buckle needs to be positioned at the front; fifth, the belt needs to have a proper marker so that when the patient changes his position, it can be put back to a default position; finally, suitable software needs to be built in order to analyse the data thoroughly and effectively instead of having to use Microsoft Excel, which is time-consuming, as it can take up to a full day to complete each subject's analysis.

It is the researcher's belief that if all of these recommendations were to be implemented, the device would then need to be examined on patients with NSCLC after having approval from the ethics Committee or Trust.

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APPENDIX A

APPENDIX ON TESTING THE DEVICE

A1. *Displacement-time tests.*

This test was performed in order to check that the monitor correctly followed a well calibrated sinusoidal motion – the period of which was similar to that expected for the breathing rate of a subject. The belt was tensioned over two pegs – one of which could be moved towards and away from the other (thereby reducing and increasing the tension in the belt). The movable peg was driven with a stepper motor controlled through a computer. The computer was programmed to activate the stepper motor so as to produce a in a series of sinusoidal displacements of the peg and the output of the belt monitored using its custom software. Figure 1 shows the recorded motion of the belt for a period of 5 seconds whilst figure 2 shows the recorded motion with an oscillatory period of 12 seconds. In each figure, the solid line represents the actual programmed motion of the peg whilst the solid dots are the recorded motion using the belt. For both figures, the recorded displacement is an average of 10 separate measurements. It is clear that the monitor is closely following the motion of the pegs with virtually no difference in the actual time displacement trace (amplitude and phase are consistent to better than 2 %). S mall discrepancy is seen where there is a rapid change – ie close to the maxima and minima of each cycle – but again this is less than 2%.

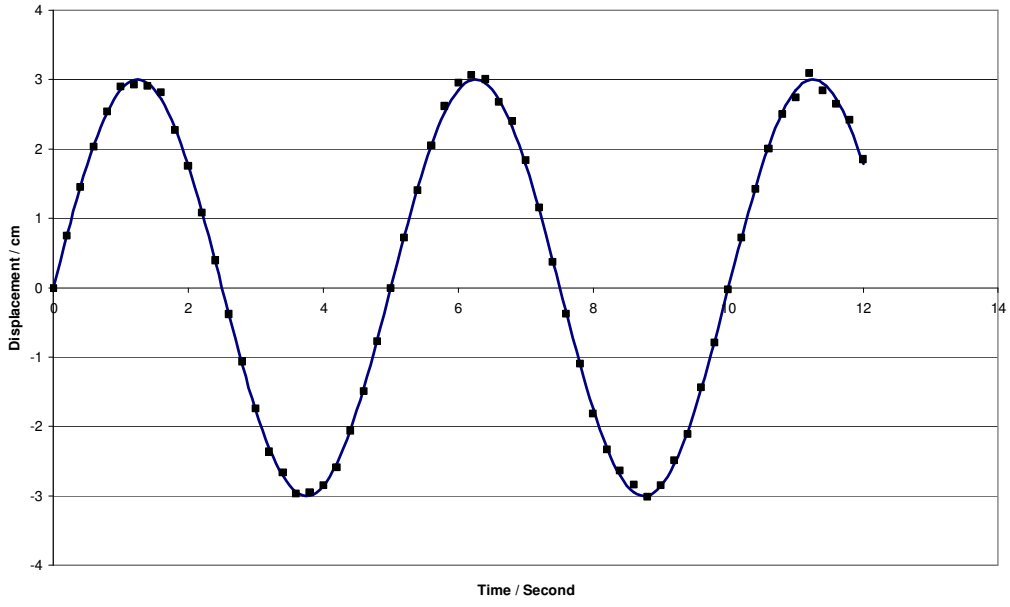


Figure 1: Displacement time trace for a cycle with 5 second period. The solid line is the actual mechanical oscillations whilst the solid symbols are the time displacement values measured using the monitor.

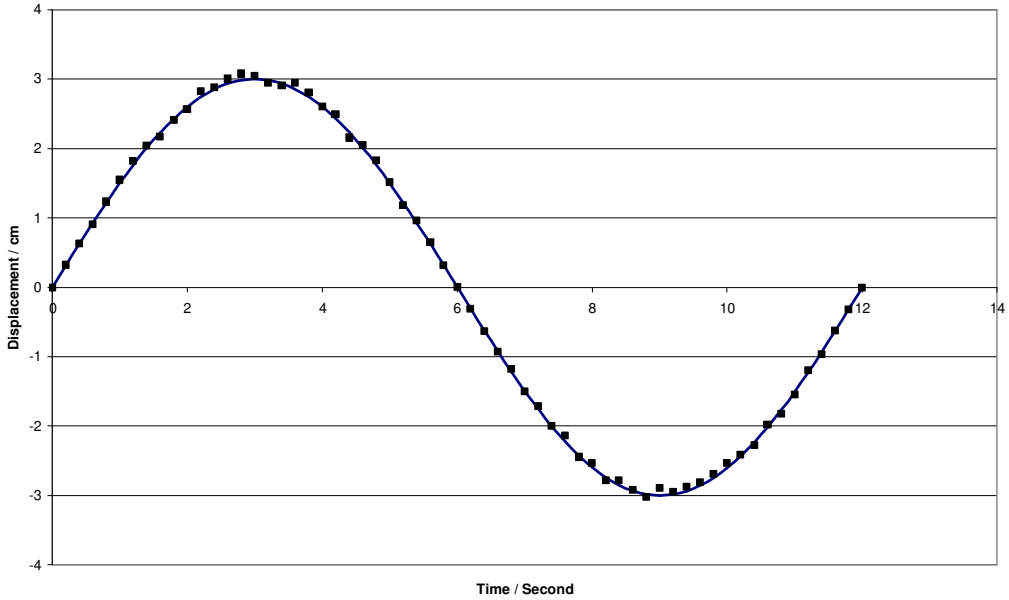


Figure 2: Displacement time trace for a cycle with 12 second period. The solid line is the actual mechanical oscillations whilst the solid symbols are the time displacement values measured using the monitor.

A2. Stability measurements.

A series of tests were performed to ensure that the monitor remained stable for a period of time – longer than the 1 hour expected for the subject tests. In this case, the belt was tensioned and the pegs remained stationary for approximately 2 hours. Output readings were taken every 1 min. Clearly these readings should be identical apart from system noise but there was a possibility that changes in environmental conditions eg temperature etc may affect the readings. For this reason, the belt and sensor were left close to an open window so that they saw any changes in local temp etc. Figure 3 shows the time trace of the output – in this case the average of five experiments. The variation is less than 1 % over the whole measurement time. Also shown on the graph is a trend line,. Ideally this should have zero slope – indicating no trend. The indicated slope is very small, amounting to a change in output of the device (over the 2 hours) far less than is statistically measurable – in other words there is no statistically significant output change over a 2 hour measurement period.

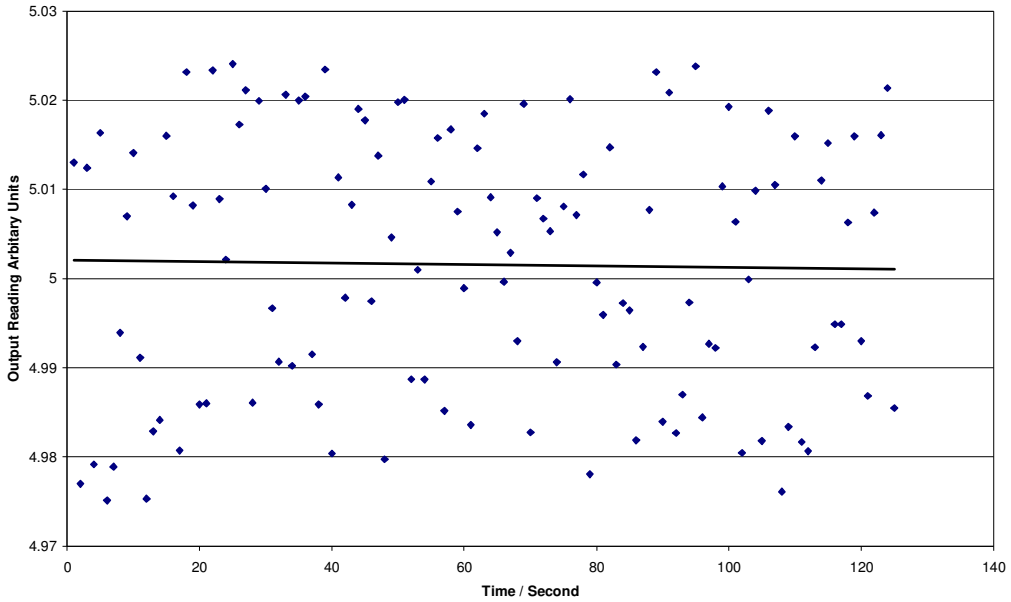


Figure 3. The stability of the output of the monitor is measured over a 2 hour period. The solid dots show the measured out put (for constant belt tension) every 1 min. The slightly sloping line is a curve fit to the data – this has zero as required.

A3 Summary

The above test clearly demonstrate that the sensor provides a signal that robustly follows the movement of the test bed – a sinusoidal oscillation with characteristics similar to that of normal human breathing (figures 1 and 2). Figure 3 demonstrates that the system is stable with respect to long term measurement (2 hours in this case) even when no attempt is made to isolate it from the changing environmental conditions.

APPENDIX B

Academic Development Unit

Northampton Square
London EC1V 0HB
[redacted]

Dr Robert Price
Department of Radiography
City University
Northampton Square
London
EC1V 0HB

16 January 2007

Dear Dr Price

Re: "Analysis of breathing patterns and development of technique to train subjects to breath in a regular and predictable manner; applications in radiotherapy practice"

I am writing to you to confirm that the research proposal detailed above has been granted formal approval from the City University Research Ethics Committee, following Chairs action.

Should you have any further queries relating to this matter then please do not hesitate to contact me. On behalf of the Research Ethics Committee I do hope that the project meets with success and many thanks for your patience.

Regards

[redacted]

Dr Naomi Hammond
Assistant Registrar (Research)
Secretary to Research Ethics Committee

[redacted]

APPENDIX C

INFORMED CONSENT FORM FOR PROJECT PARTICIPANTS

Project Title:

DEVELOPMENT OF A BREATHING MONITOR AND TRAINING SYSTEM, AND THE ANALYSIS OF METHODS OF TRAINING PATIENTS TO REGULATE THEIR BREATHING WHEN UNDERGOING RADIOTHERAPY OF LUNG CANCER

I agree to take part in the above City University research project. I have had the project explained to me and I have read the Explanatory Statement, which I may keep for my records. I understand that agreeing to take part means that I am willing to:

- participate in a breathing study for the length of approximately 45-60 minutes
- lie on a stretcher or on a clinical bed and have my breathing patterns recorded whilst following various instructions.

DATA PROTECTION

The data collected in this study will be held and processed to allow us to examine the best approach to creating a comfortable and stable breathing pattern in patients undergoing radiotherapy treatment of non small-cell lung cancer.

I understand that any information I provide is confidential and that no information that could lead to my identification will be stored or disclosed in any reports on the project or to any other party.

WITHDRAWAL FROM THE STUDY

I understand that my participation is voluntary, that I can choose not to participate in part or all of the project and that I can withdraw at any stage of the project without being penalised or disadvantaged in any way.

COMPLAINTS PROCEDURE

If at any time you have a complaint regarding the way in which the study has been conducted you may contact the secretary to the Ethics Committee, [redacted] or by letter at the following address:

Dr Roland Petchey

Chairman of the Senate Ethics Committee

City University, Northampton Square, London EC1V 0HB

Name: ..... (Please print)

Signature: ..... Date: .....

APPENDIX D

1. Please tick the following items which apply to you:

Sex: Male _____ Female _____

2. Do you have any health problems?

Yes_____ No _____

If yes please state what they are:

_____

3. Do you smoke?

Yes_____ No _____

4. Do you practise any kind of sport or exercise?

Yes_____ No _____

If yes, please state what:

_____

APPENDIX E

Form: EC1

City University London

Senate Research Ethics Committee

Application for Approval of Experiment and Investigation Involving Human Subjects

This form is to be used in conjunction with form EC2 and/or EC3. Please complete this form and return 13 copies with the completed forms to ~~Mr Alex Sandbrook, Academic Registry~~ Dr. Naomi Hammond, Deputy Academic Reg. Team.

No subject should be admitted to a trial before Senate Ethical Committee has issued its written approval. Written confirmation of Research Ethics Committee decision will be emailed to the principal investigator where possible within 48 hours of the Committee meeting.

Section A: Brief details of the Application

Title of project	*Analysis of breathing patterns and development of a technique to train subjects to breath in a regular and predictable manner; applications in radiotherapy practice*
Name of Principal Investigator(s):	Dr Robert A Price (Reader – Department of Radiography). [redacted] Huda I Al-Mohammed (PhD Researcher)
Email address:	[redacted]

1.A School(s) involved:

Department of Radiography
City University

41-53 Goswell Road

Clerkenwell

London

EC1V 7EH

1

2A Names and status of any other members of staff involved:

Dr. Robert A Price
Principal Supervisor.
Department of radiography
City University
Northampton Square
London
EC1V 0HB

3A Will students be involved in carrying out the investigation? If so please indicate what programme of study the student(s) is completing.

PhD

4A Will any part of the investigation be carried out under the auspices of an outside organisation, e.g. a teaching hospital? Is so, please give details and address of organisation.

No

5A Name and status of external co-investigators:

None

6A Have any external authorities or other University considered or other University Committees, other than City University? If so please give the contact details of the Secretary for the relevant authority/committee.

No

Section B: Details of Funding

The Royal Embassy of Saudi Arabia .

1B Please provide details of the source of financial support (if any) for proposed investigation:

Royal Embassy of Saudi Arabia, London

Saudi Cultural bureau
Education Section
29 Belgrave Square
London
SW1X 8QB

2B Total amount of funding being sought:

Student funding already obtained. Student has been regestered at City U for 12months.

3B Has funding been confirmed:

Yes

4B .If a letter indicating ethical approval has been granted please give contact details of person at funding body:

Not applicable

Section C: Abstract of Project (Continue on a separate sheet if necessary)
For clinical trials please provide the following, additional information: trial protocol; investigator's brochure; details of indemnity cover.

Radiotherapy is a standard method of treating tumours. During radiotherapy treatment, a radiation beam is used to irradiate a tumour. Ideally this beam should impinge only on the tumour plus a small amount of normal tissue. Clearly, if a tumour is moving then targeting the tumor with the radiation beam can be quite difficult. When the tumour moves, it tends to move in and out of the beam so that the actual dose received by the tumor is less than would be received if the tumour had been stationary. Intrafractional target motion is a motion of a tumour caused by respiration (breathing). It causes particular problems in the treatment of lung tumours. The severity of these problems increases with more treatment methods such as intensity modulated radiotherapy IMRT. In These advanced methods, the radiation beam is conformed very tightly to the tumour shape so that normal tissues surrounding the tumour are spared from radiation to the maximum extent – unfortunately this means that any tumour motion causes the tumour to move out of the beam to a significant extent. Techniques are being developed to try to alleviate this problem – techniques such as gating aim to turn the radiation beam on and off at well defined points in the patient's breathing cycle so that the tumour is 'theoretically' in the same place all of the time. The method of gating currently relies on training the patient to breathe in a regular fashion – sometimes by the imposition of chest clamps to reduce the breathing depth and thereby partially immobilize the organs and tumours during treatment. Typically, the patient will be asked to control his or her breathing by using deep inspiration (or expiration) breath-holding. Training usually consists of a radiographer telling the patient what to do in a 2- minute training session and then leaving the patient to effect the method during the treatment. Most of lung tumours patients tend to suffer from shortness of breath and irregular breathing patterns, which make it difficult and uncomfortable for them to control their breathing during their treatment to limit intra-fraction motion

Our goal is to investigate the use of certain breathing patterns without stressing the patient or inducing discomfort through the use of breathing restrictors. We plan to use only healthy volunteers. We will monitor the subject's standard free-breathing cycle (chest motion and air flow) over a period of approximately 2minutes. This will be recorded using a system we have developed at City University. The data will be used to present a series of training stimuli to the participant – these will be audio and visual. The participant will try to match the stimuli through a feed back mechanism until we develop good breathing patterns that the patient can follow later without any artificial respiratory manoeuvres. Our aim is to establish: 1) the best method of training ii) investigate the effects of delay in the feedback loop and iii) to develop the system so that it can be later used in hospitals. To date, no study has been undertaken to establish the best practice for training a patient to breathe in a regular fashion when not using mechanical restriction devices.

1C. What is the purpose of the investigation? How is it intended to benefit the subject?

No benefit to subjects. The purpose is to investigate methods of helping patients to maintain a regular and controlled breathing patern durring radiotherapy treatment. This part of the work will be a studty using normal subjects. At a later time and as part of a joint NHS project, we will extend our work to cover patients – this will be covered by a specific Ethics application.

2C. Will invasive procedures (medical or surgical) be used?

No

3C. In the course of the investigation, might pain, discomfort (including psychological discomfort), inconvenience or danger be caused? How will this be addressed?

No pain or discomfort is involved in this study. The work is based on recording a participants breathing pattern under normal free breathing conditions. Participants will then be asked to try to match their breathing to a generated pattern. There will be no physical restraint and no abnormal breathing patterns so hypo/hyper ventilation is not a problem. Participants are always in full control of their breathing pattern

4C. Give details of the proposed research protocol including equipment to be used and any safeguards or precautions to be taken. Include a statement of the findings of any risk analysis undertaken with regard to the subject's safety and well being.

1. Thirty – fourty healthy volunteers will participated in this study.

2. The procedures will be fully explained to each participant during the first session, all participants will be asked to sign an informed consent form.

3. Subjects will then asked to lay down supine on stretcher or on clinical bed: a respiration monitor belt will placed around the upper abdomen and the diaphragm area. The belt contains an integrated displacement sensor that will be used to monitor the displacement of the subjects chest. A non-invasive flow meter will be used to monitor the participant's air flow. Data will be sent directly to a laptop computer via an electronic conditioning unit. The whole system is low voltage batery powered and there is no risk of electrical shock.

4. The Participants then will be asked to comence quiet free breathing without any intent to hold or exaggerated their breath.

5. The free breathing patern will be recorded for approximately 2-minutes.

6. The data recorded will be used to generate training signals from the normal breathing patern.

The next step of this experiment will be to inestigate how well the participants can produce a regular breathing pattern suitable for radiotherapy gating. We will use the same technology as for the initial recording so that we can record the participant's breathing. The device allows us to present different parterns of breathing to the participant either using audio or visual or both and to simulatniously record the subjects actual breathing. Actual and ideal breathing patterns can be simultaniously presented to the participant in real-time. We can display simple matched time traces, falling and rising notes or pulses, bar charts, falling and rising couloured dots, etc. The subject will try to moderate their breathig to match the presented data match. Our aim is to investigate the effectivness of different feedback methods. We will also investigate the effectivness of generating a regular pattern based on the patient's normal breathing as well as one that has no relationship to their natural breathing cycle and depth.

7. The participants then will be asked to pay attention to their breathing pattern that will be shown in LCD screen monitor or presented in an adio fashon – they will try to match their breathing to the ideal signal with it without any attempting to hold their breath. Matching will be both amplitude and phase.

8. The total time of the experiment will be approximately 30 -45 mins.

9. No personal data will be recoded or stored.

10. There will be two people present durring the experiment at all times fo reasons of personal safety.

11. No children or vunrable adults will be used in the study.

5C. What will be the duration and frequency of the procedures?

30 -40 mins including explination time. This would be sufficient to complete the whole study on one participant in one sitting. We will discuss with each participant their time constraints.

6C. What steps will be taken to safeguard against the effects of any repetitive research?

This work involves normal subjects only and so repetative minvestigation on specific groups of people is not an issue. The study has never been conducted as far as we are aware and so it is very unlikely that the participants will have been asked to perform this type of procedure before.

7C. Any further relevant information.

None needed.

Section D: Information on Subjects

NB: No subject should be admitted to a trial before Senate Ethical Committee has issued its written approval

1D How many subjects will be involved?

Approximately 30 -40 subjects will involved

2D What is the age group and sex of the subjects?

18-60 years old. (Male and Female) No children or vunravble adults will be involved.

3D. How are the subjects to be recruited?

Participants will be recruited as volunteers: by direct contact (e.g. family members, acquaintances etc) and through through requests to City University departments.

4D. What fee will be paid to subjects? Outline procedures for payment.

No fee will be paid

5D. How and when will their consent be obtained?

The consent form will be signed at the time the subject agreed to participate in the study.

6D. How will the subject's physical and mental suitability for participation be assessed?

Participants will be asked to sign a decleration saying that they have no known problems with breathing. All participants will be observed continously durring the experiment and if any distress or discomfort is observed we will terminate the session.

7D. Will the subject's doctor be notified? If so, please provide sample letter to subject's GP. yes

No

8D. What steps, if any, will be taken to safeguard the confidentiality of the results of the investigation?

All data will be anonimised. Breathing pattern data will not be tracible back to any individuall. Data from individuals will be associated through a numerical code only.

9D. **What do you consider are the major ethical issues in this proposal?**

There are no major ethical issues with this study as no personal data will be used, no young or vunrable individuals will be included and there will be two people present at any time.

Section E: Declaration

The Principal Investigator (s) and the relevant Head of Department should sign the following declaration. If the Principal Investigator is also the Head of Department, the signature of the Dean of the School should be sought. Please note that it is bad practice for both signatures to be the same. Applications where both signatures are the same will not be accepted. Alternative signatures could be sought from the Director of Research.

I certify that to the best of my knowledge the information given above, together with any accompanying information, is complete and correct and I approve the application for submission to the Senate Research Ethics Committee.

Principal Investigator(s)

Dr Robert A Price (Reader Dept. of Radiography)

Huda I. Al-mohammed

[redacted]

Head of Department/Director of Research/Dean of School

[redacted]

Date

31.10.06

Encs: (tick box to indicate that relevant document is attached)

(i)	Statement of Principal Investigator(s) relevant qualifications and prior experience	✓
(ii)	Proposed advertisement/invitation to recruit subjects	✓
(iii)	Proposed information sheet for subjects based upon the university example	✓
(iv)	Proposed informed consent form based upon the university example	X N/A.
(v)	Proposed sample letter to subject's GP	✓
(vi)	Form EC2	

For clinical trial only, in addition to the above:

(i)	Trial protocol	X N/A
(ii)	Investigator's brochure	X N/A
(iii)	Information on payments and compensation to subjects	X N/A.

Form EC2 01_02

CITY City University London

Senate Research Ethics Committee

This form is to be used in conjunction with form EC1. Please complete this form and return 13 copies with the completed EC1 forms to Mr Alex Sandbrook, Academic Registry.

If any of the checks are incomplete or supporting documents have not been received with the research proposal the Research Ethics Committee will not consider the proposal and it will be returned to you for completion.

Title: Analysis of breathing patterns and development of a technique to train subjects to breath in a regular and predictable manner; applications in radiotherapy practice

Name of Principal Investigator(s):
Dr Robert A Price Reader Department of Radiography
Huda I Al-Mohammed (PhD Research student)

Department (s) involved: Department of Radiography, City University

	(delete as appropriate)	
1. Have all documents been thoroughly checked for grammatical and spelling errors?	YES ~~NO~~	No!
2. Has the documentation been proof read by a member of the research team other than the principal researcher?	YES ~~NO~~	No!
3. Have page numbers been included in large documents?	YES ~~NO~~	
4. Have all letters and consent forms been written in plain English?	YES ~~NO~~	
5. Are the aims and objectives of the research consistent throughout the documentation?	YES ~~NO~~	
6. Has all supporting documentation been included in the EC1 submission?	YES ~~NO~~	
7. Does the document contain copyright material? (This includes all published text and graphics). If not covered by the terms of licence granted to City University by the Copyright Licensing Agency please enclose evidence of clearance or exemption.	~~YES~~ NO	
8. Has this research proposal been reported to the departmental Ethical Committee or its equivalent?	~~YES~~ NO	N/A
9. Has this research proposal been reported to a Local Research Ethics Committee e.g. LREC; MREC; ELCHA? (If YES please attach evidence of approval from such body).	~~YES~~ NO	N/A
10. Does the document comply with the Data Protection Act 1998? Researchers must consider the act when considering the use of data, storage of data and disposing of data. Guidance on the principals of the act are available at: http://www.city.ac.uk/ic/dataprotection/Data_Protection_Rese.html	YES ~~NO~~	

I confirm that the above checks have taken place on the attached documentation and that another member of the research team has additionally checked the documentation.

Name (print [redacted] 31st Oct 06.
Principal Investigator

Name (print [redacted] Signature [redacted] 31-10-06
Head of De

City University London

Project Information Sheet

Project Title:
Analysis of breathing patterns and development of a technique to train subjects to breath in a regular and predictable manner; applications in radiotherapy practice

Purpose of the Study:
The purpose is to investigate methods of helping patients who are being treated for cancer of the lung to maintain regular and controlled breathing patterns during radiotherapy treatment. This part of the work will be a study using normal subjects, at a later time and as part of a joint NHS project, we will extend our work to cover patients – this will be covered by a specific Ethics application.

Project Summery:
During radiotherapy treatments of lung cancer patients, patients are often asked to control their breathing – either by making a regular breath with constant breathing depth or to hold their breath either after taking a deep inhalation or having performed a deep exhalation. An alternative method is to use a restricting device that is placed around the patient's chest and artificially restricts their ability to perform normal breathing. Clearly for patients who have a lung disorder, such methods may cause distress or discomfort and are therefore possibly ineffective.

In this study we aim to study ore compliant methods of helping patients to control their breathing through the use of training with feedback.

No pain or discomfort is involved in this study. The work is based on recording your breathing pattern under normal free breathing conditions. To do this we will place a sensor on your chest using an elsticated belt – this will not restrict your breathing in any way. You will be asked to lay on a medical couch and breath normally for about 2 mins whilst we record your breathing. Following this, we will repeat the exercise but this time asking you to match your breathing to different patterns that will be presented to you on a screen or through headphones. There will be no physical restraint and no abnormal breathing patterns so hypo/hyper ventilation is not a problem.

You will always be in full control and can stop the exercise at any point.

The study will take place in the clinical skills suit based in the department of Radiogrpahy at Northampton square. You will be situated in a room that has diagnostic X-ray equipment present but you will not at anny time be subject to exposure to X-rays. The equipment used to monitor your breathing is powered by a simple battery and there is no risk of electrical shock. For personal safety there will be two people present at any time and you are welcolm to have a friend or collegue come along to the sesion with you.

Contact person: Huda Al-Mohammed
Telephone/Fax:
Email : [redacted]

School address:
Department of Radiography, City University, Northampton Square, London EC1V 0HB

Funding Details: Royal Embassy of Saudi Arabia, London. Saudi Cultural Bureau Education Section, 29 Belgrave Square, London. SW1X 8QB

Do you think you could give us Ten minutes of your time?
Healthy Volunteers Required

Title: ***Analysis of breathing patterns and development of a technique to train subjects to breath in a regular and predictable manner; applications in radiotherapy practice***

Purpose: The purpose of our study is to investigate and develop methods of helping patients who are undergoing treatment for lung cancer to maintain a regular and controlled breathing pattern during radiotherapy treatment. We require healthy male and female volunteers between the ages of 18 – 70 years who are willing to allow us to record their normal breathing and to participate in a simple training schedule using audio and or visual prompts and visual feedback.

Type of the study: Non invasive study

Experimental Design: The study is based on recording a participants breathing pattern under normal free breathing conditions. Participants will then be asked to try to match their breathing to a generated pattern. There will be no physical restraint and no abnormal breathing patterns so hypo/hyper ventilation is not a problem. Participants are always in full control of their breathing pattern

If you are considering volunteering in this study of if you need more information about the research, you could contact me at my email [redacted] or at telephone: 020 7040 8939.

Before agreeing to participate in the breathing study, we describe the recording and training session to you and provide you with a short written summary. Will give you a consent form that you need to sign, by signing this form, you indicate that you understand the study and volunteer to participate. As a volunteer, you are free to withdraw from, interrupt, or refuse to take part in a study at any time.

Informed Consent Form for Project Participants

Project Title:
Analysis of breathing patterns and development of a technique to train subjects to breath in a regular and predictable manner; applications in radiotherapy practice

Statement:
I agree to take part in the above City University research project. I have had the project explained to me, and I have read the Explanatory Statement, which I may keep for my records. I understand that agreeing to take part means that I am willing to:

- Participate in breathing study for the length of an 30-40 minute
- Lay down on a stretcher or on a clinical bed for approximately 10 minutes and have my breathing patterns recording whilst following various instructions

Data Protection:
The information recorded will be held and processed to allow us to examine the best approach to creating a comfortable and stable breathing pattern in patients undergoing radiotherapy treatments of non small cell lung cancer.

I understand that any information I provide is confidential, and that no information that could lead to my identification will be stored or disclosed in any reports on the project or to any other party.

Withdrawal from study:
I understand that my participation is voluntary, that I can choose not to participate in part or all of the project, and that I can withdraw at any stage of the project without being penalized or disadvantaged in any way.

Complaints Procedure:
If at any time I have a complaint regarding the way in which the study has been conducted, you may contact the secretary to the Ethics committee:

Naomi Hammond
Dr ~~Roland Petch~~ey
Secretary
~~Chairman~~ of the Senate Ethics Committee
City University
Northampton Square
London
EC1V 0HB

Or Dr Robert A Price,
Department of Radiography,
City University
Northampton Square
London
EC1V 0HB
[redacted]

Name: .....(please print)

Signature: .....Date: .....

Principal Investigator CV

Name:
Dr Robert Alan Price

Qualifications:
BSc (hons) Theoretical Physics
BSc (Hons) Mathematics
PhD theoretical Solid State Physics
MSc Medical Physics
DIC Computational Physics
PhD Computational Radiation Transport

State Reg. Clinical Scientist, Speciality Radiotherapy Physics

Employment History:

1980 – 1986 Senior Scientific Officer, Atomic Weapons Research Establishment and Admiralty Underwater Weapons Establishment

1986 -1992 Head of Research and Development, Weymouth Technical Services

1992 -1993 Surrey University

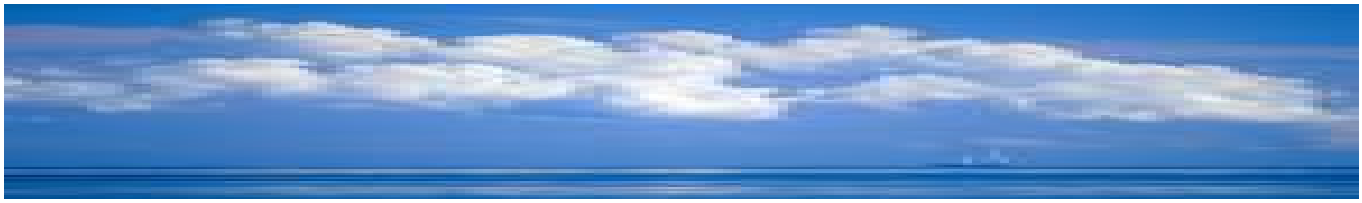
1993 -1994 Senior Lecturer, Department of Nuclear Sciences, Royal Naval College, Greenwich.

1994 -1998 Senior Research Fellow, Imperial College of Science and Technology

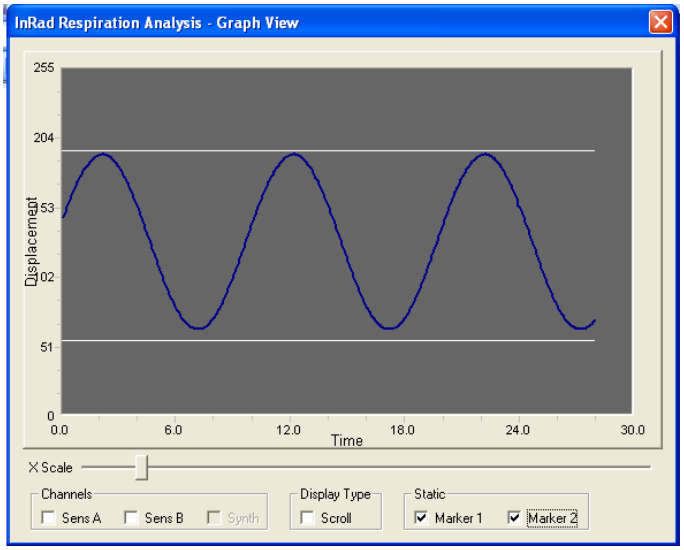
1998 – 2004 Principle Radiotherapy Physicist (Research), Clatterbridge Centre for Oncology NHS Foundation Trust.

2004 – Reader, Associate Dean (Research), City University.

APPENDIX F



Breathing



Do you have 60 minutes of your spare time to help in a breathing study? All you need to do is relax and breathe normally whilst we measure your breathing profile.

If you are [redacted]