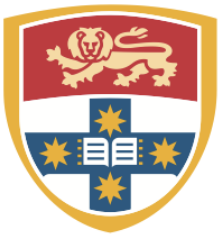
Translational Research of Audiovisual Biofeedback: An investigation of respiratory-guidance in lung and liver cancer patient radiation therapy



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A thesis submitted in fulfilment of the degree of

Doctorate of Philosophy (PhD)

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Declaration of Originality

I, Sean Pollock, declare that this thesis is my own work and has not been submitted in any form for another degree or diploma at any university or other institute of tertiary education. Information derived from the published and unpublished work of others has been acknowledged in the text and a list of references is given in each chapter.

Acknowledgements

To adequately thank and break down the contributions of each individual person who have helped and supported me over the course of my PhD would be a thesis unto itself. But it's suffice to say that the list is long and exhaustive and includes people both in and out of the University and in and out of hospitals, and without the friends, family, and colleagues I've had over the last few years, I would be far from where I am today.

First and foremost, I thank my family: my mum, dad, and sisters Sarah and Tessa. Your love and support has been such a driving force over the years in encouraging me to pursue what I'm passionate about and to always challenge myself. I can't thank you enough for how much this has contributed to my PhD, as well as everything that has led me to this point.

I express my deepest gratitude to the Radiation Physics Laboratory, whose members supported, challenged, and encouraged me every step of the way. Once I started my Master's degree I did not imagine myself going down the PhD pathway, that was until I joined the Radiation Physics Laboratory for my Master's research project and I've never looked back. Since then, opportunities that I would never have considered have been made available to me and I'm looking forward to where these will take me and I owe so much of that to this research group. And at the helm of this group is my supervisor Professor Paul Keall, whose direction, encouragement, and patience have not only facilitated this body of work but prepared me with the tools for a promising future. I would also like to thank the Bob and Nancy Edwards scholarship for providing me with the much needed financial support through my PhD which allowed me to focus all my energies on my studies.

To my fellow PhD students, Emma Colvill, Brendan Whelan, Chiara Paganelli, and Vanessa Allom. Whether it be critiquing each other's work, brain storming ideas, or the (sometimes) frequent partaking in ambrosiac liquid libations, your contribution to my overall PhD experience has been enormous.

There are of course many, many more people I would love to thank, but to name a few, in no particular order: Michael Bocock, Ollie de Vries, Katie Reeves, Brett Chapman, James Luckman, and Tom Collins. You provided the much needed "life" in my work-life balance and the emotional and social support I received from them over the years can't be overstated enough.

Through this PhD I've learned more than I could have ever anticipated; I've made incredible collaborations locally and internationally, forged valued friendships, and am incredibly excited for what comes next.

Table of Contents

List of Figures

Chapter 2 was published in Medical Physics, and as such, its figures have the nomenclature consistent with the Medical Physics journal, not this thesis.

Chapter 3 published in Physics in Medicine and Biology, and as such, its figures have the nomenclature consistent with the Physics in Medicine and Biology journal, not this thesis.

A subsection of Chapter 5 was published in BMC Cancer, and as such, its figures have the nomenclature consistent with the BMC Cancer journal, not this thesis.

Chapter 7 did not introduce any new figures; however it did show Figure 1-8 and Figure 1-15 again for clarity.

List of Tables

Chapter 2 was published in Medical Physics, and as such, its tables have the nomenclature consistent with the Medical Physics journal, not this thesis.

Chapter 3 was published in Physics in Medicine and Biology, and as such, its tables have the nomenclature consistent with the Physics in Medicine and Biology journal, not this thesis.

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List of Acronyms

CT: Computed Tomography

SBRT: Stereotactic Body Radiation Therapy

GTV: Gross Tumour Volume

IGTV: Internal Gross Tumour Volume

ITV: Internal Target Volume

PTV: Planning Target Volume

MLC: Multi-Leaf Collimator

4DCT: Four Dimensional Computed Tomography

DIBH: Deep Inspiration Breath Hold

RPM: Real-time Position Management

IR: Infra-Red

ABC: Active Breathing Coordinator

AP: Anterior-Posterior

SI: Superior-Inferior

LR: Left-Right

VCU: Virginia Commonwealth University

IGRT: Image-Guided Radiation Therapy

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analysis

PICOS: Patients, Intervention, Comparison, Outcome, Study design

MRI: Magnetic Resonance Imaging

SEM: Standard Error of Mean

MAE: Mean Absolute Error

MAD: Mean Absolute Deviation

RMSE: Root Mean Square Error

SPDM: Spectral Power Dispersion Metric

IMN: Internal Mammary Nodes

AV: AudioVisual

AVB: AudioVisual Biofeedback

XCAT: eXtended CArdiac Torso

MSE: Mean Square Error

DSC: Dice Similarity Coefficient

NCC: Normalised Cross Correlation

PMU: Physiological Measurement Unit

NSCLC: Non Small Cell Lung Cancer

kV: kiloVoltage

ANZCTR: Australian New Zealand Clinical Trials Registry

CBCT: Cone Beam Computer Tomography

FB: Free Breathing

STD: STandard Deviation

HREC: Human Research Ethics Committee

TAM: Technology Acceptance Model

TGA: Therapeutic Goods Administration

FDA: Food and Drug Administration

CE: Conformité Européenne

AIMD: Active Implantable Medical Devices

ARGMD: Australian Regulatory Guidelines for Medical Devices

SDX: SpiroDynr'X

MDCTP: Medical Device Commercialisation Training Program

IP: Intellectual Property

MSAC: Medical Services Advisory Committee

QALY: Quality Adjusted Life Years

ICER: Incremental Cost-Effectiveness Ratio

MBS: Medicare Benefits Schedule

EOFY: End of Financial Year

Abstract

Through the act of breathing, internal thoracic and abdominal anatomy is in constant motion: this motion can result in thoracic-abdominal tumours moving up to 5 cm as the patient breathes. During radiation therapy imaging and treatment delivery there are two fundamental types of errors: the errors occurring during treatment preparation (systematic) and the errors occurring during treatment delivery (random) both these types of errors are exacerbated by irregular respiratory-motion. Breathing guidance interventions operate to minimise the deleterious impacts of irregular respiration in cancer radiation therapy. Breathing guidance refers to a biofeedback system which measures patient respiration in real-time and simultaneously provides feedback to the patient on how to adjust their breathing to achieve the desired objective of regular respiration. Such breathing guidance interventions have been demonstrated to improve breathing motion regularity of both external surrogates in addition to internal anatomy as well as the tumour itself. However, much of the breathing guidance intervention investigations have not directly quantified the impact of regular breathing on radiation treatment accuracy, nor has there been a systematic review of the literature to thoroughly identify the gaps to indicate what the future direction breathing guidance investigations should take.

The overall aim of this thesis was to investigate the clinical feasibility of the audiovisual biofeedback breathing guidance intervention through translational research and potential commercial market acceptance.

The first aim of this thesis was to critically appraise the literature in terms of the use of breathing guidance interventions in the fields of radiation oncology and radiology via systematic review. Radiology was also included in this systematic review because certain radiology imaging modalities such as MRI and PET/CT are being utilised in emerging hybrid radiation treatment technologies such as the MRI-linac in addition to the use of PET/CT in radiation treatment planning. A systematic review of the literature was conducted and found that of the 27 identified studies, 21 yielded statistically significant improvements from the use of breathing guidance. None of the studies were randomised, and no studies quantified the impact of breathing guidance interventions on 4DCT image quality, the primary imaging modality utilised to plan radiation therapy for highly mobile tumours. The largely positive results found in this systematic review indicate that further clinical studies are warranted and should be focused on (1) utilising training and multiple sessions to maximize patient compliance with the breathing

guidance system, and (2) further determining the clinical impact of breathing guidance interventions by investigating outcomes pertaining to treatment margins, toxicity, and patient outcomes.

The second aim of this thesis was to quantify the impact of audiovisual biofeedback breathing guidance on 4DCT. This study utilised free breathing and audiovisual biofeedback lung cancer patient data from an MRI study to program the motion of a digital phantom prior to simulating 4DCT imaging. Audiovisual biofeedback demonstrated to significantly improved 4DCT image quality over free breathing. The results demonstrate that audiovisual biofeedback can be a beneficial intervention to improve 4DCT for cancer radiation therapy.

The third aim of this thesis was to assess the impact of audiovisual biofeedback on patient breathing over a course of radiation therapy. This was performed by monitoring the breathing motion of an external motion surrogate and implanted radio-opaque markers of liver cancer patients over the course of stereotactic body radiation therapy (SBRT). This study was the first investigation to utilise a screening procedure in addition to being the first to utilise breathing guidance over the course of SBRT. The findings of this study demonstrated the effectiveness of the screening procedure in facilitating regular respiration over the course of SBRT in addition to audiovisual biofeedback being a valuable tool in producing consistent interfraction respiratory motion between CT sim and treatment delivery.

The fourth aim of this thesis was to utilise the findings yielded by the above aims to design and implement a novel and comprehensive clinical trial investigating the use and impact of audiovisual biofeedback in radiation therapy. This fourth aim was achieved by performing a retrospective analysis of the previous audiovisual biofeedback 24 lung cancer patient study. The findings of this retrospective analysis were utilised to design and determine the statistics of the most comprehensive breathing guidance study to date: a randomised, stratified, multi-site, phase II clinical trial investigating audiovisual biofeedback over the course of lung cancer radiation therapy.

The fifth aim of this thesis was to explore the next stages of the audiovisual biofeedback technology in terms of translating evidence into broader clinical use through the commercialisation process. This aim was achieved by investigating the radiation oncology market, current medical products available in respiratory monitoring and biofeedback in this market, assessing the intellectual property position of the audiovisual biofeedback in addition to determining the product-market fit of the audiovisual biofeedback technology.

Presentation of Thesis

This thesis is presented as a combination of one systematic review and one published paper as their own chapters, with a published case report and study protocol forming subsections within chapters.

Chapter 1 provides a background to cancer radiation therapy and the deleterious impact of irregular patient breathing on cancer radiation therapy procedures before introducing audiovisual biofeedback breathing guidance as an intervention to minimise these deleterious impacts. Some background on audiovisual biofeedback is also provided in addition to recent developments towards the audiovisual biofeedback system utilised in the investigations presented in this thesis.

Chapter 2: 'Breathing guidance in radiation oncology and radiology: A systematic review of patient and healthy volunteer studies.' Published in *Medical Physics* **42**(9): 5490-5509 (2015).

Chapter 3: 'The impact of breathing guidance and prospective gating during thoracic 4DCT imaging: an XCAT study utilizing lung cancer patient motion.' Published in *Physics in Medicine and Biology* **61**(17) 6248-6501.

Chapter 4: 'Audiovisual biofeedback breathing guidance over a course of liver SBRT: A motion analysis of external and internal surrogates.' A Case Report of the first patient recruited into this study, published in the *Journal of Medical Imaging and Radiation Oncology* **59**(5) 654-656 (2015), is included in Appendix III.

Chapter 5: 'Designing and initialising a multi-institutional randomisation phase II audiovisual biofeedback clinical trial' is presented in two parts: (1) retrospective analysis of previous lung cancer patient study, and (2) the design and initiation of the randomised clinical trial. The clinical trial's study protocol was published in *BMC cancer*, **15**(1) 526-533 (2015) and is included as a sub-section of Chapter 5.

Chapter 6: 'Translating evidence into clinical practice through commercialisation' details the investigation into the commercialisation pathway of the audiovisual biofeedback technology, how these insights advanced the design and functionalities of audiovisual biofeedback, and validation testing of these new additions.

Chapter 7 provides the summary and conclusions of the work undertaken in this thesis in addition to future research directions

Publications

First author publications

Sean Pollock, Danny Lee, Paul Keall, and Taeho Kim (2013) Audiovisual biofeedback improves motion prediction accuracy, *Medical Physics*, **40**(4) 041705

Sean Pollock, Ricky O'Brien, Kuldeep Makhija, Fiona Hegi-Johnson, Jane Ludbrook, Angela Rezo, Regina Tse, Thomas Eade, Roland Yeghiaian-Alvandi, Val Gebski, and Paul Keall (2015) Audiovisual biofeedback breathing guidance for lung cancer patients receiving radiotherapy: a multi-institutional phase II randomised clinical trial, *BMC cancer*, **15**(1) 526-533

Sean Pollock, Robyn Keall, and Paul Keall (2015) Breathing guidance in radiation oncology and radiology: A systematic review of patient and healthy volunteer studies, *Medical Physics*, **42**(9) 5490-5509

Sean Pollock, Regina Tse, Darren Martin, Lisa McLean, Gwi Cho, Robin Hill, Sheila Pickard, Paul Aston, Chen-Yu Huang, Kuldeep Makhija, Ricky O'Brien, and Paul Keall (2015) First clinical implementation of audiovisual biofeedback in liver cancer stereotactic body radiation therapy, *Journal of Medical Imaging and Radiation Oncology*, **59**(5) 654-656

Sean Pollock, John Kipritidis, Danny Lee, Kinga Bernatowicz, and Paul Keall (2016) The impact of breathing guidance and prospective gating during thoracic 4DCT imaging: an XCAT study utilizing lung cancer patient motion, *Physics in Medicine and Biology*, **61**(17) 6485-6501

Co-author publications

Taeho Kim, Sean Pollock, Danny Lee, Ricky O'Brien, and Paul Keall (2012) Audiovisual biofeedback improves diaphragm motion reproducibility in MRI, *Medical Phyics,* 39(11) 6921-6928

Harry Steel, Sean Pollock, Danny Lee, Paul Keall, and Taeho Kim (2014) The internal–external respiratory motion correlation is unaffected by audiovisual biofeedback, *Australasian Physical & Engineering Sciences in Medicine,* 37(1) 97-102

Danny Lee, Sean Pollock, Brendan Whelan, Paul Keall, and Taeho Kim (2014) Dynamic keyhole: A novel method to improve MR images in the presence of respiratory motion for real-time MRI, *Medical Physics*, 41(7) 072304

Enid M Eslick, Dale L Bailey, Benjamin Harris, John Kipritidis, Mark Stevens, Bob T Li, Elizabeth Bailey, Denis Gradinscak, Sean Pollock, Chris Htun, Robin Turner, Thomas Eade, Ali Aslani, Graeme Snowdon, and Paul Keall (2015) Measurement of preoperative lobar lung function with computed tomography ventilation imaging: progress towards rapid stratification of lung cancer lobectomy patients with abnormal lung function, *European Journal of Cardio-Thoracic Surgery*, ezv276

Lee, Danny, Peter B. Greer, Joanna Ludbrook, Jameen Arm, Perry Hunter, Sean Pollock, Kuldeep Makhija, Ricky T. O'brien, Taeho Kim, and Paul Keall (2016) Audiovisual Biofeedback Improves Cine–Magnetic Resonance Imaging Measured Lung Tumor Motion Consistency, *International Journal of Radiation Oncology* Biology* Physics* **94**(3) 628-636.

Jaewon Yang, Tokihiro Yamamoto, Sean Pollock, Jonathan Berger, Maximilian Diehn, Edward E. Graves, Billy W. Loo, and Paul J. Keall (2016) The impact of audiovisual biofeedback on 4D functional and anatomic imaging: Results of a lung cancer pilot study, *Radiotherapy and Oncology* **120**(2) 267–272.

Lee, Danny, Peter B. Greer, Sean Pollock, Taeho Kim, and Paul Keall (2016) Quantifying the accuracy of the tumor motion and area as a function of acceleration factor for the simulation of the dynamic keyhole magnetic resonance imaging method, *Medical physics* **43**(5) 2639-2648.

Publications under review

Sean Pollock, Regina Tse, Darren Martin, Lisa McLean, Melissa Pham, David Tait, Reuben Estoesta, Grant Whittington, Jess Turley, Christopher Kearney, Gwi Cho, Robin Hill, Sheila Pickard, Paul Aston, Kuldeep Makhija, Ricky O'Brien, and Paul Keall (2016) The impact of audiovisual biofeedback on respiratory motion regularity and reproducibility in liver cancer SBRT, under review by *Physics and Imaging in Radiation Oncology*.

Presentations

Oral Presentations

August 2012	Enhancing respiratory motion prediction accuracy using audiovisual (AV) biofeedback. Presented at the American Association of Physicists in Medicine conference
July 2013	Respiratory guidance for cancer patients: audiovisual biofeedback. Presented at the Central Clinical School Young Investigators Symposium
Nov. 2013	A prospective clinical technology assessment of respiratory guidance: Audiovisual biofeedback for lung cancer patients. Presented at Postgraduate Cancer Research Symposium
May 2014	Breathe Well – Guidance for Stable Patient Breathing. Presented at Sydney Genesis Startup Program Final
August 2014	Audiovisual Biofeedback: Breathing guidance for lung cancer patients Presented at University of Sydney Open Day 3 Minute Thesis University Final
October 2014	Breathe Well Presented at University of Sydney Union INCUBATE Demo Day
Nov. 2014	Breathe Well - Breathing guidance to improve cancer radiation therapy Presented at Pearcey Foundation University Pitching Competition
Nov. 2014	Breathe Well Presented at 1776 Challenge Cup
May 2015	Entrepreneurial Journey of Breathe Well Presented as Keynote Speaker at Sydney Genesis Startup Program Final
Nov. 2015	Breathing guidance during liver cancer SBRT: impact of audiovisual biofeedback on liver tumour motion Presented at the Engineering & Physical Sciences in Medicine conference

Nov. 2015 The impact of audiovisual biofeedback breathing guidance on thoracic 4D-CT: a digital phantom study
Presented at the Engineering & Physical Sciences in Medicine conference

Dec. 2015 Impact of breathing guidance and prospective gating on 4DCT image quality: a digital phantom study
Presented at MedPhys15

April 2016 Impact of breathing guidance and prospective gating on 4DCT image quality: a digital phantom study
Presented at the European Society for Radiotherapy and Oncology conference

Sept. 2016 Respiratory Gating in Radiation Therapy
Presented as an invited speaker at ASTRO 2016 in the education session: "Is there a best way to manage respiratory motion?"

Poster Presentations

May 2013 Impact of audiovisual biofeedback on internal and external respiratory motion correlation.
Presented at the International Conference of the use of Computers in Radiation Therapy conference

August 2013 Respiratory guidance for lung cancer patients: an investigation of audiovisual biofeedback training and effectiveness.
Presented at the American Association of Physicists in Medicine conference

Sept. 2014: The AVIATOR trial: A multicentre phase II randomised trial of audio-visual investigation advancing thoracic radiotherapy.
Presented at the Combined Scientific Meeting

April 2015 Audiovisual biofeedback breathing training during thoracic 4DCT imaging: a digital phantom study.
Presented at the European Society for Radiotherapy and Oncology conference

July 2015 A Systematic Review of Breathing Guidance in Radiation Oncology and Radiology.

Presented at the American Association of Physicists in Medicine conference

July 2015 Audiovisual Biofeedback Reduces Image Artefacts in 4DCT: A Digital Phantom Study.
Presented at the American Association of Physicists in Medicine conference

April 2016 The first clinical implementation of audiovisual biofeedback in liver cancer SBRT.
Presented at the European Society for Radiotherapy and Oncology conference

Miscellaneous Achievements

Dec. 2012	Awarded EPSM Student Scholarship
May 2013	Awarded Best Poster Award at the International Conference of the use of Computers in Radiation Therapy conference
Nov. 2013	Awarded Best Presentation for 'Skin & lung cancers' at the Postgraduate Cancer Research Symposium
May 2014	Finalist at Sydney Genesis Startup Competition
August 2014	Awarded the 99 Scholars runner-up prize at University of Sydney 3 Minute Thesis final
Nov. 2014	NSW Pitching Competition Winner at the Pearcey Foundation University Pitching Competition
July 2015	Awarded the Edith Mary Rose travel scholarship
Nov. 2015	NSW Health Medical Device Commercialisation Training Program 2015 graduate – Distinction
Sept. 2016	Invited speaker to 2016 ASTRO conference

Awarded Postgraduate Research Support Scheme in 2013, 2014, and 2015.

List of Appendices

I. Signed statements from the co-authors of the included published manuscripts included in the body of this thesis

II. Documentation submitted to the human research ethics committees (HREC) for the two clinical trials presented Chapter 4 and Chapter 5. This includes the submitted protocols, patient information and consent forms, information brochure, patient and staff questionnaires, and toxicity report.

III. Published Case Report of patient 1 recruited into the study detailed in Chapter 4. This Case Report was published in Journal of Medical Imaging and Radiation Oncology and was the journal's Case of the Month for October 2015.

IV. Documentation provided for study site credentialing for the clinical trial presented in Chapter 5. This includes audiovisual biofeedback quality assurance, credentialing checklist and instructions.

V. User guide documentation provided to study sites participating in audiovisual biofeedback studies. User guide documentation includes instruction for audiovisual biofeedback software and/or Intel RealSense setup depending on the study setup.

VI. Media reports on the audiovisual biofeedback commercialisation process

VII. Videos recorded and produced over the course of this thesis
    a. Patient information video used in the clinical trials presented in Chapters 3 and 4
    b. Medical Device Commercialisation Program 2015 Showcase presentation
    c. Animated 3 Minute Thesis presentation: produced by 99 Scholars as a part of my runner-up prize
    d. Keynote Genesis Final Speech: detailing the courses taken and lessons learned over the commercialisation process

CHAPTER 1

Introduction

CHAPTER 1

Introduction

1.1. Cancer Radiation Therapy

External beam radiation therapy involves directing a beam of ionizing radiation at a tumour to cause double-strand breaks in the cancer cells' DNA, causing cancer cell apoptosis.[1, 2] Worldwide, there are 12.4 million new cancer cases each year,[3] of these, approximately 6.8 million (55%[4] of 12.4 million) are recommended to be treated using radiation therapy. These patients are typically treated using linear accelerators (linacs) which target the tumour with high-energy x-rays, shown in Figure 1-1(a) and Figure 1-1(b). An emerging form of high-precision external beam radiation therapy is proton therapy, shown in Figure 1-1(c). The use of linacs in radiation therapy is by far the most common form of radiation therapy with a total of 11,245 linacs worldwide,[5] whereas there are only 43 proton therapy facilities worldwide.[6]

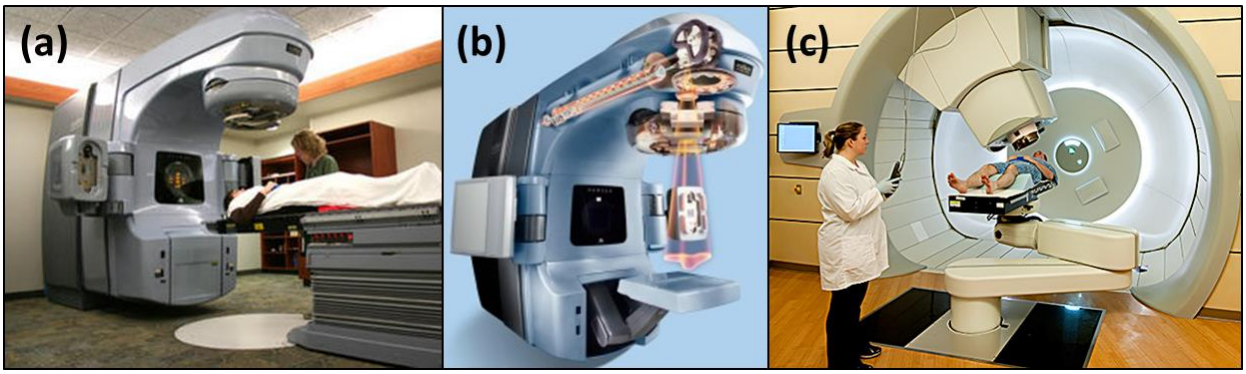


***Figure 1-1**. (a) A Varian Clinac iX linac at the Abben Cancer Center.[7] (b) Illustration of the production of a high-energy x-ray beam in a linac.[8] (c) Proton therapy treatment room at the ProCure Proton Therapy Center - Oklahoma City.[9]*

1.1.1. Cancer Radiation Therapy Workflow

The typical workflow for cancer radiation therapy is shown in Figure 1-2. It begins with the computed tomography (CT) simulation in order to determine the location, size, shape, and motion of the tumour, in addition to identifying organs at risk of receiving potential radiation damage. The obtained CT simulation images are used to determine the appropriate radiation dose to be delivered to the tumour, while keeping the dose delivered to the surrounding organs at risk as low as reasonably possible. After the patient's treatment has been planned, the patient is setup on the treatment couch as similarly as

possible to their position on the CT sim couch to have their radiation treatment delivered to the tumour site. Standard fractionation typically involves 30 fractions of radiation treatment,[10] meaning that the patient comes in for radiation treatment on 30 separate days.

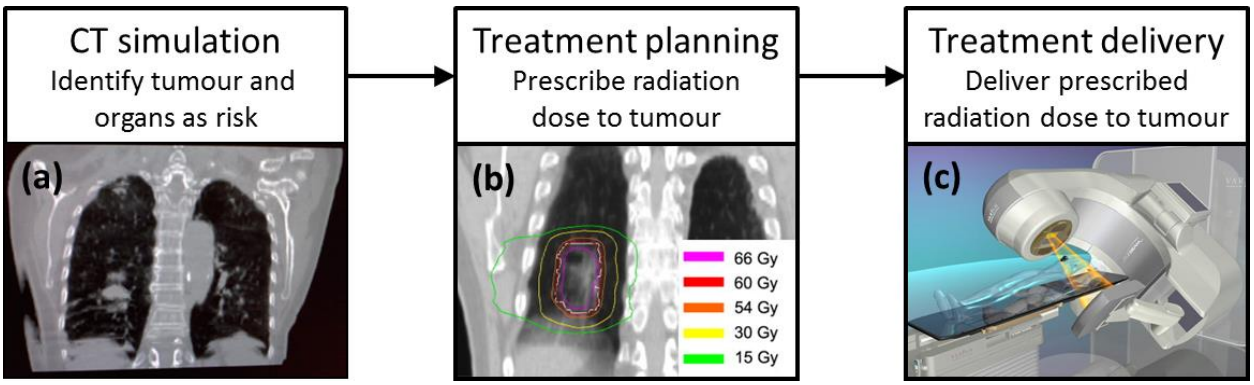


Figure 1-2. *The three main steps in the radiation therapy workflow. (a) Example of a CT simulation image of a lung cancer patient, adapted from Chen, et al. (2012).[11] (b) Example of a CT simulation image with treatment plan, indicating different regions of different prescribed radiation dose about the tumour, adapted from Admiraal, et al. (2008).[12] (c) 3D rendering of radiation treatment delivery, from Genesys Hurley Cancer Institute.[13]*

1.1.2. Lung and Liver Cancer Patients in Radiation Therapy

Lung cancer is the leading cause of cancer-related deaths, with 1.6 million new cases each year accounting for 18% of all (cancer-related and non-cancer-related) deaths in 2008.[14] There are 748 thousand new liver cancer cases each year, and is the second most frequent cause of cancer death in males and sixth highest cause of cancers death in females.[14] Radiotherapy is frequently used to treat lung and liver cancers, with a recommended radiotherapy utilization rate of 77% for lung cancers,[15] and over 54% of USA radiotherapy centres treating their liver cancer patients with stereotactic body radiation therapy (SBRT).[16] However, a complicating factor inherent to lung and liver tumours is that they are subject to respiratory-induced motion,[17] largely due their proximity to the thoracic diaphragm. A strong correlation has been demonstrated between the thoracic diaphragm with both lung tumour[18, 19] and liver tumour motion,[20] as shown in Figure 1-3.

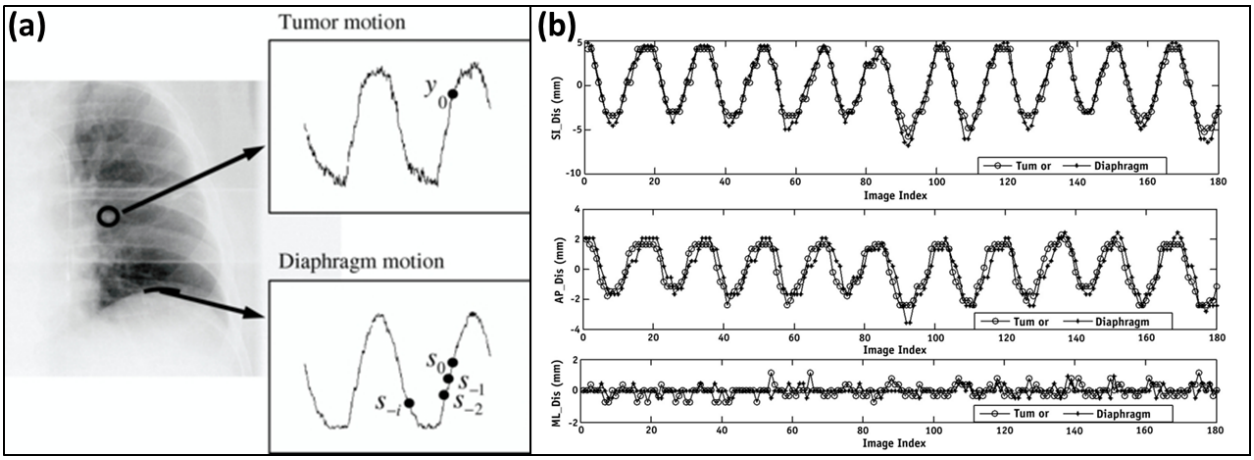


Figure 1-3.*(a) Example of lung tumour and thoracic diaphragm motion, from Cerviño, et al. (2009).*[18] *(b) Example of three-dimensions of liver tumour motion and thoracic diaphragm motion, from Yang, et al. (2014).*[20]

Lung and liver cancer patients were selected as the focus of this thesis for the investigations performed in this thesis due to the systematic review (detailed in chapter 2) which found that the most commonly researched patient cohort for breathing guidance interventions was lung cancer patients, followed by liver cancer patients. Therefore, for the translational research conducted in this thesis lung and liver cancer patients were considered to be the more ethical patient cohort to be tested with the intervention during treatment delivery, rather than a kidney or pancreas patient cohort, where acceptance and effectiveness of such an intervention is less certain at this time.

1.2. Respiratory Motion in Radiation Therapy

Through the act of breathing, internal thoracic and abdominal anatomy is in constant motion, with the largest magnitude of motion in the superior-inferior direction;[21] [22] this can result in thoracic-abdominal tumours moving up to 5 cm as the patient breathes.[17] In order to ensure that the tumour is being irradiated at all times, treatment margins, shown in Figure 1-2(b), are expanded to encompass the entire range of motion of the tumour,[23] illustrated in Figure 1-4.

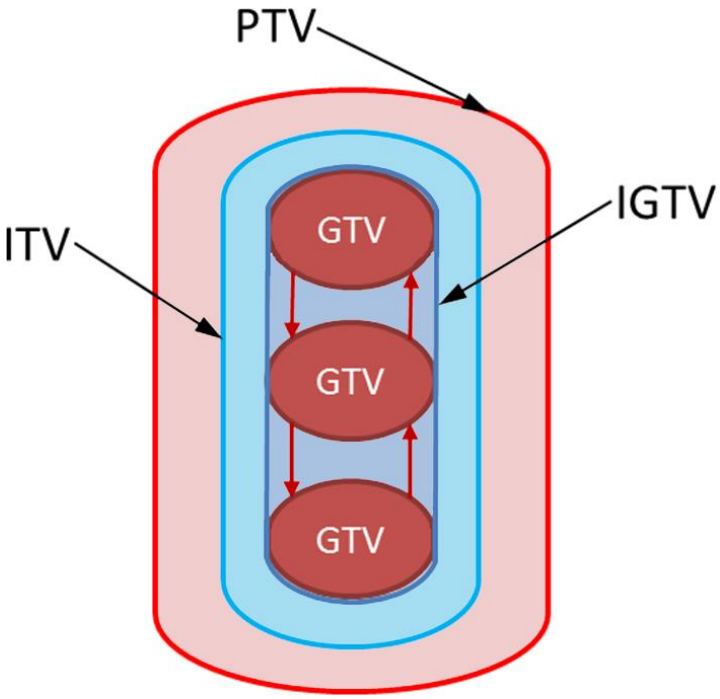


Figure 1-4. *Gross tumour volume (GTV) moving up and down as the patient breathes; its total range of motion indicated by the internal gross tumour volume (IGTV). Expanded around this is the internal target volume (ITV), which encompasses the IGTV with an additional internal margin accounting for variations in size, shape, and position of the IGTV. The planning target volume (PTV) takes into account both uncertainties accounted for by the ITV in addition to setup uncertainties.*[24]

The larger the uncertainties in patient setup, and GTV position, shape, and size, the more the margins are expanded, which ensures that the tumour is being targeted throughout its entire range of motion; however, it also increases the dose to the healthy surrounding tissue.[25] Given the observed variety of different tumour sizes and shapes, the resultant radiation beam needs to be shaped in such a way as to match the shape of the PTV. This is primarily achieved through the use of multi-leaf collimators (MLC),[26-28] and are shown in Figure 1-5.

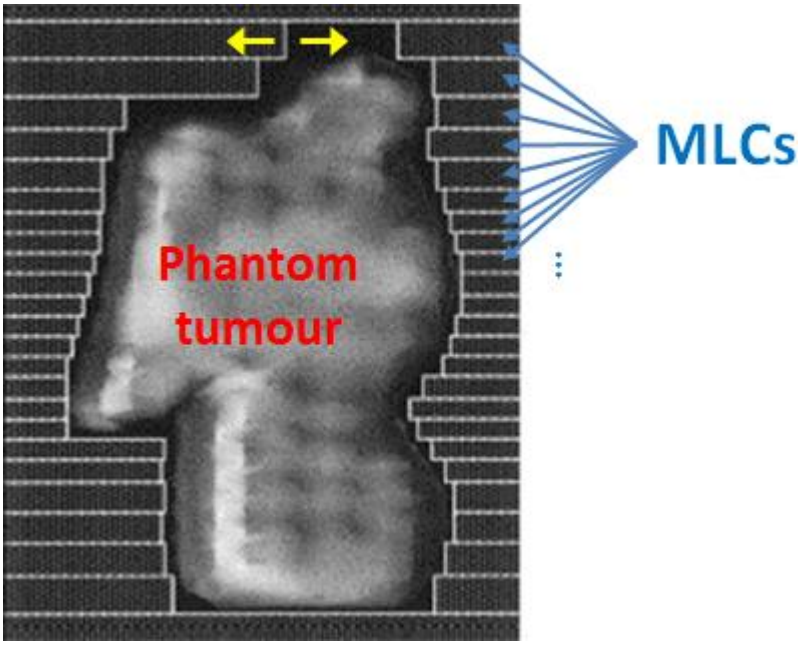


Figure 1-5. *Phantom as a surrogate for a tumour with MLCs shown conforming to the shape of the tumour. Each individual MLC can move back and forth (as indicated by yellow arrows), such that all the MLCs can create and conform to a wide range of tumour shapes and sizes. Adapted from Cosgrove, et al. (1999).*[28]

The material of each MLC is of a high atomic number, typically a tungsten[28] (atomic number: 74) alloy, allowing it to block part of the incident radiation beam, shaping it such that it conforms to the desired PTV. Each individual MLC can move independently of the others, allowing the MLCs to be able to create a wide variety of shapes and sizes.

1.2.1. Respiratory Motion Management in Radiation Therapy

In order to manage a constantly moving tumour, a number of techniques and technologies are available to reduce the deleterious impact respiratory motion can have on cancer radiation therapy. Such motion management strategies are recommended when tumour motion exceeds 5 mm.[29]

1.2.1.1. Four Dimensional Computed Tomography (4DCT)

4DCT is a type of medical imaging used for CT simulation to obtain not only three-dimensional information on tumour position and shape, but temporal information to also determine the tumour's range of motion during respiration.[30-33] During 4DCT imaging axial CT images are acquired at a number of couch positions as the patient is moved through the CT bore. At each couch position, axial CT images are acquired over the course of one respiratory cycle as monitored by a respiratory sensor (see chapter 1.2.1.5.) before moving on to the next couch position; each CT image is tagged with a respiratory position.[32] At the end of image acquisitions each couch position has an associated collection of CT images encompassing a cycle of respiration; these images are retrospectively sorted based on their

associated respiratory position.[32] This creates a 3D CT that includes information over an entire respiratory cycle, generating the 4DCT. This method of 4DCT reconstruction is referred to as cine mode and represents the conventional reconstruction 4DCT method for many scanners.[34, 35]

1.2.1.2. Breath Holds

One technique to minimise the impact of respiratory motion is for the patient to hold their breath. By suspending respiration, respiratory-induced motion is minimised,[36-38] negating much of the deleterious effects respiratory motion can have on cancer radiation therapy.[39, 40] The type of breath hold most often performed in cancer radiation therapy is the deep inspiration breath hold,[41-43] which for thoracic cancers, particularly breast cancer, has the additional benefit of further increasing the geometric distance between the heart and radiation beam thereby reducing cardiac and pulmonary dose.[44-46] An example of a deep inspiration breath hold is shown in Figure 1-6.

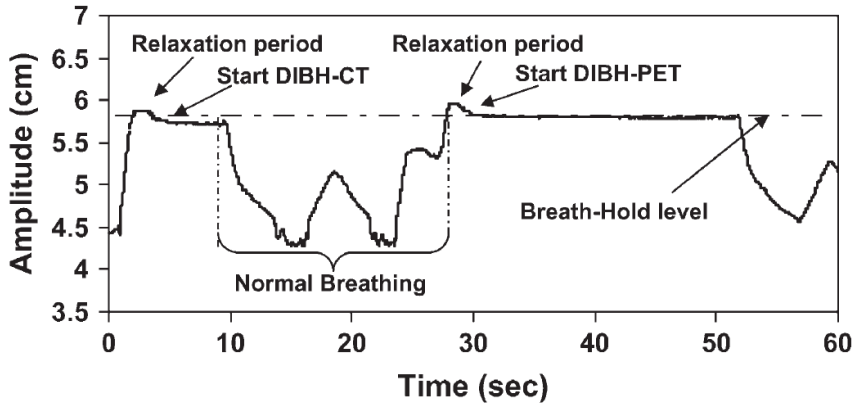


Figure 1-6. *Cancer patient respiratory signal performing deep inspiration breath holds (DIBH) demonstrating the respiratory stability of breath holds compared to free breathing. From Nehmeh, et al. (2007).*[47]

Breath holds during radiation therapy treatment delivery typically have a duration of 20-30 seconds,[48, 49] however, many treatments require a beam-on time in the order or minutes,[50, 51] not seconds. Further to this, many patients may not be able to sustain or tolerate multiple breath holds, especially lung cancer patients who have compromised lung function. Treatment times utilizing breath holds are also typically longer compared to free breathing; Mah, *et al*. (2000) noted that the average free breathing treatment time was 16 minutes, compared to 32 minutes for DIBH.[52] It should be noted that treatment time here refers to patient setup in addition to the treatment delivery itself.

1.2.1.3. Respiratory Gating

Respiratory gating refers to triggering on the radiation beam only during specific phase- or displacement-based windows of the respiratory cycle,[53, 54] windows in which respiratory motion is

minimal, typically at exhale which has demonstrated to be more reproducible than inhale.[55] Respiratory gating requires measurement of the tumour position or the use of a surrogate whose respiratory signal is synchronised with the target motion.[56] If the measurement or surrogate signal is integrated with the linear accelerator delivery, the beam on/off can be controlled, automating a gating procedure. Figure 1-7 illustrates the rationale behind the respiratory gating procedure.

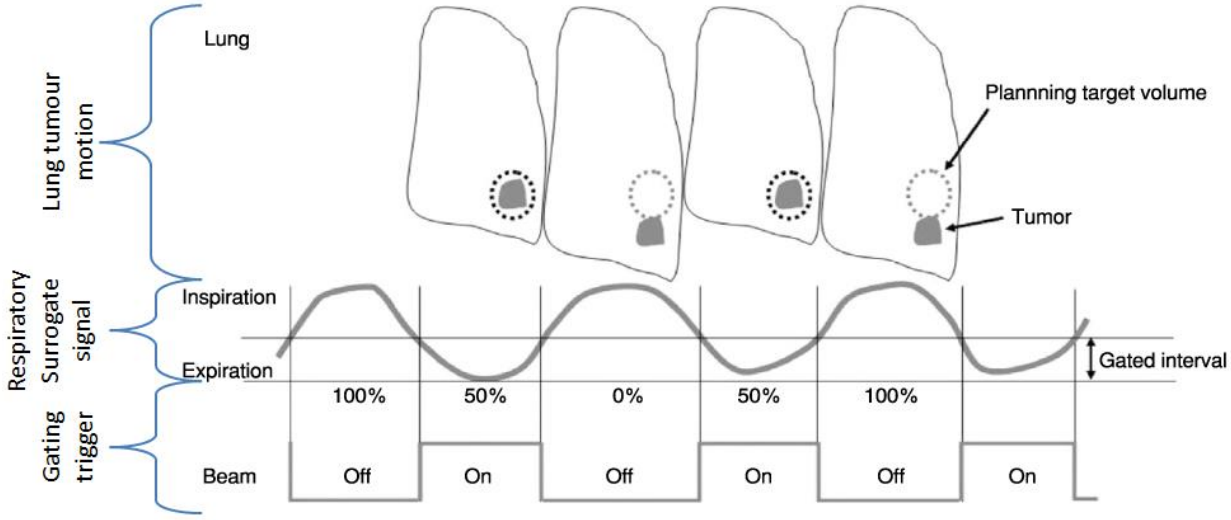


Figure 1-7. *A lung tumour moving in and out of the gating window (or interval) as the patient breathes. In this example, the gating window is set at exhale (50% of the respiratory cycle). Adapted from Kim, et al. (2008).*[57]

By only treating the tumour within a specific region, respiratory gating in radiation therapy reduces the margins shown in Figure 1-4 since it no longer needs to encompass the tumour's entire range of motion.[58-60] However, by interrupting the radiation beam each time the respiratory signal moves outside the gating window, treatment time of respiratory gating can exceed that compared to no gating. In addition to being utilised during free breathing, respiratory gating is also often used in breath hold treatments, with the gating window set at the desired breath hold amplitude level.[61, 62]

1.2.1.4. Tumour Tracking

Tumour tracking is an emerging technology to monitor and adapt to tumour motion in real-time during treatment delivery.[63, 64] Tracking of the tumour typically involves either real-time imaging of the region of interest,[65, 66] or implanted transponders about the tumour itself.[63, 67] By following the motion of the tumour itself it is not necessary to expand the margins to encompass its entire range of motion, thereby reducing the size of the margins illustrated in Figure 1-4.[67, 68] The impact of tracking, and not tracking, on delivered radiation dose to a prostate is shown in Figure 1-8.

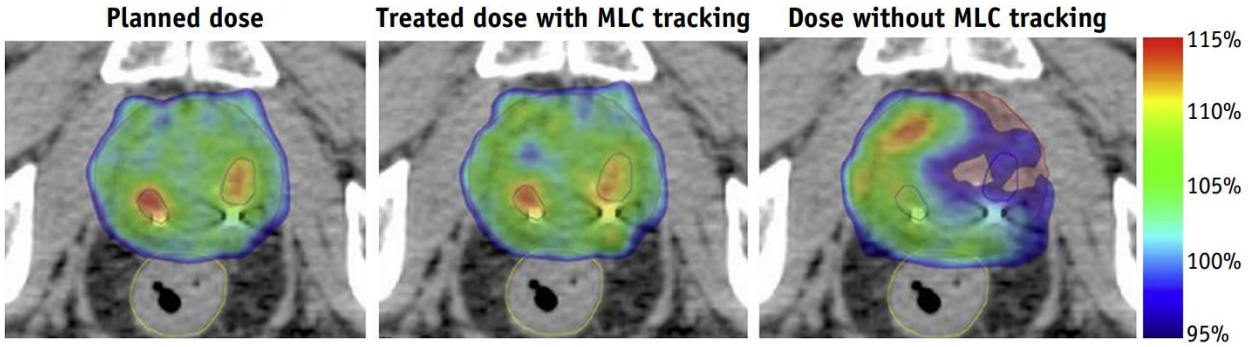


Figure 1-8. *Example of dose distributions from a prostate patient demonstrating higher agreement with the planned dose from the use of tracking compared to without tracking. From Colvill, et al. (2015).*[67]

Should the tumour move in such a way that was not accounted for in the treatment planning stage, it can lead to a deviation in radiation dose delivered from what was planned, as shown in Figure 1-8.

Motion prediction is utilised in tumour tracking to overcome the inherent latency of the treatment and imaging system.[69-71] Here, 'latency' refers to the time taken to register tumour position, speed of the MLCs, and the reaction time of the delivery system in addition to software limitations.[72, 73] During this time the tumour may have moved to a different position. As such, there is a requirement for predicting tumour motion over timescales of the system latency which can range from 50 to several hundred milliseconds.[70, 71]

1.2.1.5. Respiratory Sensors

To perform much of the procedures detailed in chapter 1.2.1.1., chapter 1.2.1.2., chapter 1.2.1.3., and chapter 1.2.1.4., respiratory sensors are utilised to track and monitor patient respiration. An overview of the available sensors is given in the following subsections.

1.2.1.5.1. Varian RPM

The Varian real-time position management (RPM) system (Figure 1-9) is comprised of an infra-red (IR) camera and an external marker block with IR reflective dots. The marker block is positioned on the patient's abdomen, mid-way between the umbilicus and xiphoid process, and its motion is tracked by the IR camera at a rate of 30 Hz in three dimensions, however, only the anterior-posterior motion is typically utilised for the respiratory signal.

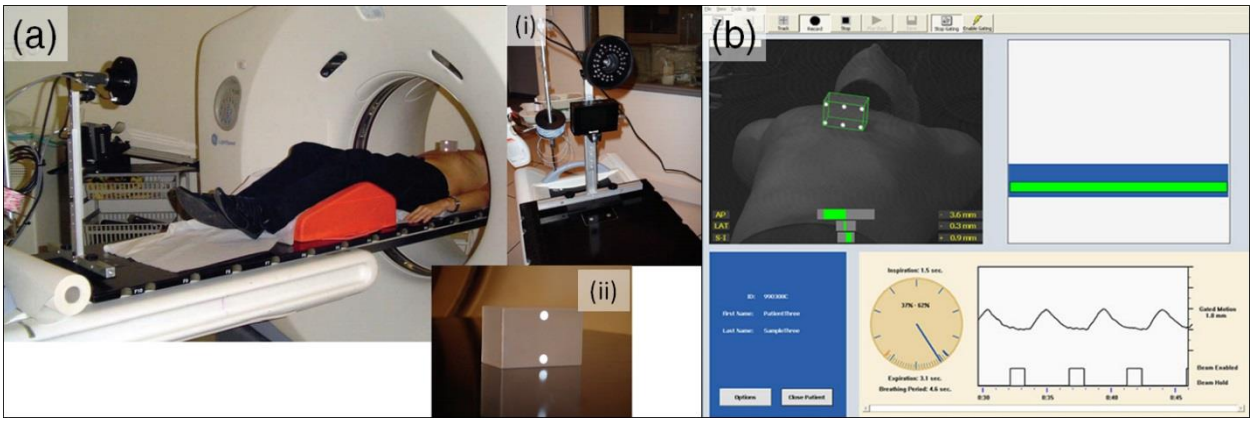


Figure 1-9. *(a) Varian RPM system setup in a CT scanner also showing (i) the infra-red camera, and (ii) the marker block with two infra-red reflective markers. Adapted from Giraud & Houle (2013).*[64] *(b) Screenshot of the Varian RPM software showing the more recent 6-dot reflective marker.*

The Varian RPM system provides a physiologically accurate respiratory signal used for gating procedures, such as during imaging[31, 74, 75] and radiation treatment delivery.[39, 58, 76]

1.2.1.5.2. Elekta ABC

The Elekta Active Breathing Coordinator (ABC) (Figure 1-10), rather than monitoring respiratory motion, monitors patient lung volume via spirometry.[77] The patient's nose is clamped closed and they breathe through a tube measuring the volume of airflow.

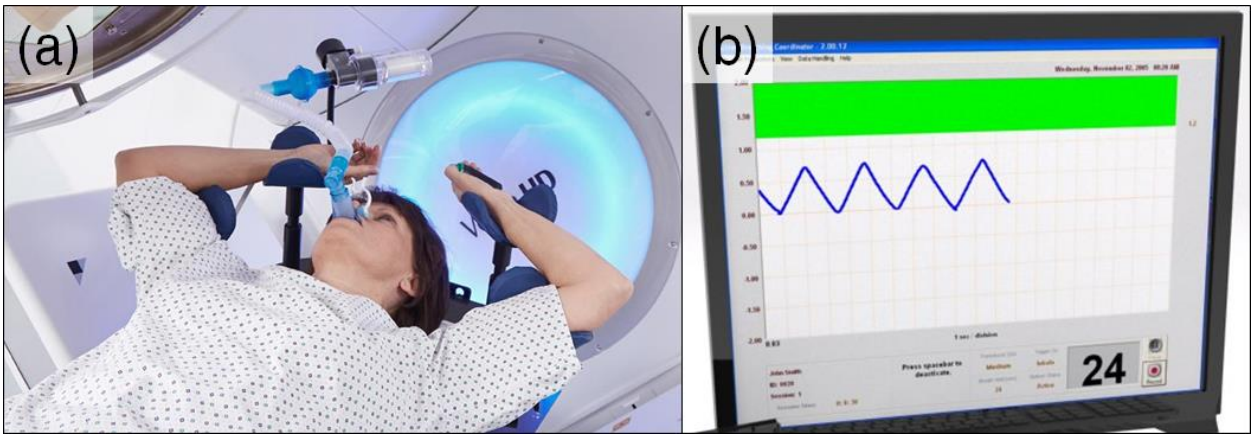


Figure 1-10. *(a) Elekta ABC system setup in a treatment room.*[78] *(b) Screenshot of the Elekta ABC software.*

The Elekta ABC can also restrict patient airflow at a particular level, such as mid ventilation or deep inspiration, by closing a valve, suspending the patient's respiration. This can result in reproducible and

accurate gated breath holds,[79, 80] however minor patient discomfort in using the Elekta ABC has been reported.[81-83]

Elekta is the second major company which, together with Varian, make up 80% of the radiation oncology market.[84] As such, the vast majority of respiratory sensors utilised in radiation therapy are either the Varian RPM or the Elekta ABC.

1.2.1.5.3. AlignRT VisionRT

The VisionRT AlignRT (Figure 1-11) is a markerless surface imaging motion sensor, utilizing stereo vision to produce 3D surface images of the patient.[85]

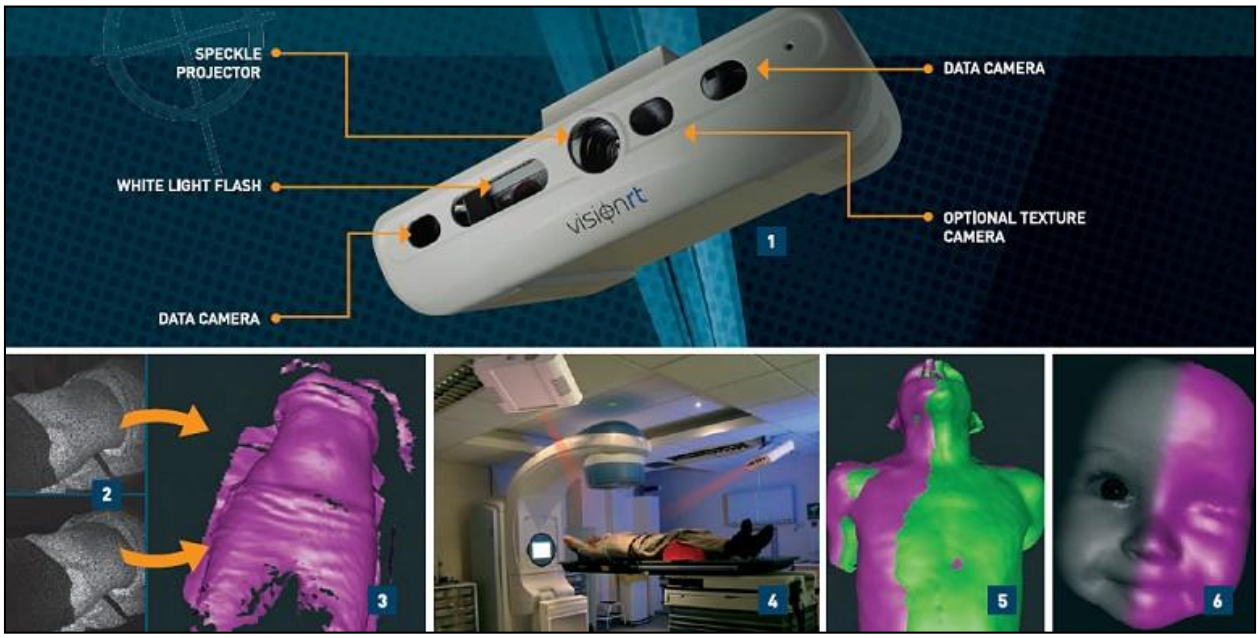


Figure 1-11. *VisionRT AlignRT camera and examples of surface images.*[86]

AlignRT is not only used for real-time respiratory motion monitoring,[87] but also patient positioning, ensuring that patient position is reproducible between fractions by comparing the 3D patient surface between fractions.[88]

1.2.1.5.4. Calypso

The Calypso system (Figure 1-12) is a method of tumour tracking that is comprised of implanted transponder beacons which generate an electromagnetic signal that is detected in real-time by a panel array.[89, 90] The Calypso system has been described as being “GPS for the body”.[91]

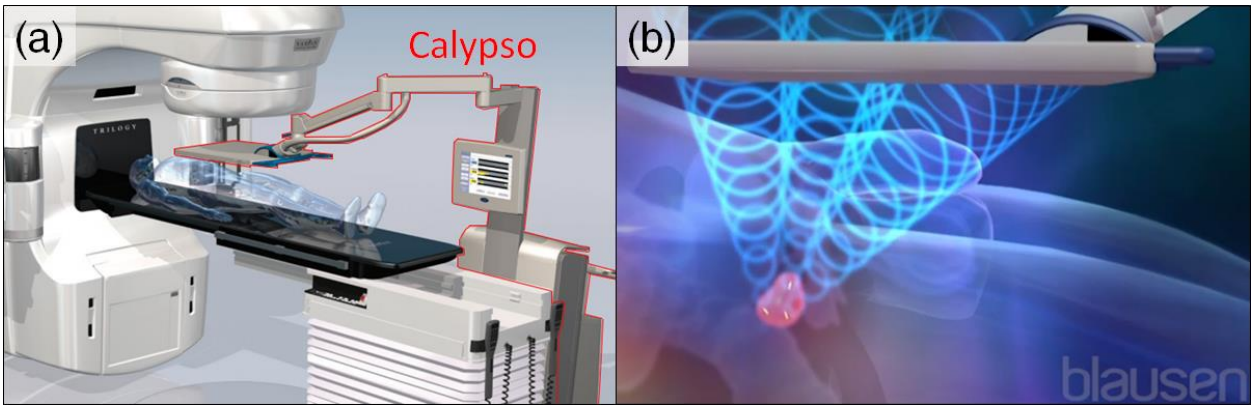


Figure 1-12. *(a) Calypso panel array in place in the treatment room.[92] (b) Implanted transponder beacons generating an electromagnetic signal detected by the panel array.[93]*

Recently, the Calypso system has been developed to position the transponder beacons on the patient as an external marker for procedures where implanted markers are not necessary (e.g. breast cancer radiation therapy).[94, 95]

1.2.1.6. Abdominal Compression

Another technique to minimise the impact of respiratory motion is to physically limit the magnitude of abdominal and thoracic diaphragm motion via abdominal compression (Figure 1-13). By applying pressure to the patient's abdomen, it physically restricts diaphragmatic motion,[96] thereby restricting the motion of tumours proximal to the diaphragm.[97]

Figure 1-13. *A patient with a plate compressing their abdomen.[98]*

1.3. Irregular Respiratory Motion in Radiation Therapy

Typical patient breathing is often irregular in nature, e.g. inconsistent amplitude, period, and baseline drifts.[73, 74] The techniques detailed in chapter 2.1., account for respiratory motion, however, the additional errors introduced by irregular respiratory motion are still present. An example of an irregular patient respiratory pattern is shown in Figure 1-14.

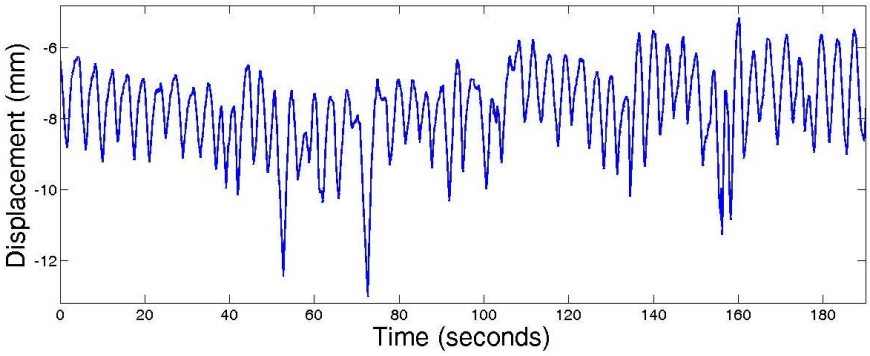


Figure 1-14. *Example of an irregular patient respiratory pattern. Demonstrating inconsistent amplitude, period, and baseline drifts (respiratory signal from data analysed in chapter 5).*

During radiation therapy imaging and treatment delivery there are two main sources of error: the errors that arise during treatment preparation and the errors that arise during treatment delivery.[99-102] These errors have a number of components including patient positioning, anatomic variations, incorrect determination of the isocentre, and setup variations. For margin calculations, these errors can be broken up into systematic and random errors, with systematic errors representing errors arising during preparation and random errors arising during treatment delivery; both these types of errors are exacerbated by irregular respiratory-motion.[34, 94, 103] Inconsistent respiratory motion also leads to variations in the ITV size over the course of patient treatment, leading to variations from what was planned for treatment.[104] Figure 1-15 shows examples of ITV size variations over time.

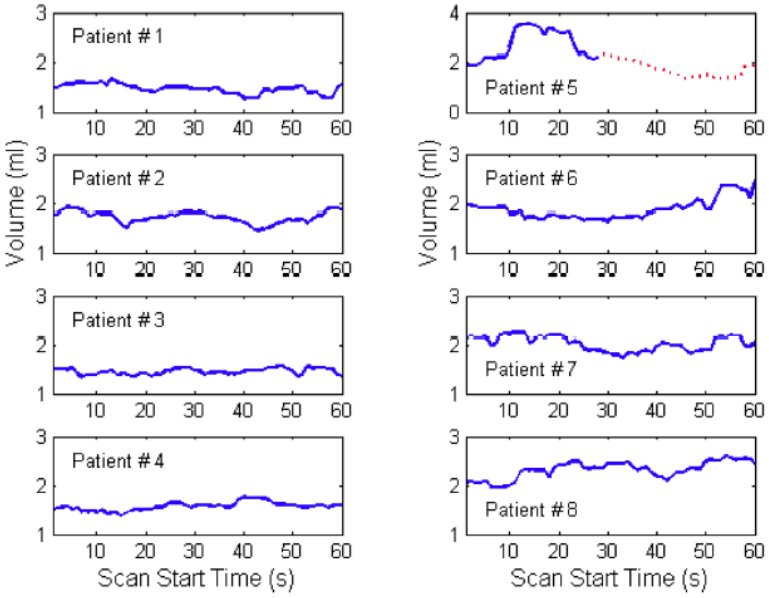


Figure 1-15. *Variations of the volume of ITV over a fraction of treatment for 8 lung cancer patients. From St James, et al. (2012).*[104]

Subsequent sections chapter 1.3.1., chapter 1.3.2., and chapter 1.3.3. detail the deleterious impact irregular respiratory motion has on the motion management methods introduced in chapter 1.2.1.

1.3.1. Four Dimensional Computer Tomography (4DCT)

4DCT image artefacts have been reported in up to 90% of 4DCT images,[34] compromising the accuracy of tumour delineation.[105] These artefacts have been linked to factors such as respiratory motion velocity and irregularity.[106-109]

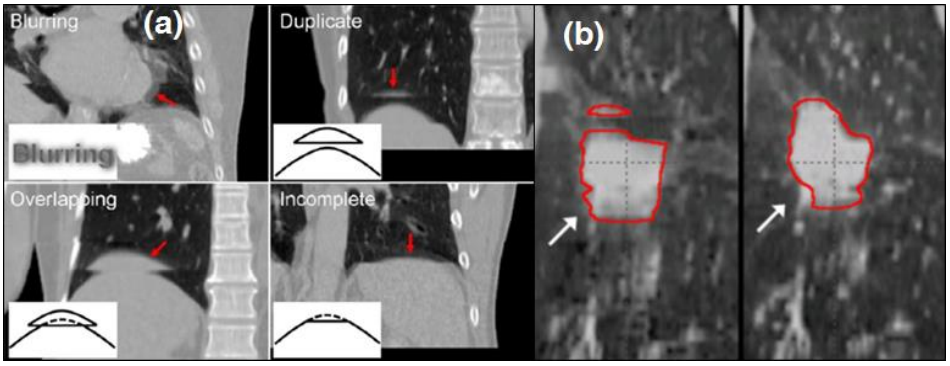


Figure 1-16. *(a) example of 4DCT image artefacts, from Yamamoto, et al., (2008).*[34] *(b) Example of delineation errors of a lung tumour due to 4DCT image artefacts, from Persson, et al., (2010).*[105]

These artefacts arise when the respiratory signal varies considerably between couch positions, resulting in anatomic mismatches amongst the same tagged respiratory position (as described in chapter 1.1.1.), Figure 1-17 illustrates the variations of a respiratory signal over a number of different couch positions that would result in 4DCT image artefacts as shown in Figure 1-16.

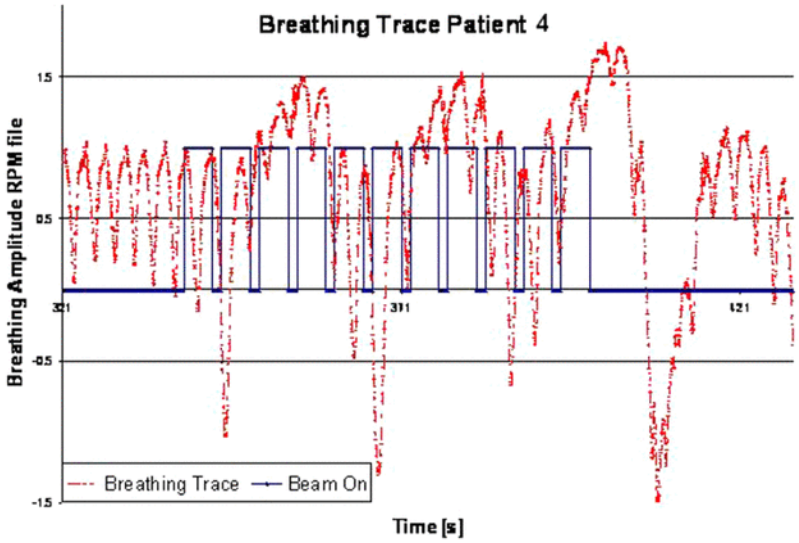


Figure 1-17. *Example of an irregular respiratory trace (red signal) of a liver cancer patient. Beam on image acquisition times across the different couch positions indicated with the blue trace. From Szegedi, et al. (2012).*[110]

1.3.2. Respiratory Gating

The rationale behind respiratory gating is that the tumour will occupy the same region in 3D space within the gating window for each breath. However, if patient breathing amplitude is inconsistent and there are baseline drifts, as shown in Figure 1-18, respiratory displacement and tumour position are inconsistent within these gating windows, leading to the radiation beam being triggered at inappropriate times. This increases the risk of underdose to the tumour and overdose to the surrounding healthy tissue.

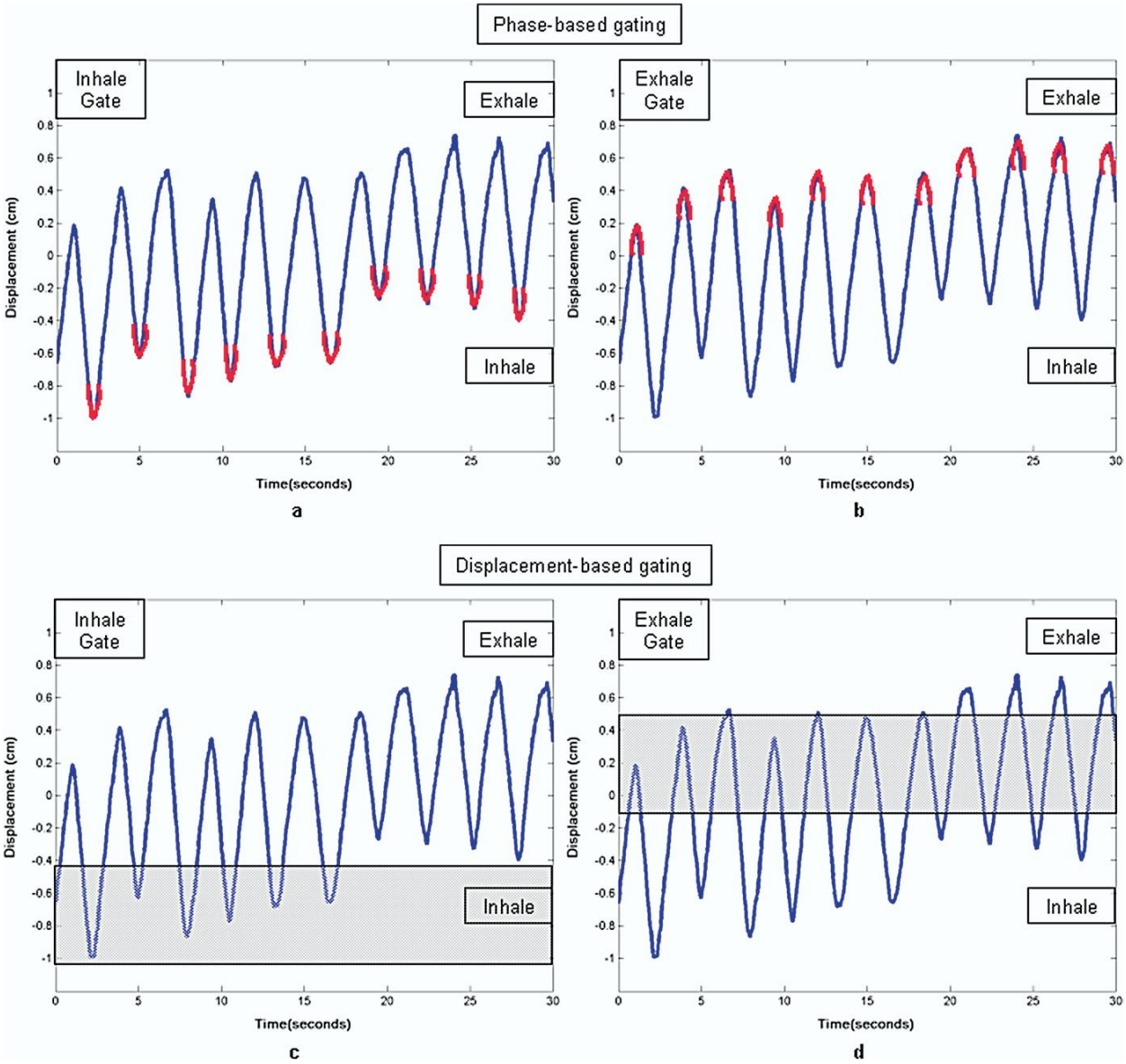


Figure 1-18. *Examples of phase-based and displacement-based gating for a respiratory signal exhibiting a baseline drift. From George, et al., (2006).*[111]

1.3.3. Tumour Tracking

Tumour tracking refers to monitoring the tumour itself (typically surrogates proximal to the tumour) during radiation treatment delivery. Tracking tumour motion during treatment delivery can further reduce the geometric uncertainties of tumour position that otherwise contribute to the expansion of treatment margins.[112, 113] Calypso, described in chapter 1.2.1.5.4., is one such example of tumour tracking, monitoring the beacons implanted proximal to the tumour during radiation treatment delivery.

However, there is inherent system latency in tumour tracking procedures. The tumour position is determined through either implanted beacons or real-time imaging, and this information is then interpreted and relayed to the linac which adjusts its MLCs in response to this information. The time required to perform these steps can accumulate to up to several hundred milliseconds,[72] during which time the tumour may have moved, potentially leading to incorrect targeting of the tumour. As such, prediction algorithms are utilised to overcome this system latency,[102, 114, 115] however, the accuracy of these prediction algorithms are compromised when respiratory motion is irregular.[73, 116-118] Figure 1-19 demonstrates the reduction of prediction accuracy with in the presence of respiratory irregularities.

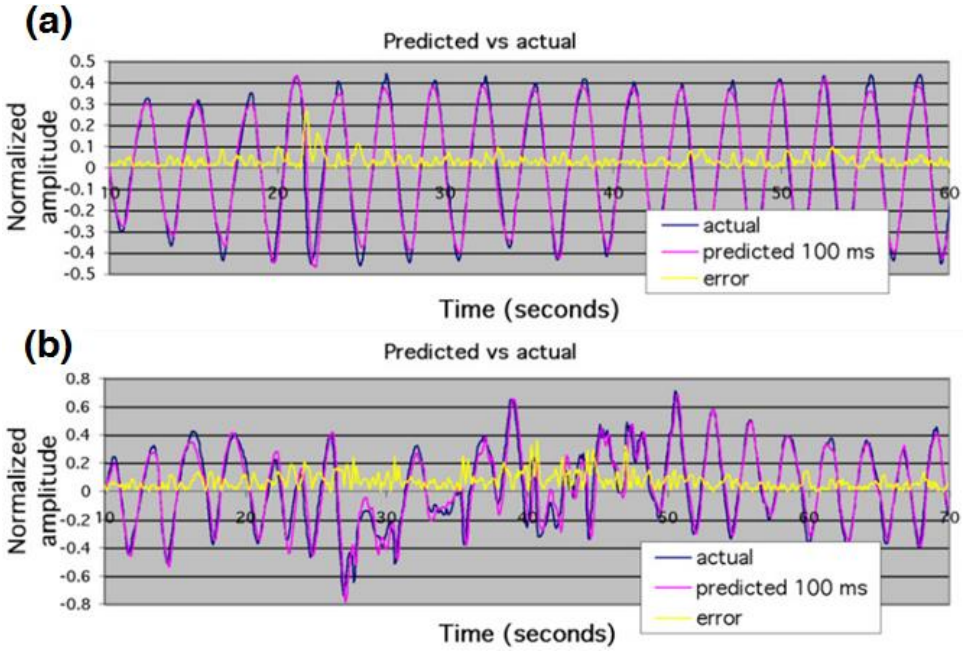


Figure 1-19. *Patient (blue) and predicted (purple) respiratory signals for (a) regular respiration, and (b) irregular respiration. Note when respiration is irregular, the error in prediction (yellow line) increases. Adapted from Murphy and Dieterich (2006).*[73]

1.4. Breathing Guidance in Radiation Therapy

Breathing guidance refers to a biofeedback system which measures patient respiration in real-time and simultaneously provides feedback to the patient on how to adjust their breathing to achieve the desired objective of either facilitating regular respiration or stable breath holds. Breathing guidance systems operate to minimise the deleterious impacts of irregular respiration outlined in chapter 1.3.1., chapter 1.3.2., and chapter 1.3.3..

1.4.1. Breathing Guidance Interventions

Table 1-1 details the range breathing guidance interventions utilised to facilitate regular breathing available in the published literature. Such breathing guidance interventions have demonstrated to improve breathing motion regularity of both external surrogates such as the Varian RPM,[111, 119, 120] in addition to internal anatomy[121] as well as the lung tumour itself.[122] However, much of the breathing guidance intervention investigations have not directly quantified the impact of regular breathing on radiation treatment accuracy. Despite imaging being performed in many of the studies presented in Table 1-1, the impact of breathing guidance on image quality has yet to be quantified. Further to this, there has not yet been a systematic review of the literature to thoroughly identify the gaps in the literature to indicate what the future direction of breathing guidance investigations should take.

The rows shaded blue in Table 1-1 indicate the development of studies investigating the audiovisual biofeedback breathing guidance intervention. The audiovisual biofeedback system is the most investigated breathing guidance intervention of all the interventions presented in Table 1-1.

Table 1-1. *Published studies investigating breathing guidance interventions to facilitate regular breathing. Table details study authors and year, participants recruited into the study, the nature of visual and/or audio prompts used to guide patient breathing, whether imaging or treatment was performed and an image of the intervention's display (if used).*

Study author (Year)	Participants	Visual prompt	Audio prompt	Imaging / Treatment
Vedam[123] & Kini[76] (2003)	5 lung cancer patients	Breathing signal & limits	Verbal commands	Fluoroscopy

Neicu (2006)[124]	5 healthy volunteers & 33 lung cancer patients	Breathing signal & limits	Verbal commands	4D-CT & treatment simulation
George (2006)[111, 125]	24 lung cancer patients	Breathing limits	Ascending & descending tones	None
Chen[126] (2007)	Phantom & 8 healthy volunteers	Cyclic moving pattern	None	IMRT delivered to phantom
Lim[120] (2007)	10 healthy volunteers	Breathing signal & waveguide	Verbal commands or tones	None
Haasbeek[127] (2008)	22 lung cancer patients	None	Verbal commands	4D-CT
Persson[128] (2008)	13 healthy volunteers	None	Verbal commands	None
Venkat[119] (2008)	10 healthy volunteers	Waveguide or bar-model	Ascending & descending tones	Venkat: None
Linthout[129] (2009)	25 lung & liver cancer patients	Breathing signal & limits	Verbal commands	Treatment delivery
Masselli[130] (2009)	10 healthy volunteers & 5 lung cancer patients	Breathing limits	None	None
Nakamura[131] (2009)	6 lung cancer patients	None	Verbal commands	Fluoroscopy
Cerviño[132] (2009)	15 healthy volunteers & 5 breast cancer patients	Breathing signal & limits.	None	None
Park[133] (2011)	10 healthy volunteers	Breathing signal & waveguide	Verbal commands	Simulated IMRT plan

Kim,[121] Pollock,[134] & Steel[135] (2012-2014)	15 healthy volunteers	Waveguide & breathing limits	Music which varies in speed	MRI
Damkjær[136] (2013)	24 breast cancer patients	Breathing limits	Verbal commands	CT
Lu[137] (2014)	13 lung & Liver cancer patients	Breathing limits	Ascending & descending tones	4D-CT
Lee[122] (2015)	9 lung cancer patients	Breathing limits	Music which fades to silence	MRI

1.4.2. Audiovisual Biofeedback

Audiovisual biofeedback is an interactive is an interactive and personalised respiratory guide which utilises audio and visual prompts to facilitate regular patient respiratory motion, thereby reducing respiratory irregularities, which is advantageous towards improved medical image quality and radiation treatment delivery. An example of an audiovisual biofeedback system is shown in Figure 1-20. As the patient breathes a marker block positioned mid-way between the xyphoid process and umbilicus move in the anterior-posterior (AP) direction. This marker block is monitored at a rate of 30 Hz by the Varian Real-time Position Management (RPM) system.[138] The AP motion information of the marker block, as tracked by the Varian RPM, is shown to the patient as a red ball moving vertically up and down on a display; anterior and posterior marker block motion on the patient's abdomen corresponds to up and down motion of the red ball on the patient display, respectively.

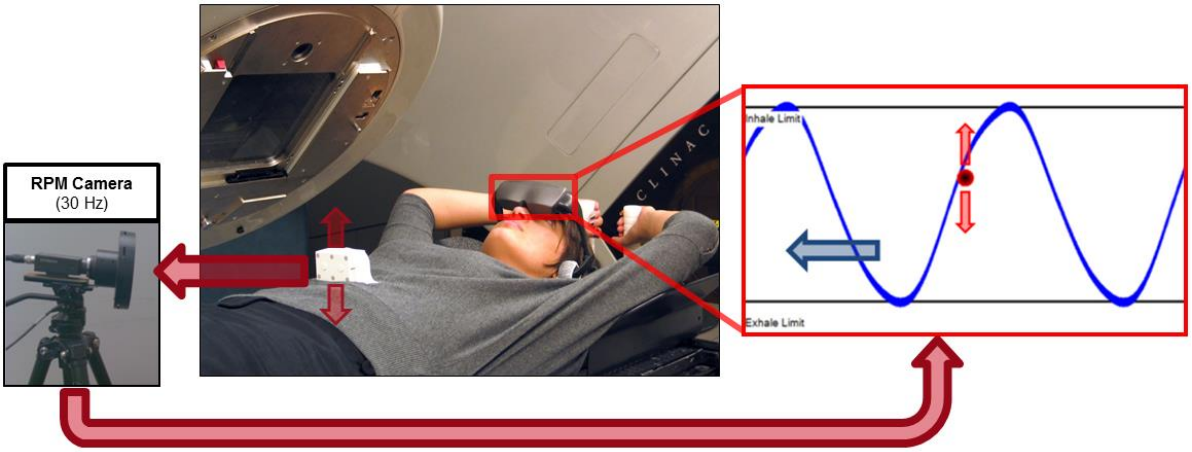


***Figure 1-20**. Feedback loop of audiovisual biofeedback, from the tracking of respiratory motion to the guiding interface shown to the patient.*

Also visible on the patient display is the inhale-exhale region indicated by two labelled black lines; there is also a blue wave moving from right-to-left across the patient display. It is the goal of the patient to adjust their breathing such that (1) the red ball traces the motion of the blue wave, and (2) keep the red ball within the inhale-exhale limits. The audio component was music which speeds up when the red ball deviates more than 15% from the blue guiding wave.

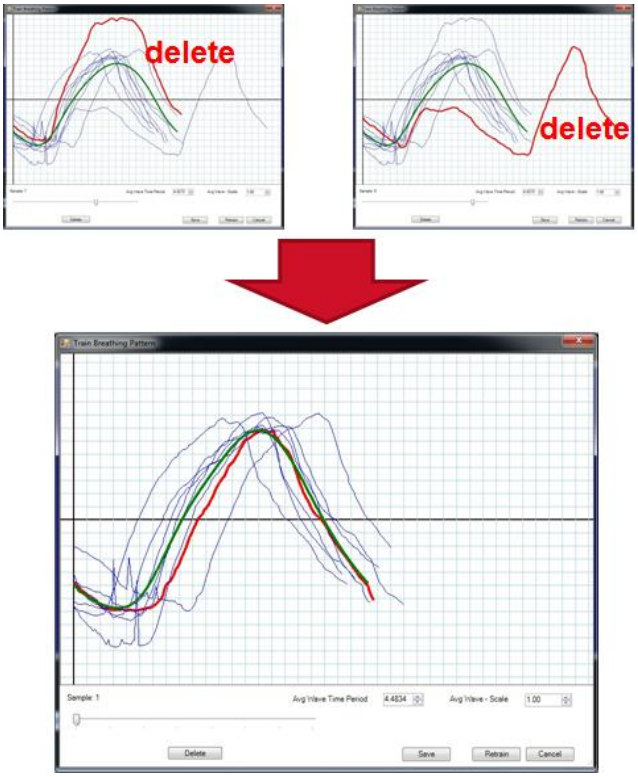


***Figure 1-21**. Deleting outlier respiratory cycles to produce the resultant guiding wave. Blue cycles indicate each individual respiratory cycle, the red cycle indicates which of the respiratory cycles has been selected for possible deletion, and the green cycle indicates the resultant guiding wave.*

This shape of this guiding wave is calculated from each patient's own breathing pattern. As described by Venkat, *et al.*,[119] a sample of respiratory cycles are acquired and a Fourier series fit is utilised to produce the resultant guiding wave. Should there be any outlier respiratory cycles amongst the collected ten, it is possible to delete them such that the resultant guiding wave is as indicative of the patient's natural breathing as possible. This process is shown in Figure 1-21. There are also options to alter the guiding wave's amplitude and period, if necessary.

Once this guiding wave has been saved, it is loaded for the patient's subsequent imaging and treatment sessions. This is to ensure that the patient is ideally reproducing the same respiratory motion for each fraction of treatment

1.4.2.1. Development of audiovisual biofeedback

While the use of audiovisual biofeedback has demonstrated positive results in previous cancer patient studies,[76, 111, 123] the development of the software and guiding interface from one generation to the next was largely conducted on healthy volunteers and motion phantoms.[119, 121, 139] When the updated version of the audiovisual biofeedback software was tested with cancer patients once again the results were less positive than those of previous findings,[140] indicating that patient acceptance of the updated guiding interface had declined.

The previous patient study utilizing the older version of audiovisual biofeedback software was conducted in 2004 at Virginia Commonwealth University (VCU);[111, 125, 141] their setup is shown below in Figure 1-22.

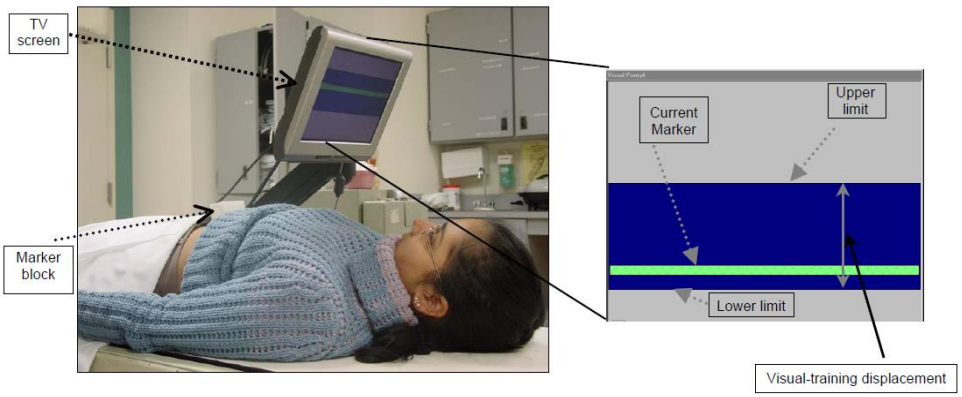


Figure 1-22. *Audiovisual biofeedback system used in the VCU study.*

The next audiovisual biofeedback study to recruit cancer patients was conducted in 2012 at Stanford University;[142, 143] their setup is shown below in Figure 1-23.

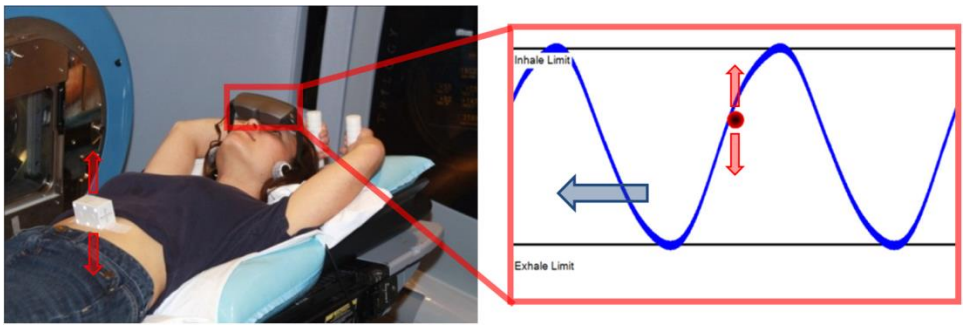
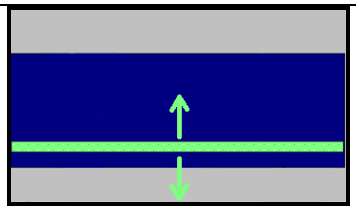
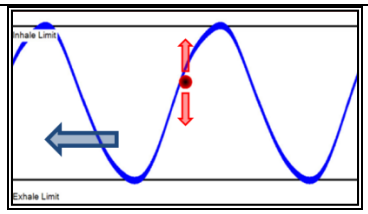


Figure 1-23. *Audiovisual biofeedback system used in the Stanford study.*

Table 1-2 summarises the differences between the two versions of audiovisual biofeedback used in these two studies, as well as differences in study design and conduct.

Table 1-2. *Comparison of the nature and conduct of the two patient studies.*		
	VCU, 2004	**Stanford, 2012**
Guiding interface		
Visual component	• Breathing surrogate (green bar) moving vertically between breathing limits. • Patient adjusts breathing to keep green bar within the breathing limits (blue area).	• Breathing surrogate (red ball) moving vertically between breathing limits and moving guiding wave (blue wave). • Patient adjusts their breathing to keep the red ball within the breathing limits and trace the motion of the moving guiding wave
Audio component	• Ascending and descending tones for inhalation and exhalation, respectively	• Music speeds up should the red ball deviate more than 15% from the guiding wave
Study characteristics	• Number of patients: 24 • Average breathing session length: 4 minutes • Number of breathing sessions: 5 • Visual modality: Monitor screen • Imaging performed: none	• Number of patients: 10 • Average breathing session length: 19 minutes • Number of breathing sessions: 1 • Visual modality: display goggles • Imaging performed: 4D PET/CT
Study results	• Significantly positive. • Breathing regularity significantly improved due to breathing guidance.	• Non-significant. • No overall improvement in breathing regularity.

The main factors distinguishing these two studies were:

(1) the audiovisual biofeedback system utilised in the Stanford study involved more audio and visual prompts than the one utilised in the VCU study

(2) the length of time the patients were using audiovisual biofeedback (4 minutes in VCU study compared to 19 minutes in the Stanford study). This is due to the additional time required to perform 4D PET/CT imaging in the Stanford study

(3) the number of patients in each of the studies

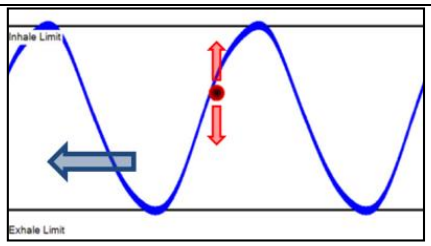
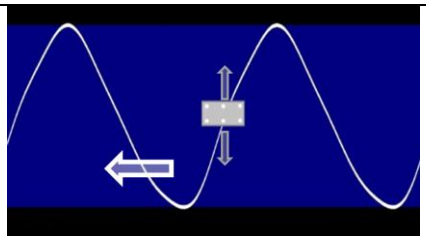
Points (1) and (2) directly relate to the patient using audiovisual biofeedback, and following a more complex audiovisual biofeedback for longer period of time may have led to higher patient fatigue and a decrease in patient compliance,[144] as evidenced by the less regular breathing yielded in the Stanford study. A decrease in patient compliance means that in the Stanford study the audio prompt of the music speeding up would have been triggered more often making the audiovisual biofeedback session a more unpleasant experience.

The use of the guiding wave in volunteer studies has produced significant improvements in breathing regularity,[119, 121] in addition to image quality,[139] and motion prediction accuracy.[134] So rather than remove the guiding wave aspect of audiovisual biofeedback, an investigation into the nature of information delivered to the patient was undertaken. Audiovisual biofeedback utilises audio and visual information delivered to the patient which are designed to prompt them when their breathing has become irregular, in addition to also prompting them when their breathing has become regular again. Audiovisual biofeedback uses the audio prompts to inform the patient about the nature of their breathing; the music speeds up, and sounds unpleasant, to inform them that they have deviated from the guiding wave by over 15%. The music returns to a normal speed once the red ball is within 15% of the guiding wave again. To phrase this in terms of learning and behaviour, when a response (deviating from the guiding wave) is followed by an adverse stimulus (sped up, unpleasant music), this is a form of punishment, positive punishment, specifically.[145] This is designed to be followed by a second set of response and stimulus; when a response (adjust breathing to follow guiding wave again) is followed by the removal of an adverse stimulus (unpleasant music), this is negative reinforcement.[145, 146]

A number of studies have detailed the superior efficiency of learning by using positive reinforcement over punishment and negative reinforcement.[146-149] Such considerations of superior learning methods were taken into account in redesigning the audio and visual components of a version of audiovisual biofeedback more easily tolerated by patients.

The differences between the Stanford version and the updated University of Sydney version are outlined below in Table 1-3.

Table 1-3. *Comparison of the version of AV biofeedback used in the Stanford study and the latest University of Sydney version.*

	Stanford, 2012	University of Sydney, 2013
Guiding interface		
Visual component	• Inhale-exhale limits • Guiding wave • Breathing motion surrogate: red ball • White background	• Inhale-exhale region (blue area) • Guiding wave • Breathing motion surrogate: grey block, similar in appearance to RPM block • Blue background
Audio component	• Midi-files. • Speeds up when red ball deviates from guiding wave	• Mp3-files. • Music fades to silence when grey block moves outside blue area
Response	• Deviating from the guiding wave • Returning to the guiding wave	• Deviating from the blue area • Returning to the blue area
Stimulus	• Sped-up music introduced • Sped-up music removed	• Music removed • Music re-introduced

In the updated University of Sydney version, a response (deviating from the blue region) being followed by the removal of a positive stimulus (music) is referred to as response cost; then another response (returning to the blue region) is followed by the appearance of a positive stimulus (music), this is a form of positive reinforcement.[145] The focus of the response and stimulus relationship was also shifted from following the guiding wave in the Stanford version to staying within the blue area in the University of Sydney version. This is because controlling breathing amplitude is considered more clinically beneficial compared to controlling breathing period.[21, 107, 150, 151] The breathing surrogate used in the visual component was changed from a red ball to the image of an RPM marker block (the real marker block can be seen on the subject's abdomen in Figure 1-23). This was done to better inform the patient of the source of breathing motion being displayed to them. The colour scheme was also altered to appear mainly blue due to the reinforcing and positive emotions studies have found it to be associated with.[152, 153] The colour scheme was also altered in order to reducing eye-strain compared to the white background present in the Stanford version to assist making prolonged breathing sessions more tolerable. The current generation of audiovisual biofeedback utilised in the studies presented in this thesis is shown in Figure 1-24.

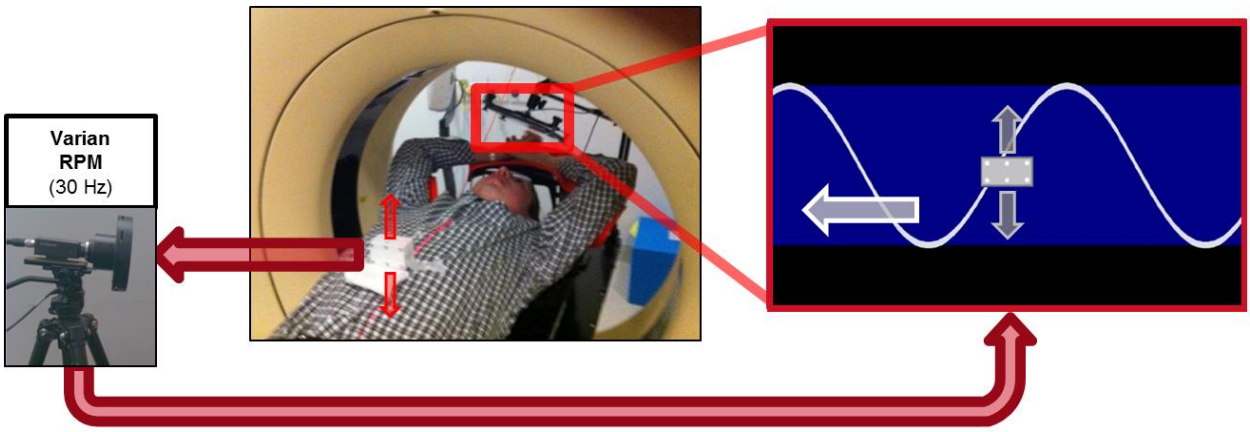


***Figure 1-24**. Updated audiovisual biofeedback system utilizing the most recent version of the guiding interface.*

For the updated version of audiovisual biofeedback, visible on the patient display is the inhale-exhale region indicated by the blue area in addition to the white guiding wave moving from right-to-left across the patient display. It is the goal of the patient to adjust their breathing such that (1) keep the grey block within the blue area, and (2) trace the motion of the guiding wave. The audio component is classical music which fades to silence should the grey block move outside the blue area.

1.5. Summary of literature review and unmet areas of research

Radiation therapy is a valuable and cost-effective method of cancer treatment. However, when the tumour target is highly mobile, as is the case with abdominal and thoracic cancers largely due to breathing motion, additional motion management measures are utilised to counter the additional margins and potential treatment inaccuracies introduced by these moving tumour targets. Further to this, irregular breathing motion has a deleterious impact on cancer radiation therapy, exacerbating systematic and random errors in addition to reducing the effectiveness of motion management strategies and technologies. To further complicate the situation, in the case of abdominal tumours, pre-treatment and 4DCT imaging is incapable of discriminating the tumour from the soft tissue.

One method to minimise breathing motion irregularities are breathing guidance interventions. These interventions refer to a biofeedback system which measures patient respiration in real-time and simultaneously provides feedback to the patient on how to adjust their breathing to achieve the desired objective of stable and regular respiration. The most thoroughly researched breathing guidance intervention to date, audiovisual biofeedback, has demonstrated to improve breathing regularity of motion surrogates, internal anatomy, and the lung tumour itself, but has yet to be utilised during patient radiation treatment nor has its impact of medical image quality been quantified. The gap in the literature lies in patient radiation therapy and imaging studies, however, a systematic review has yet to be performed to more conclusively indicate this direction of investigation.

1.5.1. Aims of this project

The aims of this thesis are:

1. To critically appraise the literature in terms of the use of breathing guidance interventions in the fields of radiation oncology and radiology via systematic review
2. To quantify the impact of audiovisual biofeedback breathing guidance on 4DCT, the primary imaging modality utilised to plan radiation therapy for highly mobile tumours
3. To assess the impact of audiovisual biofeedback on patient breathing over a course of radiation therapy
4. To utilise the findings of the above aims to design and implement a novel and comprehensive clinical trial investigating the use and impact of audiovisual biofeedback in radiation therapy

5. To explore the next stages of audiovisual biofeedback in terms of translating evidence into broader clinical use through the commercialisation process

1.5.2. Presentation of thesis

This thesis is presented as a combination of one systematic review and one published paper as their own chapters, with a published case report and study protocol forming subsections within chapters. The chapter presentation of this thesis will largely follow the aims detailed above in chapter 1.5.1., with each results chapter addressing one of the aims, following them sequentially. Chapter 1 (this chapter) provides a background to cancer radiation therapy, and the deleterious impact of irregular patient breathing on cancer radiation therapy procedures before introducing audiovisual biofeedback breathing guidance as an intervention to minimise these deleterious impacts. Some background on audiovisual biofeedback is also provided in addition to recent developments towards the audiovisual biofeedback system utilised in the investigations presented in this thesis.

Chapter 2 reports on the systematic review into the use of breathing guidance interventions in the fields of radiation oncology and radiology. Radiology was also included in this systematic review because certain radiology imaging modalities such as MRI and PET/CT are being utilised in emerging hybrid radiation treatment technologies such as the MRI-linac[154] in addition to the use of PET/CT in radiation treatment planning.[155] This systematic review was published in Medical Physics. Chapter 2 addresses aim 1, detailed in chapter 1.5.1..

Chapter 3 reports, quantitatively, on the impact of audiovisual biofeedback on 4DCT image quality. This study utilised lung cancer patient data from an MRI study to program the motion of a digital phantom prior to simulating 4DCT imaging. The 4DCTs were analysed utilising a range of image quality metrics in addition to noting the treatment time and imaging dose. This chapter also tests and compares the impact of prospective respiratory gating on 4DCT image quality. These results were published as a paper in Physics in Medicine and Biology. Chapter 3 addresses aim 2, detailed in chapter 1.5.1..

Chapter 4 reports on the impact of audiovisual biofeedback on breathing motion of an external motion surrogate and implanted radio-opaque markers of liver cancer patients over the course of stereotactic body radiation therapy (SBRT). Breathing motion was analysed in terms of the consistency of breathing displacement and period, the correlation between internal and external breathing signals, and the agreements of breathing motion between 4DCT and each treatment fraction. This study also utilised a

screening procedure; after patients were recruited into the study, a screening procedure was performed to determine which breathing condition would be utilised over their course of SBRT, free breathing or audiovisual biofeedback. This was the first investigation to utilise a screening procedure in addition to being the first to utilise breathing guidance over the course of SBRT. A case report, reporting on the first patient recruited into this study, was published The Journal of Medical Imaging and Radiation Oncology and is included as a subsection of Chapter 3's results. Chapter 4 addresses aim 3, detailed in chapter 1.5.1..

Chapter 5 reports on a retrospective analysis of the previous audiovisual biofeedback lung cancer patient study, the findings of which were utilised to design and determine the statistics of the most comprehensive breathing guidance study to date: a randomised, stratified, multi-site, phase II clinical trial investigating audiovisual biofeedback over the course of lung cancer radiation therapy. Chapter 5 is presented in two parts: (1) retrospective analysis of previous lung cancer patient study, and (2) the design and initiation of the randomised clinical trial. The clinical trial's study protocol was published in BMC Cancer and is included in as a subsection of Chapter 5's Methods section reporting on the design of the clinical trial. Chapter 5 addresses aim 4, detailed in chapter 1.5.1..

Chapter 6 builds upon the findings of the translational research presented in Chapters 3, 4, and 5 by reporting on the commercial pathway of the audiovisual biofeedback technology. Chapter 6 reports on the radiation oncology market, existing technologies, the value proposition that audiovisual biofeedback can contribute to this market, and the milestones to achieve to move this technology forward. Chapter 6 also details how these commercial insights impact the design and function of the audiovisual biofeedback technology and the validation testing that has been conducted around this. Chapter 6 addresses aim 5, detailed in chapter 1.5.1..

Chapter 7 summarises and provides conclusions of the research reported on in Chapters 2 – 6 in addition to providing details on future work.

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CHAPTER 2

Breathing guidance in radiation oncology and radiology: A systematic review of patient and healthy volunteer studies

This chapter contains the review paper titled “Breathing guidance in radiation oncology and radiology: A systematic review of patient and healthy volunteer studies” which has been published in *Medical Physics* (2015; **42**(9) 5490-5509)

Breathing guidance in radiation oncology and radiology: A systematic review of patient and healthy volunteer studies

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Purpose: The advent of image-guided radiation therapy has led to dramatic improvements in the accuracy of treatment delivery in radiotherapy. Such advancements have highlighted the deleterious impact tumor motion can have on both image quality and radiation treatment delivery. One approach to reducing tumor motion irregularities is the use of breathing guidance systems during imaging and treatment. These systems aim to facilitate regular respiratory motion which in turn improves image quality and radiation treatment accuracy. A review of such research has yet to be performed; it was therefore their aim to perform a systematic review of breathing guidance interventions within the fields of radiation oncology and radiology.
Methods: From August 1–14, 2014, the following online databases were searched: Medline, Embase, PubMed, and Web of Science. Results of these searches were filtered in accordance to a set of eligibility criteria. The search, filtration, and analysis of articles were conducted in accordance with preferred reporting items for systematic reviews and meta-analyses. Reference lists of included articles, and repeat authors of included articles, were hand-searched.
Results: The systematic search yielded a total of 480 articles, which were filtered down to 27 relevant articles in accordance to the eligibility criteria. These 27 articles detailed the intervention of breathing guidance strategies in controlled studies assessing its impact on such outcomes as breathing regularity, image quality, target coverage, and treatment margins, recruiting either healthy adult volunteers or patients with thoracic or abdominal lesions. In 21/27 studies, significant ($p < 0.05$) improvements from the use of breathing guidance were observed.
Conclusions: There is a trend toward the number of breathing guidance studies increasing with time, indicating a growing clinical interest. The results found here indicate that further clinical studies are warranted that quantify the clinical impact of breathing guidance, along with the health technology assessment to determine the advantages and disadvantages of breathing guidance.
 [http://dx.doi.org/10.1118/1.4928488]

Key words: motion management, breathing guidance, systematic review, radiation oncology, radiology

1. INTRODUCTION

The advent of image-guided radiation therapy (IGRT) has led to dramatic improvements in the accuracy of treatment delivery in radiotherapy, with the reduction of both random and systematic uncertainties.[1–6] While IGRT has improved the accuracy of radiotherapy by utilizing information about tumor motion and positioning throughout a patient's treatment, it has also shed light on the deleterious impact tumor motion can have on both image quality and radiation treatment delivery.[2,4,7–10] Anatomic motion due to breathing in the thoracic and abdominal regions is of great concern due to their proximity to the thoracic diaphragm, where respiratory-induced motion can be up to 5 cm.[11] In addition, heightened patient anxiety levels during imaging and treatment,[12,13] can result in increasingly irregular breathing, leading to erratic breathing motion of both internal anatomy and the tumor itself.[8,14,15]

The widespread utilization of IGRT has led to the investigation of an increasing number of methods to address breathing motion and therefore tumor and organ movement and the resultant uncertainties they cause. A number of image reconstruction methods and tracking systems have been developed to ameliorate these uncertainties.[16–19] However, such techniques can be expensive and do not directly manage the problem of irregular breathing motion. Addressing irregular tumor motion directly at the source by managing the patients' breathing has been of increasing interest in recent times, with several breathing guidance techniques being developed from simple buzzer signals to interactive guiding interfaces to facilitate regular and predictable tumor motion.

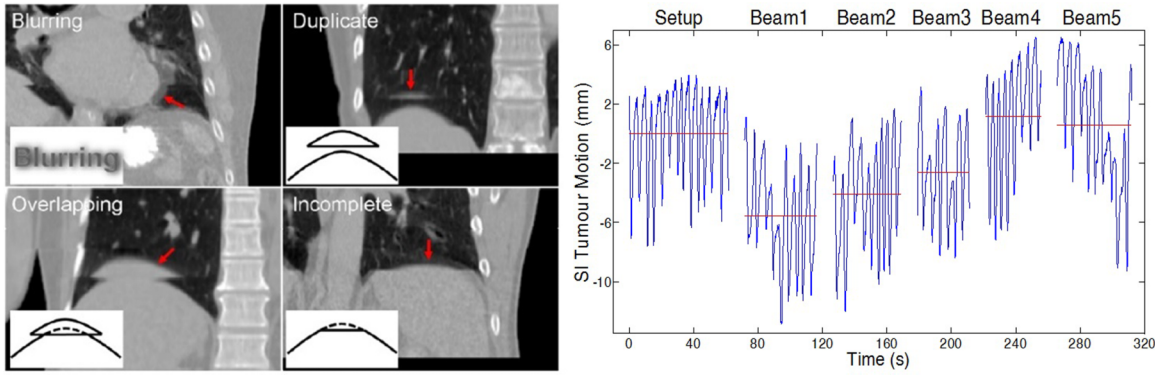


FIG. 1. Left: Examples of 4D-CT image artifacts due to irregular breathing [Reprinted with permission from Yamamoto *et al.*, "Retrospective analysis of artifacts in four-dimensional CT images of 50 abdominal and thoracic radiotherapy patients," Int. J. Radiat. Oncol., Biol., Phys. **72**(4), 1250–1258 (2008). Copyright 2008 by Elsevier]. Right: Example of irregular respiratory-induced tumor motion during treatment setup and delivery [Adapted with permission from Worm *et al.*, "Variations in magnitude and directionality of respiratory target motion throughout full treatment courses of stereotactic body radiotherapy for tumors in the liver," Acta Oncol. **52**, 1437–1444 (2013). Copyright 2013 by Informa Healthcare].

1.A. Irregular breathing in radiation oncology and radiology

The deleterious impact of irregular motion during image acquisition has been well documented for across a range of medical imaging modalities.[8,14,20–28] During radiation treatment, there are two fundamental types of errors: the errors occurring during treatment preparation (systematic) and the errors occurring during treatment delivery (random);[5,29–31] both these types of errors are exacerbated by irregular breathing motion.[9,10,27]

Systematic errors typically arise from errors in the images used to plan the patient's treatment; Fig. 1 demonstrates the irregular tumor motion and errors present in images due to such irregular breathing motion.

Random errors typically arise from variations in target position throughout the patient's treatment. Irregular breathing leads to larger variations in target position not only during treatment but also between treatments,[9,10] as shown in Fig. 2.

To account for irregular breathing motions' exacerbation of systematic and random errors, the treatment volume is expanded;[32] increasing radiation dose to the healthy surrounding tissue thus increasing the risk of post-treatment radiation complications such as radiation pneumonitis.[33–39] Such complications occur in over 60% of lung cancer patients after treatment, with 47% developing at least grade 2 pneumonitis requiring clinical intervention.[34] Such clinical interventions involve the prescription of anti-inflammatory pharmaceuticals thereby increasing healthcare costs for that patient's course of treatment.[36,40] To combat the increase of these systematic and random errors, a number of strategies directly engaging with the patient have been investigated to minimize the irregularity of patient breathing motion. These breathing guidance strategies have the advantage of being noninvasive, requiring minimal modifications to existing facilities and protocols.

Given the relatively recent widespread interest in such breathing guidance strategies, a review of such research has yet to be performed. It was therefore our aim to perform the first systematic review of breathing guidance intervention strategies within the fields of radiation oncology and radiology.

2. METHODS

This systematic review follows the preferred reporting items for systematic reviews and meta-analyses (PRISMA)-statement reporting standard.[41] Table I presents our research questions in the patients, intervention, comparison, outcome, study design (PICOS) approach; given the relatively recent

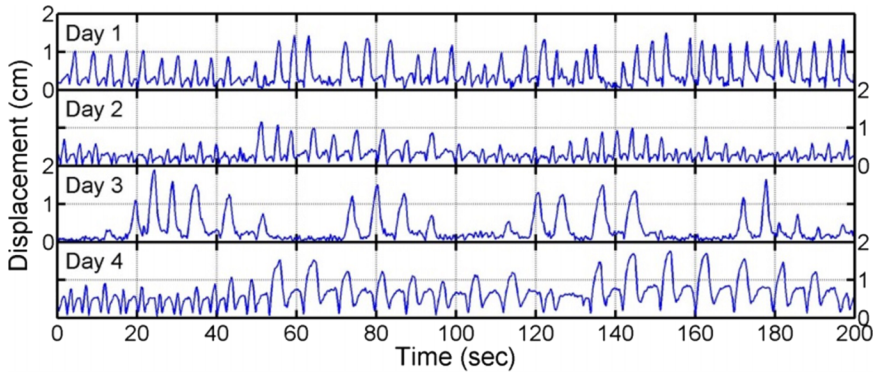


FIG. 2. Example of interfraction breathing variations [Adapted with permission from Shah *et al.*, "Real-time tumor tracking in the lung using an electromagnetic tracking system," Int. J. Radiat. Oncol., Biol., Phys. **86**, 477–483 (2013). Copyright 2013 by Elsevier].

TABLE I. PICOS approach to the systematic review following the PRISMA statement.

P—patients/participants	• Cancer patients with tumors affected by breathing motion (e.g., thoracic and abdominal tumors) receiving radiotherapy and/or medical imaging • Healthy volunteers participating as surrogates for the above patient population
I—intervention	Breathing guidance—technologies which monitor patient breathing and provide feedback to the patient informing them on how to adjust their own breathing in real time on their own accord
C—comparison	No breathing guidance of the same breathing type (i.e., nonguided breath-holds for breath-hold studies and free breathing for breathing guidance studies)
O—outcome	Regularity of breathing signal and anatomic/tumor motion, medical image quality, radiation treatment margins and coverage, medical imaging, and radiation treatment times
S—study design	Quantitative and controlled prospective or retrospective trials

interest in such breathing guidance strategies, healthy volunteer studies were also considered in addition to patient studies.

Once eligible articles were identified, they were filtered in accordance to the selection criteria. The objective of the selection criteria was to acquire scientific articles describing in sufficient detail a breathing guide intervention's utilization toward some aspect of abdominal or thoracic radiology and radiotherapy application. Articles were extracted by two authors using an electronic (Microsoft EXCEL 2010) pro forma specifying the identified articles. Where there was disagreement between the reviewers, discussion was undertaken among all authors until consensus was reached.

2.A. Selection criteria

Articles were included if they satisfied the following inclusion criteria:

(1) Quantitatively evaluate the intervention of breathing guidance relevant to the practice of either medical imaging or thoracic/abdominal radiotherapy (prospective or retrospective).
(2) Participants were human over the age of 18 (retrospective data were from adult human study).
(3) Reported in the English language.
(4) Published in a peer-reviewed journal between the years 1994–2014.
(5) Had a control group for the same breathing type:
    - For guided breathing studies, control group performed unguided free breathing.
    - For guided breath-hold studies, control group performed unguided breath-holds.

Articles which excluded, even if satisfying the above inclusion criteria, if they

(1) did not have a control group comparing intervention to no intervention for the same breathing type (free breathing *or* breath-hold),
(2) lacked a statement of statistical significance,
(3) did not describe, or reference to an article, in sufficient detail of the breathing guidance intervention,
(4) was not a scientific paper (e.g., conference abstract, conference proceeding, book, patent).

2.B. Search strategy

From August 1–14, 2014, the following online databases were searched: Medline, Embase, PubMed, and Web of Science. The search for articles initially included the fields of radiation oncology and radiology using the terms: (radiation therapy OR radiotherapy OR imaging). These search results were then refined toward breathing guidance by using the terms: (respiration OR breathing) AND (audio OR visual) AND (guidance OR training OR feedback OR biofeedback).

The findings from the above mentioned databases in addition to articles identified through hand searching of their reference lists and cross-referencing for previously unidentified articles which met the inclusion criteria. These articles were exported to a citation manager, Endnote X5 where duplicate articles were also removed. The process tree for attaining the search strategies results in shown in Fig. 3. After duplication and filtering through the selection criteria, five articles identified by this hand searching method made it into the final 27 articles.

Information extracted from each included article included (1) purpose of intervention (breath-holds, regular breathing); (2) study participants [healthy volunteers and/or patients, number recruited, disease type (if patients)]; (3) nature of audio prompt (verbal, tones, music); (4) nature of visual prompt (breathing limits, guiding-wave, etc.); (5) imaging performed (if any); (6) treatment performed (if any); (7) main findings of intervention strategy compared to control group; (8) visual display of intervention (if any).

2.C. Analysis of articles

Due to the diverse applications and results used to determine the efficacy of breathing guidance strategies, a meta-analysis was not performed; however, the main findings from each of these articles were organized in terms of statistical significance: achieving positive significant results, nonsignificant results, or negative results.

Quality assessment scoring of the identified and included articles was also performed in accordance with the *Standard*

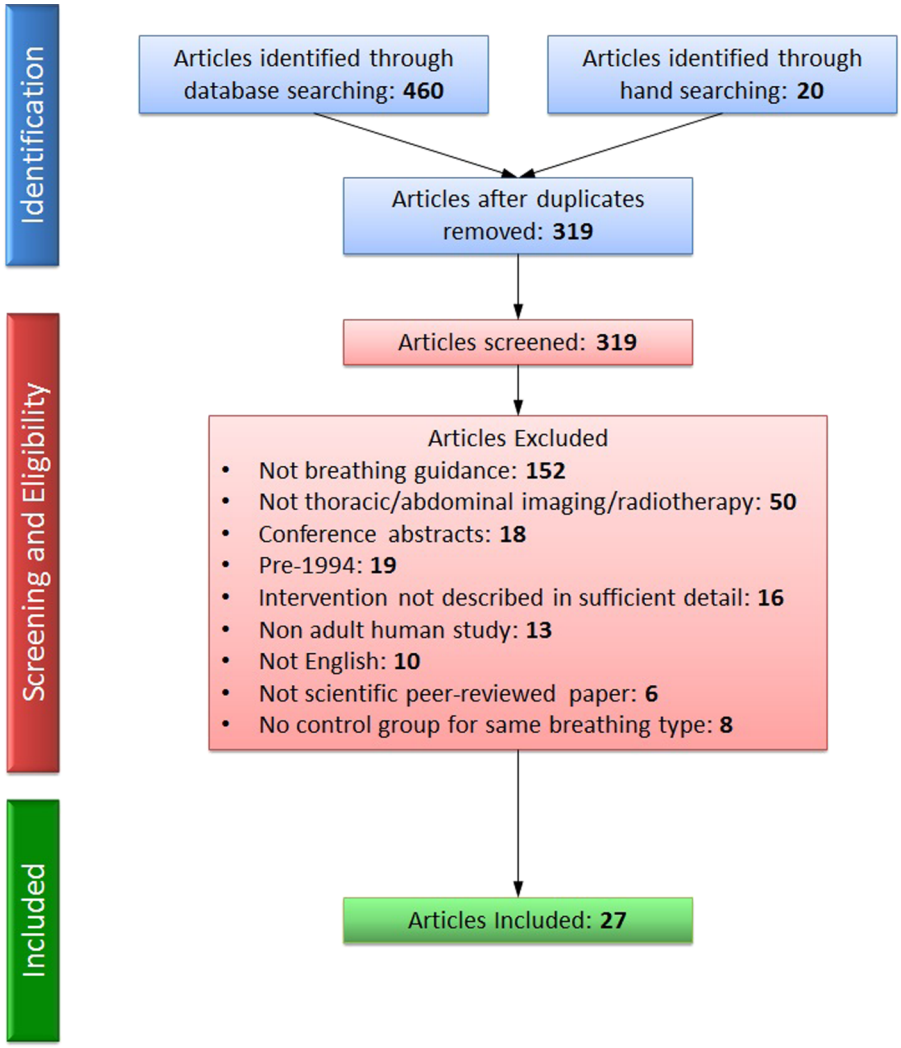


FIG. 3. Search strategy results. Screening and eligibility based on inclusion and exclusion criteria.

Quality Assessment Criteria for Evaluating Primary Research Papers From a Variety of Fields.[42] Quality assessment score is given based on 14 questions about the article, the reviewers award yes (2 points), partial (1 point), and no (0 points) or not applicable (N/A—question not counted in score). Overall, a score out of 28 (or less if N/A is chosen) is found and then converted to a percentage. Articles were scored by two authors, and when discrepancies arose in the scores allocated, a discussion was then undertaken until a consensus was reached.

3. RESULTS

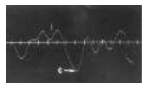
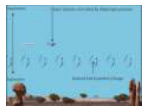
Twenty-seven articles were included as a part of this systematic review as shown in Fig. 3. After duplication and filtering through the selection criteria, four articles identified by this hand searching method made it into the final 27 articles. Tables II–V detail the development of such strategies over the past 20 yr, in addition to the quality assessment score of each article. The average quality assessment score was 79% (range: 54%–95%). Figure 4 also illustrates the timeline of these studies.

Table VI is an assembly of these 27 articles' findings and whether their results were significantly positive, negative, or nonsignificant. It should be noted that the number of outcomes exceeds the number of identified articles because most articles investigated more than one outcome.

4. DISCUSSION

Findings from the 27 identified articles yielded a diverse range of breathing guidance intervention strategies being utilized on a range of different cancer types. Breathing guidance strategies ranged from buzzer signals to customized, interactive guides. Of the 27 included articles in this systematic review, 21 yielded at least one statistically significant positive outcome from the use of breathing guidance, with a further 2 articles reporting nonsignificant improvements (or not reporting the significance of improvements) from the use of breathing guidance and 4 articles reporting at least one statistically significant negative result. Of the four studies that yielded negative results, three investigated audio-only guidance, which resulted in larger breathing motion amplitudes, an undesirable trait in most radiation oncology and radiology

TABLE II. Details of radiology breathing guidance studies.

Study author (Year)	Purpose of intervention	Participants	Visual prompt	Audio prompt	Imaging/ treatment	Breathing motion sensor	Quality assessment score (%)	Display
Wang (1995) (Ref. 43)	Breath-holds	11 healthy volunteers	None	Buzzer tone	MRI	Bellows belt	54	No display used
Locklin (2007) (Ref. 44)	Breath-holds	16 cancer patients	Breathing signal	None	CT	Bellows belt	75	
Okada (2009) (Ref. 45)	Regular breathing and breath-holds	13 healthy volunteers	Breathing signal	None	MRI	MRI navigator echo	88	
Jhooti (2011) (Ref. 46)	Regular breathing	10 healthy volunteers	Video game-type interface	None	MRI	MRI navigator echo	79	

procedures.[22,62,70–75] Of the findings assembled in Table VI, 63 were positive statistically significant, 82 were nonsignificant (or significance not reported), and 7 were negative statistically significant. It should be noted that of the 82 nonsignificant (or significance not reported) results, 35 noted improvements from the use of breathing guidance, 12 of which were reported to be nonsignificant, and 23 did not report the significance.

Of the 27 identified articles, 12 were healthy volunteer studies and 12 were patient studies, with 3 studies recruiting both healthy volunteers and patients; the most investigated cancer type was lung cancer (12 studies), followed by breast (2 studies) and liver cancer (2 studies). Of the breathing guidance intervention strategies, most were designed to facilitate regular breathing (21 articles); 4 articles detailed breath-hold guidance, 1 study investigated both regular breathing and breath-hold guidance, and 1 study investigated quasibreath-hold breathing guidance where each exhale was extended to 3, 5, or 7 s. Medical imaging was performed in 15 studies, and radiation treatment was performed (or simulated) in 4 studies. Given these numbers, and as evident from Table VI, there are areas of breathing guidance which require more investigation. For example, research into the impact of breathing guidance on radiation treatment margins and target coverage is limited and largely inconclusive, with all results thus far being nonsignificant. Further investigation into this area would be valuable as such findings would also give insight into the impact of breathing guidance strategies on patient outcomes. Further to this, of the 27 identified articles, none were randomized studies, indicating that future study designs should incorporate randomization.

Twenty of the 27 identified articles did not explicitly control for confounding; however, the authors of this review paper did not consider this to bias their results. Of the 27 articles, none declared any conflicts of interest; however, two articles acknowledged at least partial funding from either Phillips (Lu *et al.*)[69] or VisionRT (Cerviño *et al.*),[63] and two articles acknowledged research agreements with either Varian Medical Systems (Persson *et al.*)[57] or Phillips Medical Systems [Locklin *et al.* (2007)]. However, these articles received positive quality assessment scores, as such the authors of this review paper did not consider the results presented in these articles to be biased.

4.A. Breathing guidance for breath-holds

Breath-holds are a well-documented and frequently utilized strategy for minimizing anatomic motion during imaging and treatment.[43,63,68,76–84] To further improve the efficacy and reproducibility of breath-holds, measures have been taken to provide guidance to the patient to maintain breath-hold stability.[43,44,68,85] Wang utilized a buzzer signal to prompt patients to perform their breath-hold; such simple additions in this MR imaging study resulted in improved consistency of breath-holds resulting in achieving their goal of improving image quality.[43] Locklin investigated a more-comprehensive guidance system by showing the patient their own breathing signal as well as the intended breath-hold level.[44] These studies also resulted in improved image quality and intrafraction motion management.

Breathing guidance has also been developed for deep-inspiration breath-holds (DIBH).[63,68] DIBH is often performed by the patient in left breast cancer radiotherapy to minimize the radiation damage to the lung and heart.[79,80,82,83,86] Given the increased difficulty in achieving deep-inspiration and maintaining it for the adequate duration of imaging and treatment, DIBH an attractive technique to implement with a breathing-guidance strategy. The use of breathing guidance for DIBH improved the consistency of breath-holds as demonstrated by Cerviño, leading to an increased sparing of organs at risk in breast radiation therapy, as demonstrated by Damkjær.[63,68]

4.B. Breathing guidance for regular breathing

While breath-holds have positively impacted imaging and radiotherapy, they can be taxing on the patient who often

TABLE III. Metrics and results of radiology breathing guidance studies.

Study author (Year)	Metric(s) used	Result(s)
Wang (1995) (Ref. 43)	Standard deviation of superior–inferior (SI) position of cardiac structures	• Without breathing guidance: Standard deviation of right coronary artery SI position was 2.0 mm[a] • Breathing guidance: Standard deviation of right coronary artery SI position was 0.9 mm[a]
	Slice misregistration	• Without breathing guidance: The total number of slices was 35 • Breathing guidance: The total number of slices was 19, much less than no breathing guidance[b] • Total number of breath-holds needed reduced by almost a factor of 2[b]
	Improving image quality	• With breathing guidance, there were less missing cardiac structures[b] • Image quality improved in six (of eight) subjects whose image quality was evaluated by a radiologist and a physicist[a]
Locklin (2007) (Ref. 44)	Standard error of the mean (SEM) of breath-hold position readings	• With breathing guidance: ◦ SEM reduced for inspiratory breath-holds ($p = 0.0693$)[c] ◦ SEM reduced for expiratory breath-holds ($p = 0.0083$)[d] ◦ SEM reduced for midbreath breath-holds ($p = 0.053$)[c]
Okada (2009) (Ref. 45)	Five point grading system of image quality by assessors	• Worse scores were observed for breathing guidance compared to free breathing ($p < 0.05$)[d] ◦ Of the 15 coronary artery segments that were scored, 5 were scored significantly worse for breathing guidance ◦ Of the 15 coronary artery segments that were scored, none were scored significantly better for breathing guidance
	Scan time	• Free breathing: Mean scan time was 10.0 ± 2.2 min • Breathing guidance: Mean scan time was 10.0 ± 2.5 min, no significant difference compared to free breathing[c]
Jhooti (2011) (Ref. 46)	Respiratory efficiency (the minimum time required to acquire a full dataset within a 5 mm range of respiratory motion)	• Free breathing: Respiratory efficiency was 45% • Breathing guidance: Respiratory efficiency was 56%, significantly improved over free breathing ($p = 0.006$)[d]
	Scan time	• Free breathing: Scan time was 7 min 44 s • Breathing guidance: Scan time was 5 min 43 s, significantly shorter than free breathing ($p = 0.026$)[d]
	Image quality	• No different in image quality[c]

[a]No p-value, no statement of significance.
[b]No p-value, but significance stated.
[c]$P \geq 0.05$ (nonsignificant).
[d]$P < 0.05$ (significant).

has compromised respiratory function and are typically not feasible beyond 20 s. As such, techniques to dynamically control breathing during imaging and treatment have been developed to, rather than immobilize the tumor, minimize the irregular motion of the tumor, which would otherwise compromise the accuracy of radiation targeting[7,8,14,22,87] and image quality.[8,14,21,22,24–27]

Prompts used to guide patient toward regular breathing have undergone considerable development and refinement over the years as detailed in Tables II–V. Audio-only guidance typically appeared in the form of verbal instructions or tones,[50–52,56,57,62] and while the regularity of breathing was improved, it also increased the amplitude of breathing motion.[48,56,57,62] Increased tumor motion, even if it is regular, is undesirable in a patient's treatment planning and delivery.[22,62,70–75] Visual guidance has garnered positive results not only over free breathing[44,63] but also over audio-only guidance.[47,48,50,62,68,81] However, utilizing both audio and visual guiding prompts together has yielded the most significant improvements over free breathing.[47,48,50–52,58,60,64–66,69] Both audio and visual guiding prompts have led to significant improvements over audio-only and visual-only guidance as well.[50,60] On top of this, as noted by Venkat, utilising audio and visual prompts together poses no increase in the patient's cognitive load, i.e., it does not require additional concentration for the patient to incorporate two different sensory forms of guidance at once.[58]

The guiding prompts of breathing guidance have developed from a buzzer sounding to provide a queue for breath-holds, to a patient display presenting breathing-surrogates superimposed with a guiding interface. Additional constraints have been added to the visual prompts to further manage respiration, such as the displaying of inhale and exhale limits,[47,48,50,60] a waveguide with fixed period and amplitude for the

Table IV. Details of radiation oncology breathing guidance studies.

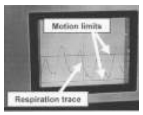
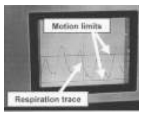
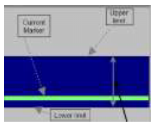
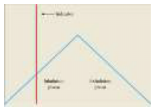
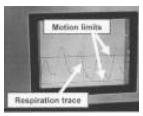
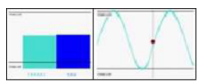
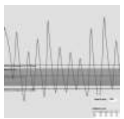
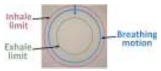
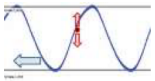
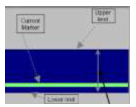
Study author (Year)	Purpose of intervention	Participants	Visual prompt	Audio prompt	Imaging/ treatment	Breathing motion sensor	Quality assessment score (%)	Display
Vedam and Kini (2003) (Refs. 47 and 48)	Regular breathing	Five lung cancer patients	Breathing signal and limits	Verbal commands	Fluoroscopy	Real-time position management system (RPM)	Vedam: 73 Kini: 55	
Neicu (2006) (Ref. 49)	Regular breathing	5 healthy volunteers and 33 lung cancer patients	Breathing signal and limits	Verbal commands	4D-CT and treatment simulation	RPM	68	
George (2006) (Refs. 50 and 51) and An (2013) (Ref. 52)[a]	Regular breathing	24 lung cancer patients	Breathing limits	Ascending and descending tones	None	RPM	George (a): 91 George (b): 95 An: 55	
Chen (2007) (Ref. 53)	Regular breathing	Phantom and eight healthy volunteers	Cyclic moving pattern	None	IMRT delivered to phantom	RPM	59	
Lim (2007) (Ref. 54)	Regular breathing	Ten healthy volunteers	Breathing signal and waveguide	Verbal commands or tones	None	Respiratory monitoring mask with thermocouple	77	
Vedam (2007) (Ref. 55)	Regular breathing	90 lung cancer patients	Breathing signal and limits	Verbal commands	CT	RPM	82	
Haasbeek (2008) (Ref. 56)	Regular breathing	22 lung cancer patients	None	Verbal commands	4D-CT	RPM	77	No display used
Persson (2008) (Ref. 57)	Regular breathing	13 healthy volunteers	None	Verbal commands	None	RPM	91	No display used
Venkat (2008) and Yang (2012) (Refs. 58 and 59)[a]	Regular breathing	Ten healthy volunteers	Waveguide or bar-model	Ascending and descending tones	Venkat: None Yang: PET	RPM Phantom programmed with RPM motion	Venkat: 77 Yang: 86	
Linthout (2009) (Ref. 60)	Regular breathing	25 lung and liver cancer patients	Breathing signal and limits	Verbal commands	Treatment delivery	ExacTrac	82	

TABLE IV. (*Continued*).

Study author (Year)	Purpose of intervention	Participants	Visual prompt	Audio prompt	Imaging/ treatment	Breathing motion sensor	Quality assessment score (%)	Display
Masselli (2009) (Ref. 61)	Regular breathing	Ten healthy volunteers and five lung cancer patients	Breathing limits	None	None	Pneumatic strain gauge	73	
Nakamura (2009) (Ref. 62)	Regular breathing	Six lung cancer patients	None	Verbal commands	Fluoroscopy	RPM	91	No display used
Cerviño (2009) (Ref. 63)	Deep inspiration breath-holds	15 healthy volunteers and 5 breast cancer patients	Breathing signal and limits.	None	None	GateCT-RT	91	
Park (2011) (Ref. 64)	Quasibreath-hold	Ten healthy volunteers	Breathing signal and waveguide	Verbal commands	Simulated IMRT plan	Infrared-based stereo camera	82	
Kim, Pollock, and Steel (2012–2014) (Refs. 65–67)	Regular breathing	15 healthy volunteers	Waveguide and breathing limits	Music which varies in speed	MRI	RPM (abdominal motion) and MRI (thoracic diaphragm motion)	Kim: 95 Pollock: 86 Steel: 82	
Damkjær (2013) (Ref. 68)	Deep inspiration breath-holds	24 breast cancer patients	Breathing limits	Verbal commands	CT	RPM	91	
Lu (2014) (Ref. 69)	Regular breathing	13 lung and liver cancer patients	Breathing limits	Ascending and descending tones	4D-CT	RPM and active breathing coordinator	83	

[a]Retrospective analysis.

TABLE V. Metrics and results of radiation oncology breathing guidance studies.

Study author (Year)	Metric(s) used	Result(s)
Vedam and Kini (2003) (Refs. 47 and 48)	Standard deviation of thoracic diaphragm motion	• Free breathing: Standard deviation of 0.36 cm • Audio guidance: Standard deviation of 0.71 cm, higher than free breathing[a] • Visual guidance: Standard deviation of 0.47 cm, comparable to free breathing[a]
	Measure of ability to predict diaphragm motion (standard deviation of relative position between actual and predicted motion traces)	• Free breathing: Standard deviation of 0.09 cm • Audio guidance: Standard deviation of 0.09 cm • Visual guidance: Standard deviation of 0.11 cm • Breathing guidance comparable to free breathing[a]
	Vedam: Relationship between respiratory signal and diaphragm motion	• Strong linear relationship between respiratory signal and diaphragm motion ($p < 0.001$) over all sessions, regardless of the type of breathing guidance or whether it was used at all ($p = 0.19$)
	Kini: Average and standard deviation in breathing period	• Audio breathing guidance: Reproducible breathing frequency compared to free breathing[a] • Visual breathing guidance: Further improved reproducibility in breathing frequency compared to free breathing[a]
	Kini: Average and standard deviation in breathing range of motion	• Audio guidance: Higher variations and magnitude in breathing range of motion compared to free breathing[a] • Visual guidance: Lower variations in breathing range of motion compared to audio guidance[b]
Neicu (2006) (Ref. 49)	User acceptance of breathing guidance	• All five healthy volunteers were able to follow audio-visual breathing guidance • Of the 33 lung cancer patients: ◦ 10 could follow audio-visual breathing guidance ◦ 13 could follow only audio breathing guidance ◦ 4 were not able to follow breathing guidance ◦ 6 had naturally regular breathing, so breathing guidance was deemed unnecessary
	SMART duty cycle	• Lung cancer patients: ◦ Free breathing: Only 3 patients had duty cycles higher than 60% ◦ Audio-visual breathing guidance: Most patients had duty cycles around 80% or larger, and all patients had duty cycles higher than 60%[a] ◦ Audio breathing guidance: 5 patients had duty cycles higher than 80%, and higher than 60% for 7 patients[a]
	Duty cycles for simulated amplitude gating	• Healthy volunteers: ◦ Simulated amplitude gating: . Free breathing: Average duty cycle was 32% . Audio-visual breathing guidance: Average duty cycle was 36%, an improvement over free breathing[a] . Audio breathing guidance: With the exception of patients 6, 8, and 11, breathing guidance reduced intrasession variations in period from about 23% to 11%[a] ◦ Simulated hybrid amplitude/phase gating: . Free breathing: Average duty cycle was 21% . Breathing guidance: Average duty cycle was 32%, an improvement over free breathing[a] • Lung cancer patients: ◦ Simulated amplitude gating and hybrid amplitude/phase gating: . Audio-visual breathing guidance: Four patients demonstrated good improvements over free breathing, one patient demonstrated worse results with breathing guidance, and the rest of the patient demonstrated similar results to free breathing[a] . Audio breathing guidance: Six patients demonstrated slight improvements over free breathing, one patient demonstrated worse results, and the rest of the patient demonstrated similar result to free breathing[a]

TABLE V. (*Continued*).

Study author (Year)	Metric(s) used	Result(s)
	Intrasession breathing amplitude variations	• Healthy volunteers: ◦ Breathing guidance reduced intrasession standard deviations in amplitude by a factor of 3[a] ◦ Baseline drift almost entirely removed from the use of breathing guidance[a] • Lung cancer patients: ◦ Audio-visual breathing guidance: . Breathing guidance did not have much difference to free breathing for intrasession variations in amplitude[a] . Breathing guidance typically increases breathing amplitude[a]
	Intrasession breathing period variations	• Healthy volunteers: ◦ Breathing guidance reduced intrasession standard deviations in period by a factor of 2[a] • Lung cancer patients: ◦ Audio-visual breathing guidance: . Breathing guidance reduced intrasession variations in period by about 12%[a] . Breathing guidance typically increases breathing period[a] ◦ Audio breathing guidance: . With the exception of patients 6, 8, and 11, breathing guidance reduced intrasession variations in period from about 23% to 11%[a] . Breathing guidance typically increases breathing period[a]
	Intrasession breathing end-of-inhale and end-of-exhale variations	• Healthy volunteers: ◦ Breathing guidance reduced standard deviations of the end-of-inhale and end-of-exhale positions, normalized to the average amplitude, by a factor of 2–3[a] • Lung cancer patients: ◦ Audio-visual breathing guidance: . With the exception of patient 6, breathing guidance reduced standard deviations of end-of-exhale positions by a factor of 2.5[a] . Breathing guidance produced mixed results for the standard deviations of end-of-inhale positions[a]
	Intersession breathing variations	• Healthy volunteers: ◦ Intersession standard deviations of amplitude and period for breathing guidance were about 3 times smaller than free breathing[a]
George (2006) and An (2013) (Refs. 50–52)[c]	George (a): Residual breathing motion (standard deviation of displacement) within a duty cycle at inhale and exhale for phase-based gating	• Gating at inhale with 40% duty cycle: ◦ Free breathing: Mean residual motion was 0.47 cm ◦ Audio breathing guidance: Mean residual motion was 0.47 cm, no significant difference to free breathing[a] ◦ Audio-visual breathing guidance: Mean residual motion was 0.36 cm, significantly improved over free breathing and audio guidance[b] • Gating at exhale with 40% duty cycle: ◦ Free breathing: Mean residual motion was 0.32 cm ◦ Audio breathing guidance: Mean residual motion was 0.31 cm, no significant difference to free breathing[a] ◦ Audio-visual breathing guidance: Mean residual motion was 0.27 cm, significantly improved over free breathing and audio guidance[b] • Duty cycles of 30% and 50% were also tested and demonstrated similar results

TABLE V. (*Continued*).

Study author (Year)	Metric(s) used	Result(s)
	George (a): Residual breathing motion (standard deviation of displacement) within a duty cycle at inhale and exhale for displacement-based gating	• Gating at inhale with 40% duty cycle: ◦ Free breathing: Mean residual motion was 0.42 cm ◦ Audio breathing guidance: Mean residual motion was 0.44 cm, no significant difference to free breathing[a] ◦ Audio-visual breathing guidance: Mean residual motion was 0.31 cm, significantly improved over free breathing and audio guidance[b] • Gating at exhale with 40% duty cycle: ◦ Free breathing: Mean residual motion was 0.27 cm ◦ Audio breathing guidance: Mean residual motion was 0.27 cm, no significant difference to free breathing[a] ◦ Audio-visual breathing guidance: Mean residual motion was 0.21 cm, significantly improved over free breathing and audio guidance[b] • Duty cycles of 30% and 50% were also tested and demonstrated similar results
	George (b): Relationship between patient, tumor, and treatment variables with breathing residual motion	• Inhale based gating: ◦ Correlation between residual motion and visual training displacement ($p < 0.05$)[d] ◦ Correlation between residual motion and breathing guidance types ($p < 0.05$)[d] • A number of other correlations were investigated; however, they were independent from breathing guidance (e.g., Karnofsky performance status and dose-per-fraction) and therefore were not included in these results
	An: Breathing reproducibility of internal motion (variation of range of motion in the first session compared to the subsequent four sessions)	• Free breathing: Breathing reproducibility of range of motion decreased by $28.5\% \pm 27.9\%$ • Audio-visual breathing guidance: Breathing reproducibility of range of motion improved by $21.4\% \pm 20.7\%$, significantly more reproducible than free breathing ($p < 0.05$)[d]
	An: CTV coverage	• Free breathing: CTV coverage decreased by 7.0% • Audio-visual guidance: CTV coverage improved by 20.2%, an improvement over free breathing[a]
Chen (2007) (Ref. 53)	Mean percent error in breathing	• Free breathing: Mean percent error was 21% • Breathing guidance: Mean percent error was 1.8%, considerably less than free breathing[a]
	Intrapatient breathing standard deviation	• Intrapatient standard deviations decreased with breathing guidance[b]
Lim (2007) (Ref. 54)	Standard deviation of breathing amplitudes	• Free breathing: Standard deviation of amplitudes was 0.0029 (arbitrary units) • Breathing guidance: Standard deviation of amplitudes was 0.00139 (arbitrary unites), significantly improved over free breathing ($p = 0.029$)[d]
	Standard deviation of breathing periods	• Breathing guidance reduced standard deviation of periods from 0.359 to 0.202 s ($p = 0.002$)[d]
Vedam (2007) (Ref. 55)	Difference between simulated and delivery gate threshold determined by using the mean displacement from within the phase interval	• Gating phase interval of 40%–60%: ◦ Free breathing: Mean difference was 0.14 ◦ Breathing guidance: Mean difference was 0.08, significantly improved compared to free breathing[d] • Gating phase interval of 30%–70%: ◦ Free breathing: Mean difference was 0.08 ◦ Breathing guidance: Mean difference was 0.04, significantly improved compared to free breathing[d] • The above improvements due to breathing guidance had p-values between 0.01 and 0.02

TABLE V. (*Continued*).

Study author (Year)	Metric(s) used	Result(s)
	Difference between simulated and delivery gate threshold determined by using the maximum of average displacements from within the selected phase	• Gating phase interval of 40%–60%: ◦ Free breathing: Mean difference was 0.18 ◦ Breathing guidance: Mean difference was 0.11, significantly improved compared to free breathing[d] • Gating phase interval of 30%–70%: ◦ Free breathing: Mean difference was 0.17 ◦ Breathing guidance: Mean difference was 0.11, significantly improved compared to free breathing[d] • The above improvements due to breathing guidance had p-values between 0.01 and 0.02
Haasbeek (2008) (Ref. 56)	Lung volume	• End-inspiration lung volume: ◦ Audio breathing guidance increased lung volume by 415 ml (10.2%) compared to free breathing ($p = 0.001$)[d] • End-expiration lung volume: ◦ Audio breathing guidance increased lung volume by 131 ml (2.9%) compared to free breathing ($p = 0.08$)[e] • Between inspiration and expiration lung volume: ◦ Audio breathing guidance increased lung volume by 671 ml (19.2%) compared to free breathing ($p < 0.001$)[d]
	Displacement of internal target volume (ITV)	• Free breathing: Mean displacement of 3D ITV center of mass was 9.2 ± 8.3 (range: 0–27 mm) • Breathing guidance: Mean displacement of 3D ITV center of mass was 13.0 ± 12.9 (range: 0–46 mm), significantly larger compared to free breathing ($p = 0.008$)[d]
Persson (2008) (Ref. 57)	Breathing amplitude	• Compared to free breathing, more volunteers had larger breathing amplitudes (p values between <0.0001 and 0.0237):[d] ◦ 7 of 12 volunteers (and 6 of 12) had significantly larger amplitude for type 1 (and type 2) audio guidance ◦ 2 of 12 (and 2 of 12) volunteers had significantly lower amplitude for type 1 (and type 2) audio guidance
	Standard deviation of breathing amplitude intrafractionally	• No significant difference in the standard deviation of the breathing amplitude distribution between guidance and free breathing[e]
Venkat (2008) and Yang (2012) (Refs. 58 and 59)[c]	Venkat: Root mean square (RMS) variations in breathing motion displacement	• Free breathing: Mean RMS variation in displacement was 0.16 cm • Bar-model breathing guidance: Mean RMS variation in displacement was 0.10 cm, 40% more regular than free breathing ($p = 0.005$)[d] • Wave-model breathing guidance: Mean RMS variation in displacement was 0.08 cm, 55% more regular than free breathing, and significantly more regular than bar-model breathing guidance ($p = 0.006$)[d]
	Venkat: RMS variations in breathing motion period	• Free breathing: Mean RMS variation in period was 0.77 s • Bar-model breathing guidance: Mean RMS variation in period was 0.33 s, 50% more regular than free breathing ($p = 0.002$)[d] • Wave-model breathing guidance: Mean RMS variation in period was 0.2 s, 75% more regular than free breathing and significantly more regular than bar-model breathing guidance ($p = 0.005$)[d]
	Yang: Motion blurring (quantified by target size)	• Free breathing: Average increase in target diameter was 1.3 ± 2.2 mm • Breathing guidance: Average increase in target diameter was 0.6 ± 1.6 mm, a significant improvement in target size compared to free breathing ($p < 0.001$)[d]
	Yang: Dice coefficient	• Free breathing: Average Dice coefficient was 0.88 ± 0.10 • Breathing guidance: Average Dice coefficient was 0.90 ± 0.07, a significant improvement compared to free breathing ($p < 0.001$)[d]

TABLE V. (*Continued*).

Study author (Year)	Metric(s) used	Result(s)
	Yang: Recovery coefficient	• For all targets, breathing guidance had consistently higher recovery coefficients than free breathing[a] • Target size had a greater impact on recovery coefficient values than breathing motion[a] • For the largest target: ◦ Free breathing: Recovery coefficient was 0.97 ± 0.04 ◦ Breathing guidance: Recovery coefficient was 1.00 ± 0.04 • For the smallest target: ◦ Free breathing: Recovery coefficient was 0.36 ± 0.05 ◦ Breathing guidance: Recovery coefficient was 0.39 ± 0.03
Linthout (2009) (Ref. 60)	Delivery time of gated treatment	• Free breathing: 1.7 ± 0.6 min/100 MU • Visual breathing guidance: 1.4 ± 0.4 min/100 MU, a nonsignificant reduction in delivery time compared to free breathing ($p = 0.249$)[e] • Audio-visual breathing guidance: 0.9 ± 0.2 min/100 MU, a significant reduction in delivery time compared to free breathing ($p = 0.004$)[d] and a significant reduction in treatment time compared to visual breathing guidance ($p = 0.008$)[d]
Masselli (2009) (Ref. 61)	Baseline shift	• Removal of baseline drift[a]
	Average amplitude	• Healthy volunteers: ◦ Free breathing: Average amplitude was 10 ± 2 mm ◦ Breathing guidance: Average amplitude was 6 ± 1 mm, lower compared to free breathing[b] • Lung cancer patients: ◦ Free breathing: Average amplitude was 8 ± 2 mm ◦ Breathing guidance: Average amplitude was 5 ± 1 mm, lower compared to free breathing[b]
	Variability of breathing amplitude	• No significant difference in standard deviation of amplitude[e]
	Average breathing frequency	• Healthy volunteers: ◦ Free breathing: Breathing frequency was 17 breaths/min ◦ Breathing guidance: Breathing frequency was 37 breaths/min, more than free breathing[b] • Lung cancer patients: ◦ Free breathing: Breathing frequency was 15 breaths/min ◦ Breathing guidance: Breathing frequency was 45 breaths/min, more than free breathing[b]
Nakamura (2009) (Ref. 62)	Mean SI tumor displacement	• Free breathing: Mean SI tumor displacement was 10.4 mm • Breathing guidance: Mean SI tumor displacement was 23.0 mm, a significant increase compared to free breathing ($p < 0.01$)[d]
	Mismatches between SI lung tumor position and abdominal position	• Free breathing: The average position mismatch was 1.70 mm • Breathing guidance: The average position mismatch was 2.09 mm ◦ Compared to free breathing, SI lung tumor position mismatches became larger in 75% of sessions with breathing guidance ($p = 0.01$)[d]
	Correlation between abdominal displacement and lung tumor motion	• Free breathing: Correlation coefficients ranged from 0.89 to 0.97 • Breathing guidance: Correlation coefficients ranged from 0.93 to 0.99, significantly improved compared to free breathing ($p < 0.01$)[d]
Cerviño (2009) (Ref. 63)	Reproducibility of breath-holds: Maximum difference between difference breath-hold levels	• Without guidance: Average reproducibility was 2.1 mm • Breathing guidance: Average reproducibility was 0.5 mm, significantly improved compared to free breathing ($p < 0.001$)[d]

TABLE V. (*Continued*).

Study author (Year)	Metric(s) used	Result(s)
	Stability of breath-holds: Maximum of the amplitude change between initial and end time points of a breath hold	• Without guidance: Average stability was 1.5 mm • Breathing guidance: Average stability was 0.7 mm, significantly improved compared to free breathing ($p < 0.01$)[d]
Park (2011) (Ref. 64)	Simulated treatment time	• Free breathing: Average treatment time was 530.4 ± 9.0 s • Quasibreath-hold with 3 s exhale (QBH_3) guidance: Average treatment time was 466.8 ± 26.5 s, significantly lower than free breathing ($p < 0.001$)[d] • QBH_5 guidance: Average treatment time was 452.3 ± 29.9 s, significantly lower than free breathing ($p < 0.001$)[d] • QBH_7 guidance: Average treatment time was 430.8 ± 8.3 s, significantly lower than free breathing ($p < 0.001$)[d]
	Mean absolute error (MAE) between the guiding wave and measured breathing signal	• Free breathing: Average MAE was 0.9 ± 0.7 s • QBH_3 guidance: Average MAE was 0.8 ± 0.6 s, lower than free breathing ($p = 0.497$)[e] • QBH_5 guidance: Average MAE was 0.7 ± 0.6 s, significantly lower than free breathing ($p = 0.013$)[d] • QBH_7 guidance: Average MAE was 0.6 ± 0.7 s, significantly lower than free breathing ($p = 0.021$)[d]
	Mean absolute deviation (MAD) of the measured breathing signal	• Free breathing: Average MAD was 0.7 ± 0.7 s • QBH_3 guidance: Average MAD was 0.5 ± 0.5 s, motion variations lower than free breathing ($p = 0.144$)[e] • QBH_5 guidance: Average MAD was 0.5 ± 0.4 s, motion variations significantly lower than free breathing ($p = 0.006$)[d] • QBH_7 guidance: Average MAD was 0.5 ± 0.6 s, motion variations significantly lower than free breathing ($p = 0.029$)[d]
Kim, Pollock, and Steel (2012–2014) (Refs. 65–67)	Kim: Root mean square error (RMSE) of breathing motion displacement	• Abdominal breathing motion: ◦ Free breathing: Average RMSE in displacement was 1.3 mm ◦ Breathing guidance: Average RMSE in displacement was 0.7 mm, 46% more regular than free breathing ($p < 0.0001$)[d] • Thoracic diaphragm breathing motion: ◦ Free breathing: Average RMSE in displacement was 2.6 mm ◦ Breathing guidance: Average RMSE in displacement was 1.6 mm, 38% more regular than free breathing ($p < 0.0001$)[d]
	Kim: RMSE of breathing period	• Abdominal breathing motion: ◦ Free breathing: Average RMSE in period was 1.6 s ◦ Breathing guidance: Average RMSE in period was 0.3 s, 81% more regular than free breathing ($p < 0.0001$)[d] • Thoracic diaphragm breathing motion: ◦ Free breathing: Average RMSE in period was 1.7 s ◦ Breathing guidance: Average RMSE in period was 0.3 s, 82% more regular than free breathing ($p < 0.0001$)[d]
	Kim: Spectral power dispersion metric (SPDM) of thoracic diaphragm breathing motion	• Free breathing: Average SPDM was 2.1 • Breathing guidance: SPDM was 0.7, 67% more regular than free breathing ($p = 0.005$)[d]
	Kim: Baseline drift of breathing motion	• Abdominal breathing motion: ◦ Free breathing: Average baseline drift was 0.21 mm/min ◦ Breathing guidance: Average baseline drift was 0.05 mm/min, 75% more regular than free breathing ($p < 0.0001$)[d] • Thoracic diaphragm breathing motion: ◦ Free breathing: Average baseline drift was 1.6 mm/min ◦ Breathing guidance: Average baseline drift was 0.9 mm/min, 44% more regular than free breathing ($p = 0.012$)[d]

TABLE V. (*Continued*).

Study author (Year)	Metric(s) used	Result(s)
	Kim: Breathing regularity difference from breathing session 1 to breathing session 2	• Abdominal breathing motion: ◦ $RMSE_{AV}/RMSE_{FB}$ in displacement: . Breathing session 1: 0.700 . Breathing session 2: 0.509, a larger discrepancy between free breathing and breathing guidance regularity ($p = 0.053$)[e] ◦ $RMSE_{AV}/RMSE_{FB}$ in period: . Breathing session 1: 0.386 . Breathing session 2: 0.237, a larger discrepancy between free breathing and breathing guidance regularity ($p = 0.093$)[e] ◦ Baseline $drift_{AV}$/baseline $drift_{FB}$: . Breathing session 1: 0.904 . Breathing session 2: 1.684, a larger discrepancy between free breathing and breathing guidance regularity ($p = 0.230$)[e] • Thoracic diaphragm breathing motion: ◦ $RMSE_{AV}/RMSE_{FB}$ in displacement: . Breathing session 1: 0.875 . Breathing session 2: 0.639, a larger discrepancy between free breathing and breathing guidance regularity ($p = 0.170$)[e] ◦ $RMSE_{AV}/RMSE_{FB}$ in period: . Breathing session 1: 0.426 . Breathing session 2: 0.269, a larger discrepancy between free breathing and breathing guidance regularity ($p = 0.212$)[e] ◦ Baseline $drift_{AV}$/baseline $drift_{FB}$: . Breathing session 1: 1.426 . Breathing session 2: 0.926, a larger discrepancy between free breathing and breathing guidance regularity ($p = 0.212$)[e]
	Pollock: RMSE between breathing signal and predicted breathing position	• Abdominal breathing motion: ◦ Free breathing: Average RMSE was 1.4 ± 1.0 mm ◦ Breathing guidance: Average RMSE was 1.0 ± 0.8 mm, 26% more accurate than free breathing ($p < 0.001$)[d] • Thoracic diaphragm breathing motion: ◦ Free breathing: Average RMSE was 2.8 ± 2.1 mm ◦ Breathing guidance: Average RMSE was 2.0 ± 1.4 mm, 29% more accurate than free breathing ($p < 0.001$)[d]
	Steel: Correlation between abdominal and thoracic diaphragm breathing motion	• Free breathing: Average correlation was 0.96 ± 0.02 • Breathing guidance: Average correlation was 0.96 ± 0.03, no significant difference to free breathing ($p = 0.88$)[e]
	Steel: Correlation between RMSE in displacement and abdomen–diaphragm correlation	• Free breathing: Minimal correlation between RMSE values and motion correlation values ($R = 0.079$) • Breathing guidance: Minimal correlation between RMSE values and motion correlation values ($R = -0.33$)
	Steel: Correlation between SPDM and abdomen–diaphragm correlation	• Free breathing: Weak correlation between SPDM values and motion correlation values ($R = -0.0633$) • Breathing guidance: Weak correlation between SPDM values and motion correlation values ($R = -0.0471$)
Damkjær (2013) (Ref. 68)	Mean inspiration level	• Unguided: Mean inspiration level was 16.6 ± 1.66 mm • Guided breath-holds: Mean inspiration level was 20.5 ± 0.38 mm, a significant increase compared to unguided ($p < 0.002$)[d]
	Mean dose to CTV ($D_{mean,CTV}$)	• Unguided: Mean $D_{mean,CTV}$ was 50.1 Gy • Guided breath-holds: Mean $D_{mean,CTV}$ was 50.0 Gy, a nonsignificant difference compared to unguided ($p > 0.05$)[e]
	Relative volume receiving more than 95% of the prescribed dose ($V_{95\%,CTV}$)	• Unguided: Mean $V_{95\%,CTV}$ was 93.9% • Guided breath-holds: Mean $V_{95\%,CTV}$ was 92.6%, a nonsignificant difference compared to unguided ($p > 0.05$)[e]
	If internal mammary nodes (IMN) were included in the target volume, relative volume receiving 90% of the prescribed dose ($V_{90\%,IMN}$)	• IMN included in target area for 19 of 24 patients • Unguided: Mean $V_{90\%,IMN}$ was 70.6% • Guided breath-holds: Mean $V_{90\%,IMN}$ was 76.1%, a nonsignificant difference compared to unguided ($p > 0.05$)[e]

TABLE V. (*Continued*).

Study author (Year)	Metric(s) used	Result(s)
	Volume receiving more than 107% of the prescribed dose ($V_{107\%,\text{body}}$)	• Unguided: Mean $V_{107\%,\text{body}}$ was 7.3 cm^3 • Guided breath-holds: Mean $V_{107\%,\text{body}}$ was 7.3 cm^3, a nonsignificant difference compared unguided ($p > 0.05$)[e]
	Absolute volume of the left lung (V_{leftlung})	• Unguided: Mean V_{leftlung} was 1982 cm^3 • Guided breath-holds: Mean V_{leftlung} was 2286 cm^3, 11% larger than unguided ($p < 0.0004$)[d]
	Relative volume of the lung receiving 20 Gy or more ($V_{20\text{Gy,leftlung}}$)	• Unguided: Mean $V_{20\text{Gy,leftlung}}$ was 29.6% • Guided breath-holds: Mean $V_{20\text{Gy,leftlung}}$ was 27.1%, a 9% decrease in lung dose compared to unguided ($p < 0.002$)[d]
	Maximum dose to the left anterior descending coronary artery (LAD) ($D_{\text{max,LAD}}$)	• Unguided: Mean $D_{\text{max,LAD}}$ was 16.1 Gy • Guided breath-holds: Mean $D_{\text{max,LAD}}$ was 16.1 Gy, a nonsignificant difference compared to unguided ($p > 0.05$)[e]
	Mean dose to the heart ($D_{\text{mean,heart}}$)	• Unguided: Mean $D_{\text{mean,heart}}$ was 2.41 Gy • Guided breath-holds: Mean $D_{\text{mean,heart}}$ was 2.49 Gy, a nonsignificant difference compared to unguided ($p > 0.05$)[e]
	Volume of heart receiving more than 25 Gy ($V_{25\text{Gy,heart}}$)	• Unguided: Mean $V_{25\text{Gy,heart}}$ was 0.8% • Guided breath-holds: Mean $V_{25\text{Gy,heart}}$ was 0.7%, a nonsignificant difference compared to unguided ($p > 0.05$)[e]
Lu (2014) (Ref. 69)	Volume ratio between two methods of ITVs generation: ITV_{10} and ITV_{MIP}	• Free breathing: ITV_{10}/ITV_{MIP} was 1.19 • Breathing guidance with RPM: ITV_{10}/ITV_{MIP} was 1.21 • Breathing guidance with ABC: ITV_{10}/ITV_{MIP} was 1.19 • No significant impact of breathing guidance ($p > 0.05$)[e]
	Centroid difference between ITV_{10} and ITV_{MIP}	• Free breathing: Centroid difference between ITV_{10} and ITV_{MIP} was 1.9 mm • Breathing guidance with RPM: Centroid difference between ITV_{10} and ITV_{MIP} was 1.7 mm • Breathing guidance with ABC: Centroid difference between ITV_{10} and ITV_{MIP} was 2.3 mm • No significant impact of breathing guidance ($p > 0.05$)[e]
	Overlap between ITV_{10} and ITV_{MIP} quantified by Dice coefficient	• Free breathing: Dice coefficient was 0.87 • Breathing guidance with RPM: Dice coefficient was 0.88 • Breathing guidance with ABC: Dice coefficient was 0.86 • No significant impact of breathing guidance ($p > 0.05$)[e]
	RMS difference between surfaces of ITV_{10} and ITV_{MIP}	• Free breathing: RMS distance was 2.7 mm • Breathing guidance with RPM: RMS distance was 2.6 mm • Breathing guidance with ABC: RMS distance was 3.0 mm • No significant impact of breathing guidance ($p > 0.05$)[e]
	Correlation coefficient between the best cosine fit and the original breathing signal	• Free breathing: Correlation coefficient was 0.66 • Breathing guidance with RPM: Correlation coefficient was 0.72, a nonsignificant difference compared to free breathing[e] • Breathing guidance with ABC: Correlation coefficient was 0.77, significantly more regular than free breathing ($p < 0.05$)[d]
	Power dominant frequency (PDF) of breathing signal	• Free breathing: The PDF was 0.04 • Breathing guidance with RPM: The PDF was 0.08, significantly more regular than free breathing ($p < 0.05$)[d] • Breathing guidance with ABC: The PDF was 0.08, significantly more regular than free breathing ($p < 0.05$)[d]

[a]No p-value, no statement of significance.
[b]No p-value, but significance stated.
[c]Retrospective analysis.
[d]$P < 0.05$ (significant).
[e]$P \geq 0.05$ (nonsignificant).

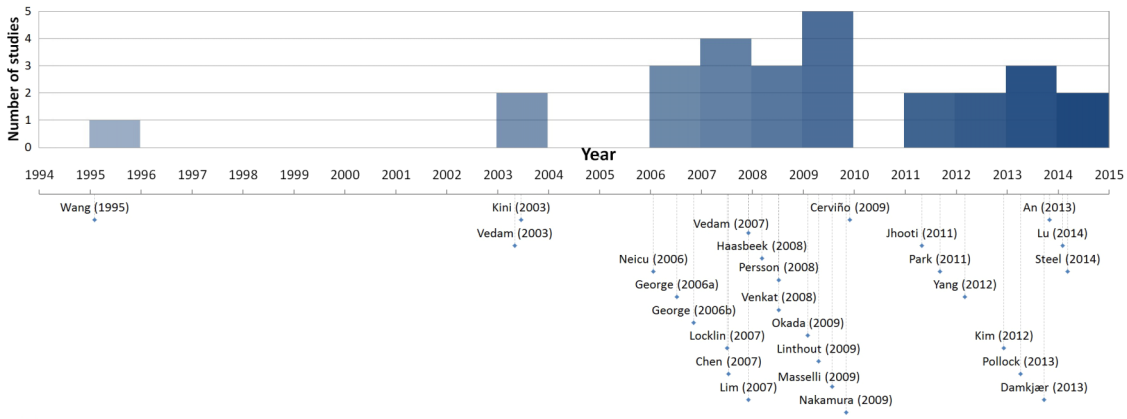


FIG. 4. Timeline of the number of breathing guidance studies (top) and the study publications (bottom) from 1995 to 2014, detailed in Tables II–V.

patient to match their own breathing to,[54] and combinations thereof.[58,64,65]

In addition to the nature of guiding prompts utilized, study design has also factored into influencing patient acceptance and compliance with the breathing guidance intervention. Studies in which patients used breathing guidance multiple times demonstrated improved breathing consistency with time.[50,58,65] Hence, to achieve optimal compliance with breathing guidance, patient training and repeated sessions are of importance to bolster their familiarity with the system; such elements have been absent in previous patient studies which yielded nonsignificant results.[69,88,89]

While this systematic review yielded 27 articles, it should be noted that some articles that were in contention required considerable discussion between the authors to conclude on their exclusion from the final selection. The main factor influencing the decision to exclude these articles was the control group criterion; while several studies investigated a breathing guidance intervention strategy, the control group was not of the same breathing type (see inclusion criterion 5).[81,84–86,89–92]

While the search undertaken and review of articles by the authors was performed as objectively as possible, it should be noted that two of the authors of this systematic review, Sean Pollock and Paul Keall, are either first- or co-authors of 3 and 9 of the 27 included articles, respectively, investigating the breathing guidance intervention: audiovisual biofeedback. Their familiarity with breathing guidance strategies led to the identification that a gap in the literature existed in that a review of such research had yet to be performed; however, unintentional bias may have permeated this review toward audiovisual biofeedback. To minimize this bias, co-author Robyn Keall was invited to review and screen the identified 319 (see Fig. 3); where there was disagreement between reviewers, a discussion was undertaken among all authors until consensus was reached.

While 21 of the 27 included articles reported at least one statistically significant positive finding from the use of breathing guidance interventions, bias should also be noted that papers reporting on positive results are more likely to be published than papers with negative results.[93,94] This notes the systemic bias in scientific reporting and the possibility that negative results on breathing guidance may not have been published.

The largely positive results found in this systematic review indicate that further clinical studies are warranted and should be focused on (1) utilizing training and multiple sessions to maximize patient compliance with the breathing guidance system, and (2) further determining the clinical impact of breathing guidance interventions by investigating outcomes pertaining to treatment margins, toxicity, and patient outcomes. Such factors are being explored in ongoing and upcoming studies, with some preliminary results presented thus far.[95–97]

TABLE VI. Number of study outcomes investigated and their statistical significance (references in brackets).

	Positive results	Nonsignificant results[a]	Negative results
Breathing regularity and tumor motion	27/60 (Refs. 48, 52–54, 58, 61, 64, 65, and 69)	28/60 (Refs. 48, 49, 53, 56, 57, 61, 64, 65, and 69)	5/60 (Refs. 56, 57, and 62)
Breath-hold stability and reproducibility	3/6 (Refs. 44, 63, and 68)	3/6 (Refs. 43 and 44)	
Gating efficiency	17/42 (Refs. 46, 50, and 55)	25/42 (Refs. 47, 49, and 50)	
Image quality	3/7 (Refs. 43 and 59)	3/7 (Refs. 43, 46, and 59)	1/7 (Ref. 45)
Reduced margins		8/8 (Ref. 69)	
Reduced dose to healthy tissue	2/6 (Ref. 68)	4/6 (Ref. 68)	
Improved target coverage		4/4 (Refs. 52 and 68)	
Reduced treatment/imaging time	6/8 (Refs. 43, 46, 60, and 64)	2/8 (Refs. 45 and 60)	
Other[b]	5/11 (Refs. 51, 62, and 66)	5/11 (Refs. 47 and 67)	1/11 (Ref. 62)
Total	63	82	7

[a]Or significance of results not stated.
[b]Motion correlation, motion prediction, and correlation with disease type.

5. CONCLUSION

A systematic review of breathing guidance intervention strategies in radiotherapy and radiology has been performed and 27 studies were identified. In 21 studies, statistically significant improvements from the use of breathing guidance were observed. No studies observed worse breathing consistency with guidance; however, audio-only guidance, while facilitating regular breathing, also increased respiratory amplitude which is undesirable in most circumstances. Studies that have repeated breathing guidance across multiple sessions have observed an improvement in participant compliance from one session to the next, emphasizing the importance of patient practice and training. Such insights are valuable in designing breathing guidance studies in terms of both guiding prompts used and patient familiarity with the intervention to maximize the effectiveness of the intervention. The largely positive results found here indicate that further clinical studies are warranted to further assess and quantify the clinical impact of breathing guidance, along with the health technology assessment to determine the advantages and disadvantages of the use of breathing guidance strategies.

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CHAPTER 3

The impact of breathing guidance and prospective gating during thoracic 4DCT imaging: an XCAT study utilizing lung cancer patient motion

This chapter contains the paper titled “The impact of breathing guidance and prospective gating during thoracic 4DCT imaging: an XCAT study utilizing lung cancer patient motion” which has been published in *Physics in Medicine and Biology* (2016; **61**(17) 6485-6501)

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The impact of breathing guidance and prospective gating during thoracic 4DCT imaging: an XCAT study utilizing lung cancer patient motion

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Abstract

Two interventions to overcome the deleterious impact irregular breathing has on thoracic-abdominal 4D computed tomography (4DCT) are (1) facilitating regular breathing using audiovisual biofeedback (AVB), and (2) prospective respiratory gating of the 4DCT scan based on the real-time respiratory motion. The purpose of this study was to compare the impact of AVB and gating on 4DCT imaging using the 4D eXtended cardiac torso (XCAT) phantom driven by patient breathing patterns.

We obtained simultaneous measurements of chest and abdominal walls, thoracic diaphragm, and tumor motion from 6 lung cancer patients under two breathing conditions: (1) AVB, and (2) free breathing. The XCAT phantom was used to simulate 4DCT acquisitions in cine and respiratory gated modes. 4DCT image quality was quantified by artefact detection (NCC_{diff}), mean square error (MSE), and Dice similarity coefficient of lung and tumor volumes (DSC_{lung}, DSC_{tumor}). 4DCT acquisition times and imaging dose were recorded.

In cine mode, AVB improved NCC_{diff}, MSE, DSC_{lung}, and DSC_{tumor} by 20% ($p = 0.008$), 23% ($p < 0.001$), 0.5% ($p < 0.001$), and 4.0% ($p < 0.003$), respectively. In respiratory gated mode, AVB improved NCC_{diff}, MSE, and DSC_{lung} by 29% ($p < 0.001$), 34% ($p < 0.001$), 0.4% ($p < 0.001$),

respectively. AVB increased the cine acquisitions by 15 s and reduced respiratory gated acquisitions by 31 s. AVB increased imaging dose in cine mode by 10%.

This was the first study to quantify the impact of breathing guidance and respiratory gating on 4DCT imaging. With the exception of DSC_{tumor} in respiratory gated mode, AVB significantly improved 4DCT image analysis metrics in both cine and respiratory gated modes over free breathing. The results demonstrate that AVB and respiratory-gating can be beneficial interventions to improve 4DCT for cancer radiation therapy, with the biggest gains achieved when these interventions are used simultaneously.

Keywords: 4DCT, thoracic imaging, breathing guidance, respiratory gating

(Some figures may appear in colour only in the online journal)

1. Introduction

4D computed tomography (4DCT) is an imaging modality frequently utilized to incorporate breathing motion in the treatment planning stage of radiotherapy (Ford *et al* 2003, Vedam *et al* 2003, Keall 2004, Pan *et al* 2004). However, image artefacts have been reported in up to 90% of 4DCT images (Yamamoto *et al* 2008), compromising the accuracy of tumor delineation (Persson *et al* 2010). These artifacts have been linked to irregular breathing (Mutaf *et al* 2007, Clements *et al* 2013, Zhang *et al* 2013). An additional problem is inconsistent inter-fraction breathing motion, where the tumor motion observed during 4DCT treatment planning is not consistent with the motion observed during treatment delivery (Ge *et al* 2012), resulting in an increase in the irradiated healthy tissue (Schmidt *et al* 2013). The radiation treatment volume itself is often expanded to account for these additional errors (Roman *et al* 2012), increasing the radiation dose to the healthy surrounding tissue, thus further increasing the risk of post-treatment radiation toxicities (Rancati *et al* 2003, Matsuo *et al* 2012, Wang *et al* 2013, Scotti *et al* 2014).

To reduce the errors associated with irregular breathing motion, the patient breathing guidance system, audiovisual biofeedback (AVB) has been utilized to facilitate regular and consistent respiratory-motion (George *et al* 2006, Venkat *et al* 2008, Masselli *et al* 2009, Kim *et al* 2012, Pollock *et al* 2015a, 2015b) to improve image quality (Yang *et al* 2012, Cossmann 2012), imaging and treatment time (Jhooti *et al* 2011, Park *et al* 2011, Cossmann 2012), and treatment accuracy (Chen *et al* 2007). However, the assessment of patient breathing guidance on 4DCT image quality has yet to be quantified. A study by Cossmann (2012) noted that the more consistent breathing motion as provided by breathing guidance improved the quality of 4DCT images (Cossmann 2012), but this improvement was not quantified. Another study by Lu *et al* (2014) investigated the impact of breathing guidance on the match between ITV_{MIP} (internal target volume generated by contouring in the maximum intensity projection scan) and ITV_{10} (ITV generated by combining the gross tumor volumes contoured over the 10 phases of a 4DCT) (Lu *et al* 2014); however, no analysis of image quality was performed.

A second method to reduce irregular breathing motion artefacts is prospective gating, which limits the 4DCT 'beam-on' time to regular breathing, defined in terms of real-time displacement, velocity and/or phase criteria. A number of experimental and simulation studies have suggested a potential improvement to 4DCT image quality using real-time prospective gating, at some cost to acquisition time (Keall *et al* 2007, Langner and Keall 2010, Bernatowicz *et al*

2015). Bernatowicz *et al* (2015) simulated prospective gated 4DCT acquisition for 8 patients, using the realistic 4D eXtended cardiac-torso (XCAT) deformable digital human phantom (Segars *et al* 2010, Bond *et al* 2012) synchronized to measured tumor motion patterns (Mishra *et al* 2012). They found prospective respiratory gated 4DCT reduced the mean square error (MSE) difference between reconstructed and ground truth thoracic 4DCT images as much as 46% on average, but with an average acquisition time 84% longer than cine mode. Computer-controlled prospective gated 4DCT has yet to be implemented clinically, in part because the anticipated increase in acquisition time may be considered a disadvantage in busy hospital environments. Meanwhile the XCAT has been utilized in a number of simulation studies to quantify the impact of breathing motion on image quality (Cai *et al* 2011, Rong *et al* 2012, Bernatowicz *et al* 2015) and on treatment delivery (Ecclestone *et al* 2013, Koybasi *et al* 2014).

The goal of this study is to perform the first comparisons of AVB and prospective gating technologies in view of their impacts on 4DCT image analysis metrics and acquisition time. This is also the first study to investigate the impact of breathing guidance on 4DCT image analysis metrics directly. As in the Bernatowicz study, this work employs the 4D XCAT but with an added emphasis on realistic patient motion. This is achieved by incorporating not only tumor motion, but also simultaneous measurements of chest wall, abdominal wall, and thoracic diaphragm motion. This data is derived from a study by Lee *et al* (2016) who performed magnetic resonance imaging (MRI) on lung cancer patients whilst they breathed both with and without the aid of AVB (Lee *et al* 2016). The Lee *et al* (2016) study extracted lung tumor and thoracic diaphragm motion information from the 2D MR images as well as monitoring external breathing motion from the real-time position management (RPM) system and the Siemens physiological measurement unit (PMU) chest belt.

By programming the 4D XCAT with separate internal and external breathing motion patterns, we aim to perform realistic comparisons of 4DCT imaging across two breathing conditions (AVB and free breathing) and two acquisition modes (cine mode and prospective respiratory gating). We hypothesize that the more regular breathing motion as provided by AVB will result in improved 4DCT image analysis metrics over free breathing, and that the largest improvement in image analysis metrics will come from the use of both AVB and respiratory gating interventions. Other metrics, such as acquisition time, could be more dependent on couch-stay time than motion regularity, particularly in cine mode.

2. Method and materials

To simulate 4DCT imaging as realistically as possible, the XCAT digital phantom was programmed with both the internal and external motion information in addition to lung tumor size and position information obtained in the Lee *et al* (2016) MRI study (Lee *et al* 2016).

2.1. Breathing motion data

Breathing guidance utilized by the 10 lung cancer patients in the Lee *et al* (2016) study was the AVB system, as developed by Venkat *et al* (2008). Lee *et al* (2016) analyzed the lung tumor motion regularity of these 10 lung cancer patients and found that AVB significantly improved the regularity of lung tumor motion period and displacement by 73% and 34%, respectively (Lee *et al* 2016).

10 non-small cell lung cancer (NSCLC) patients underwent two MR imaging sessions, the second session occurring 3–6 weeks after the first. Each session involved imaging the patient under two breathing conditions: (1) with AVB, and (2) free breathing. Sagittal MR

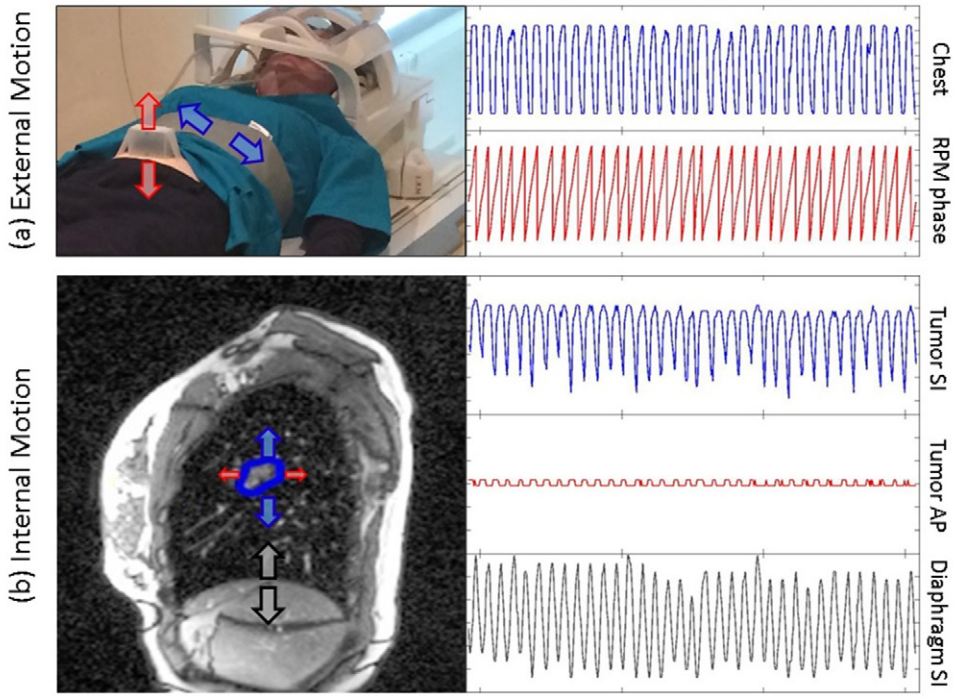

Figure 1. (a) External and (b) internal respiratory motion utilized to program the motion of the XCAT phantom. Sagittal MR image shown with segmented lung tumor.

images yielded 2D lung tumor motion (superior–inferior (SI) and anterior–posterior (AP)). Tumor motion was extracted from the centroid of the segmented tumor, tumor segmentation was performed by a region-growing algorithm (Lee *et al* 2016). External breathing motion of chest motion and abdominal motion was also monitored during MR imaging. Chest motion was monitored by the Siemens PMU belt, and abdominal motion was monitored by the Varian RPM system. Figure 1 illustrates the motion utilized to program the motion of the XCAT phantom.

XCAT programmable motion inputs include chest AP motion, thoracic diaphragm SI motion, tumor AP, SI and left–right (LR) motion. Other XCAT inputs include tumor position within the lung and tumor volume. External motion utilized was the chest displacement information from PMU belt. PMU belt motion was used to program the XCAT chest motion, while diaphragm SI motion, and tumor SI and AP motion was used to program the XCAT internal motion. XCAT tumor LR motion was disabled as it could not be obtained from the sagittal MR images. RPM phase information was used for 4DCT binning. It should be noted that chest motion from the PMU belt was originally normalized and without units. To obtain absolute chest displacement, the PMU motion data was rescaled to have one quarter of the AP motion range of the corresponding RPM signal. This is in accordance with findings presented by Kaneko and Horie (2012).

The inclusion criteria for this study was that free breathing tumor motion be greater than 0.5 cm as stated in the management of respiratory motion in radiation oncology report of AAPM Task Group 76 (Keall 2006). This inclusion criteria made 6 patients across 10 MRI sessions eligible for simulation in this study.

Table 1. Patient tumor motion information, peak-to-peak amplitude is given in brackets.

Patient	Session number	Tumor volume (cm^3)	Tumor motion range from MRI (max–min) Free breathing (peak-to-peak amplitude) (cm)	Tumor motion range from MRI (max–min) AVB (peak-to-peak amplitude) (cm)
1	1	21	0.8 (0.7)	0.7 (0.5)
	2	15	0.7 (0.5)	0.9 (0.4)
2	1	19	0.6 (0.2)	0.7 (0.3)
	2	7	0.8 (0.3)	0.6 (0.4)
3	1	29	0.6 (0.2)	0.5 (0.2)
4	1	19	1.9 (1.0)	2.1 (1.6)
	2	20	2.2 (1.4)	2.9 (2.0)
5	1	73	0.7 (0.2)	0.6 (0.3)
	2	58	0.9 (0.2)	0.3 (0.2)
6	2	46	0.5 (0.2)	0.4 (0.2)
Average (range)		55 (7–73)	1.0 (0.5) (0.5–2.2 (0.2–1.4))	1.0 (0.6) (0.3–2.9 (0.2–2.0))

Table 1 details the patient characteristics included in this study, the mean age of patients was 66 years (range: 54–79) with 3 male and 3 female.

2.2. Simulation of 4DCT acquisition using XCAT

Our method for simulating 4DCT acquisitions proceeds similar to the retrospective method used by Bernatowicz *et al* (2015). Briefly, for each simulation the first 60 s of RPM displacement/phase data are analyzed to determine the average breathing period T_{Avg}, as well as the mean (D_{Mean}) and std. dev. (D_{SD}) of displacement in each of 10 phase bins. The subsequent RPM data is then analyzed to derive a schedule of couch shifts and kilovoltage (kV) image acquisitions, used to extract axial slices from the 4D XCAT programmed with the measured patient motion. Figure 2 details the workflow of this study.

In these simulations, the cine mode uses a constant kV imaging frequency corresponding to a gantry rotation time of 0.3 s, and a constant couch-shift frequency corresponding to a cine duration of $T_{\text{Avg}} + 1$ s for each of 30 couch positions. The CT slice acquisition time was determined by multiplying a typical 0.5 s gantry rotation time by a factor of approximately 220/360 (accounting for the angular span required for a single complete reconstruction) resulting in a 0.3 s acquisition time for each CT slice. Cine mode represents the conventional reconstruction 4DCT method for many scanners (Yamamoto *et al* 2008, Langner and Keall 2010). The respiratory gated mode is similar to the cine mode, except that kV acquisition is triggered only when the real-time respiratory motion falls within a phase-specific displacement gating window $D_{\text{Mean}} \pm D_{\text{SD}}$. The respiratory gated mode disallows duplicate kV acquisitions at the same couch position/phase bin and allows early couch shifts once all 10 phase bins are acquired. The gated mode allows a maximum couch stay of 2500 s at any one couch position, but this limit was never exceeded in any of the simulations. For each kV imaging timepoint, we generate an instantaneous 3D XCAT volume, and extract 4 axial slices (spaced 2.5 mm apart) corresponding to the given couch position. The simulation method does not include a forward/backprojection step (i.e. the simulated CT slices are not reconstructed from a simulated sinogram, rather they are extracted directly from the XCAT volume). This is appropriate as our focus is on motion-induced anatomic discontinuities, rather than image blur.

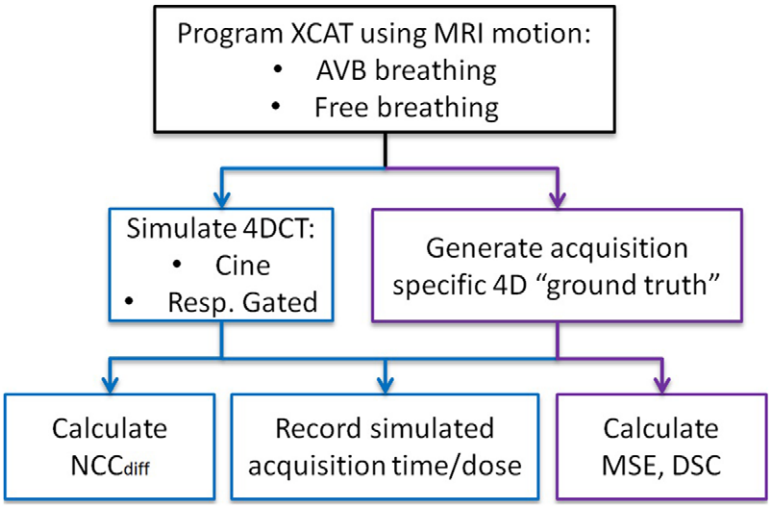

Figure 2. Workflow of study from driving XCAT motion to simulating and analyzing 4DCTs. Purple boxes indicate workflow and metrics utilizing the ground truth images. Blue boxes indicate workflow and metrics that did not utilize the ground truth.

For the case of perfect 4D sampling (i.e. no duplicate or missing phase/couch combinations), each simulation will nominally produce 1200 axial slices that are binned into 10 respiratory phase bins. We also generate a set of 'Ground truth' 4D phase images, which give the average of all instantaneous XCAT volumes generated for each phase bin. These motion-blurred images represent the 'average' anatomic geometry during beam-on time. We note that while our simulation of the respiratory gated acquisition was performed retrospectively, the kV triggering is nevertheless based on measured, real-time RPM phase/displacement data as would be the case for a clinical implementation of this gating method.

2.3. Image analysis metrics

Image quality was quantified by (1) an automated method of assessing the presence of image artefacts (Cui *et al* 2012), (2) MSE intensity difference between the simulated 4DCT and ground images (Bernatowicz *et al* 2015), and (3) the dice similarity coefficient (DSC) between simulated 4DCT and ground truth images (Bernatowicz *et al* 2015).

Respiratory related 4DCT image artefacts were assessed utilizing a method developed by Cui *et al* (2012). Specifically, for each 4DCT phase image we calculate the normalized cross correlation (NCC) of pixel values between each pair of adjacent axial slices:

$$\mathrm{NCC}(i,z) = \frac{\sum_{x,y} I(i,z)I(1,z+1)}{\sqrt{\sum_{x,y} I(i,z)^2 \times \sum_{x,y} I(1,z+1)^2}} \tag{1}$$

In equation (1), i specifies the phase bin, z specifies the axial slice and x, y refer to the pixel location in the transverse plane. An NCC value closer to 1 indicates better agreement in pixel values between adjacent slices, conversely a value closer to 0 indicates poor agreement. Unlike the DSC metric, the NCC values are calculated in the absence of any tumor intensification. We then obtain an artefact rating, NCCdifff which accounts for the sum of differences in NCC values at couch transition points across each reconstructed 4DCT phase image:

$$\mathrm{NCC}_{\mathrm{diff}}(i) = \sum_{z=2}^{z_{\max}-1} \left| \frac{1}{2} \left[(\mathrm{NCC}(1, n_{\mathrm{bound}} - 1) + \mathrm{NCC}(i, n_{\mathrm{bound}} + 1)) - \mathrm{NCC}(i, n_{\mathrm{bound}}) \right] \right| \quad (2)$$

Where n_{bound} represents the slice index for the transition between the nth and $(n+1)$th couch position. Here, a value of $\mathrm{NCC}_{\mathrm{diff}}$ closer to 0 indicates smaller differences in the NCC values between adjacent axial slice pairs across the image, and hence fewer anatomic discontinuities.

We note that $\mathrm{NCC}_{\mathrm{diff}}$ should not be interpreted as an absolute artefact 'count' as it may also capture information about non-artefactual anatomic discontinuities. For example, a slice pair straddling the diaphragm edge will likely exhibit a poorer NCC value than for slice pairs where both slices are just above or just below the edge. Since all 4DCT reconstructions have the same geometry at exhale (aside from the tumor), and thus similar contributions to $\mathrm{NCC}_{\mathrm{diff}}$ from non-artefact discontinuities, we interpret $\mathrm{NCC}_{\mathrm{diff}}$ as an artefact 'rating' or 'quality factor'.

DSC between simulated and ground truth images was assessed in terms of lung volume ($\mathrm{DSC}_{\mathrm{lung}}$) and lung tumor volume ($\mathrm{DSC}_{\mathrm{tumor}}$). To more easily evaluate the tumor volume, the tumor volume was intensified by a factor of 10, as per the method described by Bernatowicz *et al* (2015). The intensity values of tumor voxels was multiplied by a factor of 10 to aid in segmentation; this modification of the tumor intensities was performed only for the $\mathrm{DSC}_{\mathrm{tumor}}$ analysis so does not affect the NCC or MSE values.

These image analysis metrics were compared across the two breathing conditions (AVB and free breathing) for the two 4DCT acquisition modes (cine and respiratory gated) using the Student's *t*-test. 4DCT imaging dose and acquisition times were also recorded across the two breathing conditions and two reconstruction methods. It should be noted that the image dose estimate is based on the number of acquired slices; results presented here will be in number of slices as a surrogate for imaging dose.

2.4. Correlation between image analysis metrics and respiratory motion

The correlation between the image analysis metrics and lung tumor motion regularity in addition to acquisition time and lung tumor motion regularity was assessed using the Pearson's correlation coefficient (R), and a p-value for testing the hypothesis of no correlation. Pearson's correlation coefficient has been utilized as the correlation test in previous internal–external respiratory motion studies (Ionascu *et al* 2007, Steel *et al* 2014). Respiratory motion regularity was quantified by the root mean square error (RMSE) in displacement (Venkat *et al* 2008) of the respiratory signal of chest motion during beam-on time only. A lower value of RMSE is indicative of more regular motion. We investigated the potential dependence of imaging time on displacement RMSE for both cine and respiratory gated acquisition modes. For the respiratory-gated mode it seems intuitive that highly irregular breathing could affect the scan time. For cine mode the connection between displacement RMSE and scan time is more subtle; since in our study the cine mode uses a 'patient specific' cine duration set at one breathing period (T_{Avg}) + 1 s, it follows that irregularities in the breathing period (or alternately, displacement) could affect the cine mode scan times as well.

3. Results

3.1. Reconstructed 4DCT Images of XCAT Phantom

Figure 3 illustrates the original MRI and 4DCTs for Patient 4, whose resultant $\mathrm{NCC}_{\mathrm{diff}}$ value in cine mode was the median.

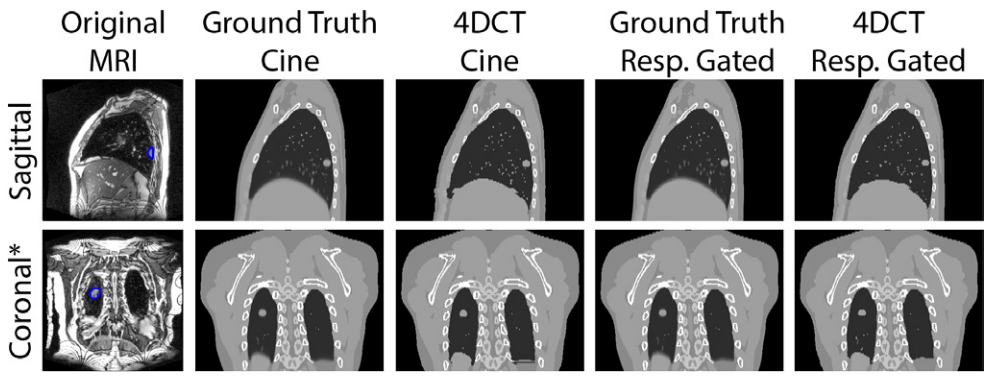

Figure 3. Left to right: Original MR image (tumor outlined in blue), simulated inhale phase images for cine ground truth 4DCT, cine mode 4DCT and respiratory gated (Resp. Gated) ground truth 4DCT, and Resp. Gated 4DCT in the sagittal (top) and coronal (bottom) planes for Patient 4. *Coronal MR images acquired at different times to sagittal MR images, only data from sagittal MR images was used to program XCAT motion. Coronal MR image is shown here to demonstrate anatomic comparison to reconstructed 4DCT coronal images.

The ground truth images in figure 3 also demonstrate some blurring, particularly around the thoracic diaphragm. This blurring arises because the ground truth was constructed from a range of anatomic positions during beam-on time.

3.2. 4DCT Image Analysis Metrics

NCC_{diff}, MSE, DSC_{lung}, and DSC_{tumor} values were generated for each 4DCT respiratory bin, as such, 10 metric values were generate for each simulated 4DCT. The results for these metrics are shown in figure 4; average values and their statistical significance are shown in table 2.

Merging the data from the AVB and free breathing conditions, cine mode yielded mean NCC_{diff}, MSE, DSC_{lung}, and DSC_{tumor} values of 0.099, 9.4×10^{-7}, 0.980, and 0.889 respectively. Respiratory gating improved the NCC_{diff}, MSE, DSC_{lung}, and DSC_{tumor} values by 36% ($p < 0.001$), 42% ($p < 0.001$), 0.7% ($p < 0.001$), and 2.3% ($p = 0.01$), over cine mode respectively. With the exception of DSC_{tumor}, the largest improvements were obtained when utilizing both AVB and respiratory gating together, which improved NCC_{diff}, MSE, DSC_{lung}, and DSC_{tumor} values by 52% ($p < 0.001$), 59% ($p < 0.001$), 1.2% ($p < 0.001$), and 3.5% ($p = 0.01$), respectively, compared to cine mode 4DCT under free breathing. For the DSC values, this translates to an additional 38 cm^3 of correctly imaged lung volume and an additional 0.9 cm^3 of correctly imaged tumor volume. While we cannot guarantee that the volumes encompassed by these respective contours are imaged correctly, from a treatment planning perspective the impact of modified contours on the dose-volume calculations may still be significant. A surprising result here is that the use of AVB and respiratory gating yielded inferior (though non-significant) DSC_{tumor} values compared to AVB with cine mode in addition to free breathing with respiratory gating.

3.3. Image dose and acquisition time

Figure 5 shows the mean $\pm$ standard deviation 4DCT acquisition times and imaging dose across cine mode and respiratory gated mode for AVB and free breathing patients. Number of slices acquired is given as a surrogate for imaging dose.

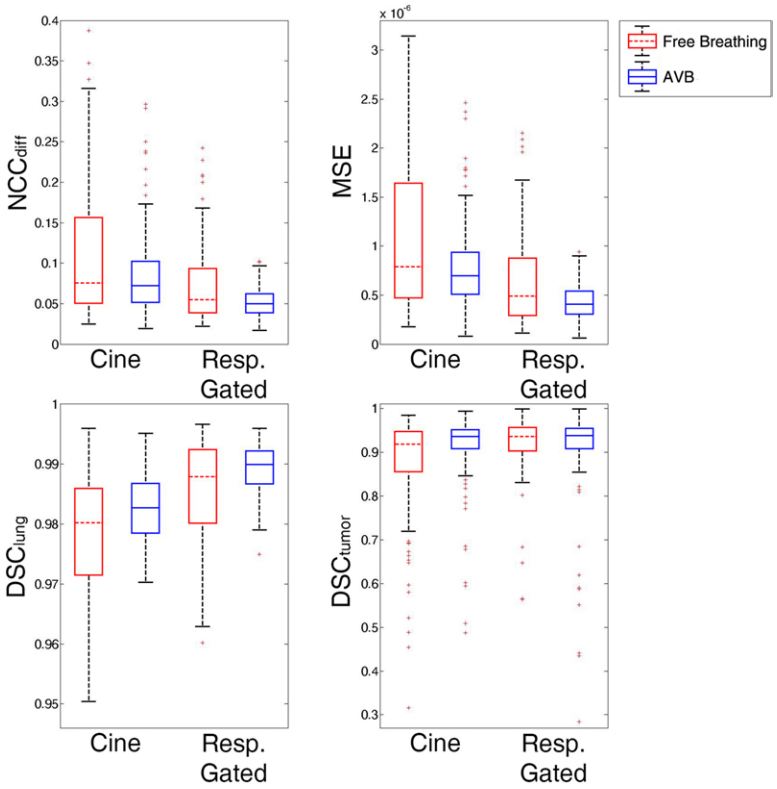

Figure 4. Image analysis metrics, from left to right: NCC_{diff}, MSE, DSC_{lung}, and DSC_{tumor} for both cine and respiratory gated (Resp. Gated) reconstruction modes. AVB shown as blue boxes, solid lines. Free breathing shown as red boxes, dashed lines. The data plotted are each of the 10 respiratory phase bins for each patient. The horizontal edges of each box represent the 25th, 50th and 75th percentile values. Whiskers represent other points extending out to 1.5 times the interquartile range. Any points beyond the whiskers ('+') are considered outliers.

Merging the data from the AVB and free breathing conditions, cine mode yielded a (mean $\pm$ STD) acquisition time of 227 $\pm$ 23 s, 31% faster than respiratory gated mode which had an acquisition time of 328 $\pm$ 89 s. Interestingly, the impact of AVB on acquisition times was opposite between the two acquisition modes. In cine mode, AVB increased the average imaging time by 15 s compared to free breathing ($p = 0.02$); whereas in respiratory gated mode, AVB reduced the average imaging time by 31 s compared to free breathing ($p = 0.41$). In cine mode, AVB increased the estimated average imaging dose by 10% compared to free breathing ($p = 0.05$); whereas the respiratory gated mode always acquired 1200 slices by construction as this represents the ideal 4D sampling for this simulation (10 phase bins with 120 slices each). It should be noted that the number of slices in respiratory gated mode was 1200 by construction, as 1200 slices represents the ideal dose for this simulation.

3.4. Correlation between image analysis metrics and respiratory motion

Table 3 compares values of the displacement RMSE during beam-on time for different breathing conditions and acquisition modes.

Table 2. Average AVB and free breathing image analysis metrics values for cine and respiratory gated 4DCT reconstruction methods.

NCC_{diff}			
	Free breathing	AVB	Improvement due to AVB
Cine	0.111	0.089	20% ($p = 0.008$)
Respiratory gated	0.075	0.053	29% ($p < 0.001$)
Improvement due to resp. gated	32% ($p < 0.001$)	40% ($p = 0.001$)	
MSE			
	Free breathing	AVB	Improvement due to AVB
Cine	10.6×10^{-7}	8.2×10^{-7}	23% ($p < 0.001$)
Respiratory gated	6.5×10^{-7}	4.3×10^{-7}	34% ($p < 0.001$)
Improvement due to resp. gated	39% ($p < 0.001$)	47% ($p < 0.001$)	
DSC_{lung}			
	Free breathing	AVB	Improvement due to AVB
Cine	0.978	0.982	0.5% ($p < 0.001$)
Respiratory gated	0.986	0.989	0.4% ($p < 0.001$)
Improvement due to resp. gated	0.8% ($p < 0.001$)	0.7% ($p < 0.001$)	
DSC_{tumor}			
	Free breathing	AVB	Improvement due to AVB
Cine	0.871	0.907	4.0% ($p = 0.003$)
Respiratory gated	0.917	0.901	−1.6% ($p = 0.20$)
Improvement due to resp. gated	5.2% ($p < 0.001$)	−0.6% ($p = 0.63$)	

Note. Values presented here represent the average of all respiratory phase bins across all patients.

For each combination of breathing condition and acquisition mode, the RMSE values are different owing to the different acquisition timing.

Figure 6 shows the variation of the image analysis metrics (NCC_{diff}, MSE, DSC_{lung}, and DSC_{tumor}) and acquisition time as a function of the RMSE values, separated according to breathing condition and acquisition mode. For any given acquisition mode, AVB produced a smaller range of RMSE values compared to free breathing. For each panel of figure 6, table 4 shows the Pearson's correlation coefficient irrespective of breathing condition.

4. Discussion

This was the first study to quantify the impact of AVB breathing guidance on 4DCT image analysis metrics. As shown in tables 2 and 3, with the exception of DSC_{tumor} in respiratory gated mode, AVB significantly improved 4DCT image analysis metrics across both acquisition

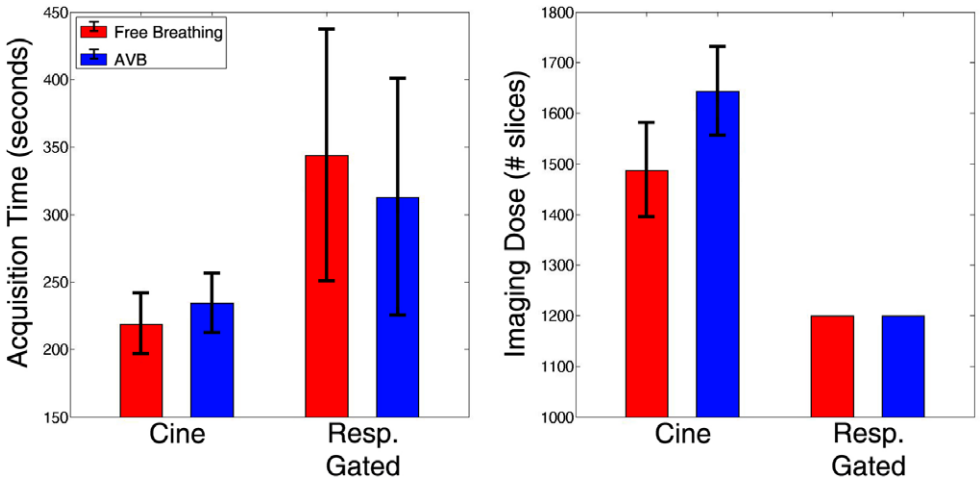

Figure 5. 4DCT acquisition times (left) and imaging dose (right) with number of slices as a surrogate for dose, for AVB (blue) and free breathing (red) patients for both cine mode and respiratory gated mode.

Table 3. Mean ± STD RMSE in displacement during beam-on time for AVB and free breathing for the two acquisition modes.

	RMSE in displacement (cm)		
	Free breathing	AVB	Improvement due to AVB
Cine	0.91 ± 0.99	0.61 ± 0.28	33% ($p = 0.30$)
Respiratory gated	0.52 ± 0.58	0.30 ± 0.14	42% ($p = 0.23$)
Improvement due to Resp. Gated	43% ($p = 0.02$)	51% ($p < 0.001$)	

modes. The impact to DSC values, while mostly significant, were small (<1%); whereas the magnitude of the impact of AVB to NCC_{diff} and MSE was considerably larger. Compared to conventional free breathing 4DCT in cine mode, the addition of both AVB and respiratory gated mode improved DSC_{lung}, NCC_{diff}, and MSE by 1.2% ($p < 0.001$), 52% ($p < 0.001$), and 59% ($p < 0.001$), respectively. As illustrated by figure 4, respiratory gated mode yielded better 4DCT image analysis metrics over cine mode, which is consistent with the findings of previous investigations (Langner and Keall 2010, Bernatowicz *et al* 2015). Bernatowicz *et al* (2015) reported slight, but significant, improvements in lung errors of 0.4% due to respiratory gated mode compared to cine mode (Bernatowicz *et al* 2015); comparable to the 0.7% improvement of respiratory gated mode over cine mode demonstrated here.

As shown in table 4, motion regularity (RMSE) during beam-on time significantly correlated with DSC_{lung}, NCC_{diff}, and MSE in cine and respiratory gated acquisition modes, in addition to significantly correlating with acquisition time in respiratory gated mode. It is important to note that other factors beyond RMSE in displacement will impact image analysis metrics and acquisition time. For instance, the average period increased from 4.3 s under free breathing to 4.8 s using AVB. Thus the use of AVB lead to increased cine duration time ($T_{Avg} + 1$ s) explaining why AVB produced longer cine acquisition times and increased imaging dose compared to free breathing in figure 5. It should be noted that will not be the case for clinical 4DCT

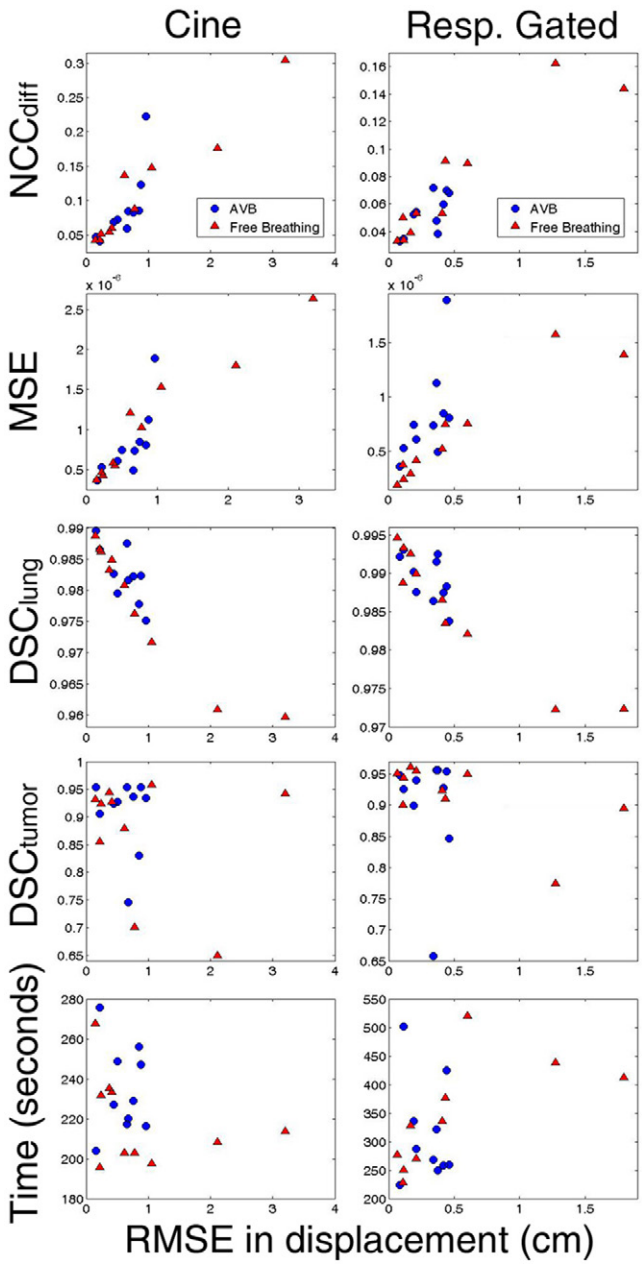

Figure 6. From top to bottom: NCC_{dif}, MSE, DSC_{lung}, DSC_{tumor}, and acquisition time verses RMSE in displacement for bean-on time for AVB (blue) and free breathing (red) patients for both cine mode (left) and respiratory gated mode (right).

protocols using a fixed cine-duration time (as opposed to the patient specific cine duration of $T_{Avg} + 1$ s). In respiratory gated mode, AVB reduced acquisition times as a result of improved motion regularity, which has been shown to improve gating efficiency in previous studies (George *et al* 2006, Linthout *et al* 2009, Lee *et al* 2014). Also, each simulation will nominally

Table 4. Pearson's correlation coefficient values (r) and their p-values for the correlations between respiratory motion regularity (RMSE) and image analysis metrics irrespective of breathing condition.

	Correlation between RMSE and	r value	p-value
Cine	NCC_{diff}	0.89	<0.001
	MSE	0.91	<0.001
	DSC_{lung}	−0.92	<0.001
	DSC_{tumor}	−0.23	0.32
	Acquisition time	−0.29	0.21
Respiratory gated	NCC_{diff}	0.91	<0.001
	MSE	0.68	<0.001
	DSC_{lung}	−0.91	<0.001
	DSC_{tumor}	−0.30	0.19
	Acquisition time	0.46	0.04

produce 1200 axial slices that are binned into 10 respiratory phase bins and respiratory gating is optimized to produce exactly 1200 axial slices, which is why the mean ± standard deviation number of slices for respiratory gating are 1200 ± 0 for both AVB and free breathing, as shown in figure 5.

Furthermore, while DSC_{tumor} was the only image analysis metric not to significantly correlate with motion regularity, it was found that DSC_{tumor} did significantly correlate with the tumor motion range values (given in table 1) for both cine mode ($r = -0.79$, $p < 0.001$) and respiratory gated mode ($r = -0.86$, $p < 0.001$). Given that the average peak-to-peak amplitude of free breathing was 0.5 cm and 0.6 cm for AVB, this may explain why an improvement was not observed for AVB in respiratory gated mode. Further to this, 4DCT gating and binning is based on the signal of an external surrogate and not the motion of the tumor itself.

This study builds upon previous investigations which assessed the impact of breathing guidance interventions on medical image quality. Yang *et al* (2012) found that AVB reduced motion blurring and improved Dice coefficient of the tumor in PET images of a thoracic phantom (Yang *et al* 2012). Jhooti *et al* (2011) and Lee *et al* (2014) observed a reduction in MRI scan time from the use of breathing guidance with only the Lee *et al* (2014) study noting an improvement in image quality. Importantly, table 4 indicates that respiratory motion regularity (RMSE in displacement) during beam-on time may be a useful metric for predicting quantitative aspects of 4DCT image analysis metrics. It would be interesting to test how well RMSE correlates with other clinically relevant measures of 4DCT image quality (e.g. absolute artefact counts).

A limitation of this study, as evident from figure 3, is that the anatomy of the XCAT digital phantom did not exactly match that of the original MR images. Differences in tumor shape, organ shapes, and organ volumes between the XCAT and MRI scans may be observed. Despite these differences, the XCAT represents a population averaged anatomy, based on visible human data from the National Library of Medicine (Segars *et al* 2010, National Library of Medicine), so these results should be relevant to a large percentage of the adult (male) population receiving 4DCT scans. An additional limitation is that our 4DCT simulations assumed x-ray collimation of 4 × 2.5 mm at the detectors, whereas newer scanners might have 8×, 16 × , or more which would decrease the number of couch transition regions where breathing-induced image discontinuities might occur. In other words, our simulations may overestimate the impact of AVB or respiratory gating for wide field of view 4DCT scanners. This study

attempted to adapt the XCAT simulations to the MRI acquisition as much as possible by utilizing the several elements of the MRI patient data: tumor motion, diaphragm motion, chest motion, abdominal motion, tumor volume, and tumor position. Despite this, diseased lung can exhibit localised variations in the motion field that are not so easily modelled using XCAT. For tumors in the vicinity of emphysematous or fibrotic regions, the measured motion may appear different compared to the XCAT motion which assumes smoothly varying motion over the lung. Further to this, the MRI data utilized in this study had an acquisition time of approximately 158 s, shorter than the time needed to complete a 4DCT simulation. As such, the motion traces were repeated until the 4DCT image acquisition was complete; the discontinuity between these repeated motion segments is not ideal.

Additionally, a limitation of our RMSE calculation is that we generated a 'mean' cycle based on only 10 phase bins, as opposed to a much larger number (e.g. 360) in other studies (Venkat *et al* 2008, Pollock *et al* 2015c). This seemed appropriate due to the instantaneous nature of the simulated beam-on events which leads to a sparse amount of displacement data during beam on time, resulting in a larger magnitude of RMSE results compared to previous investigations.

The results presented here support our hypothesis that AVB resulted in improved 4DCT image analysis metrics over free breathing. The respiratory gated mode resulted in improved 4DCT image analysis metrics over cine mode, however, acquisition time was faster in cine mode compared to the respiratory gated mode. This study indicates that respiratory gated mode can benefit from AVB not only in terms of improved image analysis metrics, but also in reduced acquisition times compared to free breathing. AVB and respiratory gated mode represent two emerging techniques to improve the quality of 4DCT images, producing the best image analysis metrics when used simultaneously.

5. Conclusion

This was the first study to compare the impacts of AVB breathing guidance, and prospective respiratory gated acquisition on 4DCT image analysis metrics compared to free breathing cine mode 4DCT. Compared to free breathing, AVB was demonstrated to significantly improve the image analysis metrics of both cine and respiratory gated modes of 4DCT acquisition, and can reduce the amount of time needed to acquire a respiratory gated 4DCT scan. Meanwhile, respiratory-gating consistently yielded better image analysis metrics over cine mode irrespective of the breathing condition. The results presented here demonstrate both AVB and the respiratory gated acquisition mode as potential tools to implement in CT simulation for cancer radiation therapy. Statistically significant improvements in image analysis metrics can be realized for a small increase in time when AVB and respiratory gated mode are utilized simultaneously.

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CHAPTER 4

Audiovisual biofeedback breathing guidance over a course of liver SBRT: A motion analysis of external and internal surrogates

CHAPTER 4

Audiovisual biofeedback breathing guidance over a course of liver SBRT: A motion analysis of external and internal surrogates

4.1. Introduction

Stereotactic body radiotherapy (SBRT) is a high-precision, high-dose irradiation of a lesion in a small number of fractions.[1] SBRT has been incorporated into the treatment of liver cancer due to its demonstrated effectiveness in clinical studies as well as improving survival rate[2, 3] with over 54% of liver cancer patients being treated with SBRT in America.[4] Liver tumours are considered highly mobile due to their proximity to the thoracic diaphragm. When this breathing motion is irregular, it exacerbates systematic and random errors,[5-7] compromising the quality of radiation therapy;[6, 8-11] which is a particular concern for such hypofractionated treatments as SBRT.

To counter this exacerbation of systematic and random errors due to irregular breathing motion a number of breathing guidance strategies have been investigated to engage with the patient to facilitate stable and regular breathing.[12-15] Such breathing guidance strategies have also been investigated with liver cancer patients with demonstrated benefits.[16, 17] A study by Linthout *et al.* (2009) investigated the use of breathing guidance during lung and liver cancer SBRT and found that audio-visual breathing guidance significantly reduced gated treatment times by 17%.[16] The audiovisual biofeedback system, developed by Venkat *et al.*,[14] has demonstrated to significantly improve breathing regularity for both external motion surrogates and internal anatomic motion.[13, 14] A volunteer study by Kim, *et al.* found that audiovisual biofeedback significantly improved the regularity of thoracic diaphragm breathing motion.[13] An MRI lung cancer patient study by Lee, *et al*. found that audiovisual biofeedback significantly improves the regularity of lung tumour motion.[18] However, based on a recently performed systematic review on breathing guidance interventions, provided in chapter 2., only 2 of the 27 identified articles recruited liver cancer patients.[15] Despite being highly mobile tumours being treated increasingly with hypofractionated treatments, a gap in the literature exists in terms of investigating the use of breathing guidance with liver cancer patients during radiation treatment.

This study was the first to implement a screening procedure prior to CT simulation to ensure that the most regular breathing condition (free breathing or audiovisual biofeedback) was utilised throughout the patient's treatment. The primary objective of this clinical trial was to evaluate the improvement in the reproducibility of respiratory-related motion for liver cancer patients with the

audiovisual biofeedback system. The reproducibility of respiratory motion was evaluated both intrafractionally and interfractionally for both external and internal surrogates. Secondary objectives include assessing the proportion of patient for whom audiovisual biofeedback improved respiratory motion regularity, evaluation of the correlation between internal fiducial marker and external marker motion, and an evaluation of the patient and operator experience with the audiovisual biofeedback system though a survey will be performed. A direct comparison between free breathing and audiovisual biofeedback was performed during the screening procedure when each patient underwent both breathing conditions. An unpaired comparison between free breathing and audiovisual biofeedback patients was then performed for subsequent CT sim and treatment sessions when each patient exclusively utilised either free breathing or audiovisual biofeedback breathing conditions.

Presented here are the findings of subsequent liver cancer patients recruited into the study.

4.2. Method

The ethics, governance, legal, and regulatory processes were completed prior to the initiation of the clinical trial. The clinical trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR), trial ID: ACTRN12613000110785. The protocol accepted by ethics is provided in Appendix II.

4.2.1. Patient information

The eligibility criteria for patients to be recruited in this study are as follows:

- Liver cancer patients, either primary hepatocellular carcinoma or liver metastases, eligible for stereotactic radiotherapy
- Older than 18 years old
- No gender or ethnic restrictions
- Radio-opaque markers implanted (fiducials and/or surgical clips previously implanted in the liver)
- Able to give written informed consent and willingness to participate and comply with the study
- No pregnant/lactating women

Table 4-1 details the information of patients recruited into this study.

***Table 4-1**. Patient and treatment information.*				
Age	**Sex**	**Prescribed dose**	**Number of fractions**	**Tumour surrogate**
65	M	36 Gy	6	Surgical clips
75	M	36 Gy	6	Fiducial markers
59	M	36 Gy	6	Surgical clips
53	M	48 Gy	6	Surgical clips
58	M	48 Gy	6	Fiducial markers

4.2.2. Audiovisual Biofeedback

The audiovisual biofeedback system, developed by Venkat *et al*,[14] and described in chapter 1.4.2. utilises audio and visual prompts to guide the patient to facilitate regular breathing. The real-time breathing signal is from the Real-time Position Management system (RPM, Varian Medical Systems, Palo Alto, USA). The setup of audiovisual biofeedback in the linac and CT sim rooms is shown below in *Figure 4-1*. The audiovisual biofeedback equipment setup was the same in both rooms, with the system being mounted to the patient table.

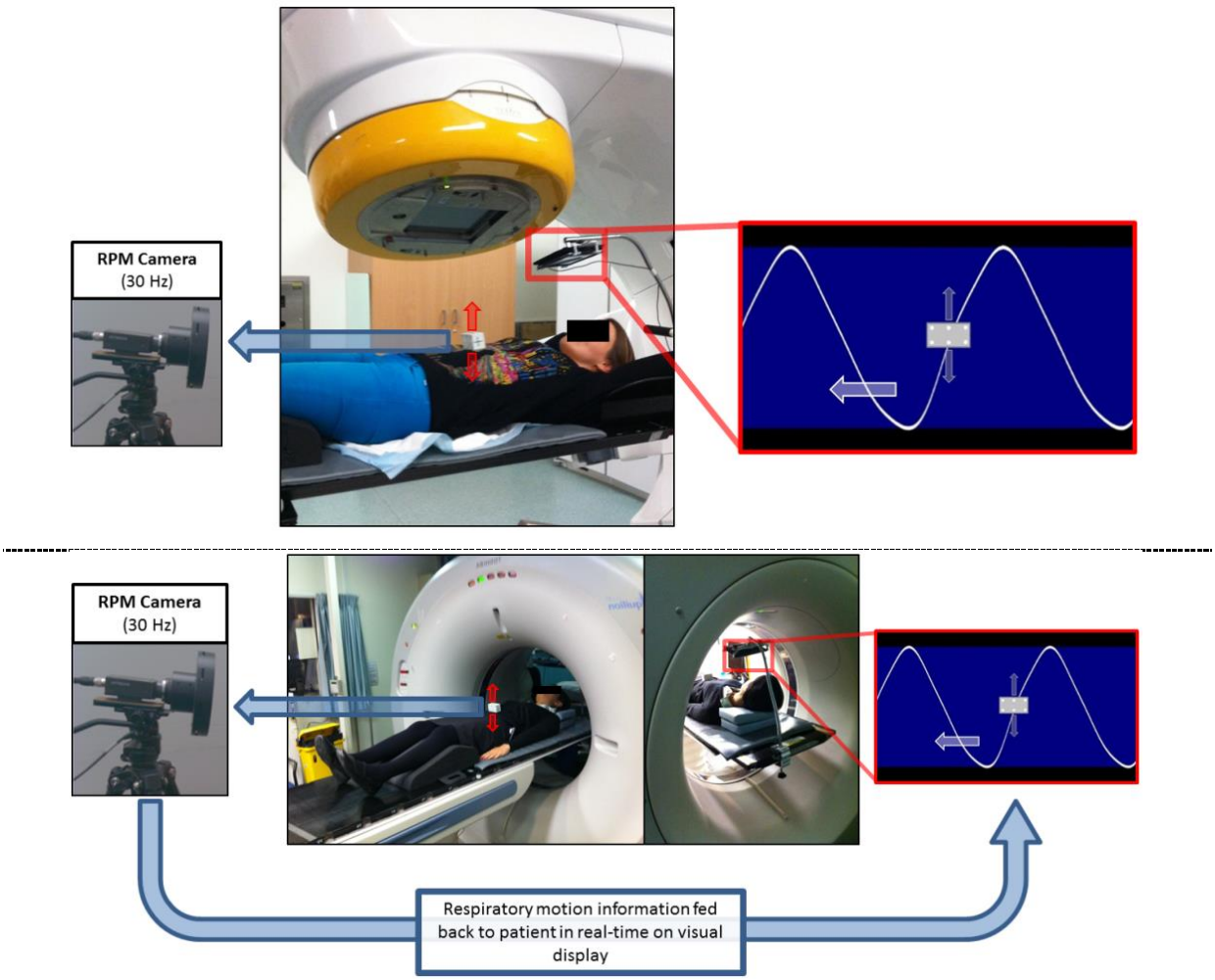


***Figure 4-1**. Study setup in Linac (top) and CT sim (bottom) rooms*

The use of audiovisual biofeedback required the addition of a patient display in each of the rooms with the controlling software being operated by a radiation therapist in the control room. The patient display was held over the patient's head at a comfortable distance by a goose-neck clamp which was mounted to the patient couch by a c-clamp. Gantry clearance from the patient display & clamp was checked each day in the linac room. Real-time breathing signal was acquired from the RPM system; the RPM infra-red camera was mounted on the ceiling of each room.

4.2.3. Study Protocol & Workflow

After the patient consented to participating in the study they underwent a screening procedure to determine which breathing condition will be utilised in their imaging and treatment, either (1) free breathing, or (2) audiovisual biofeedback. After the screening procedure, either free breathing or

audiovisual biofeedback would be utilised in their 4D-CT imaging and subsequent course of SBRT. Study workflow is shown in Figure 4-2.

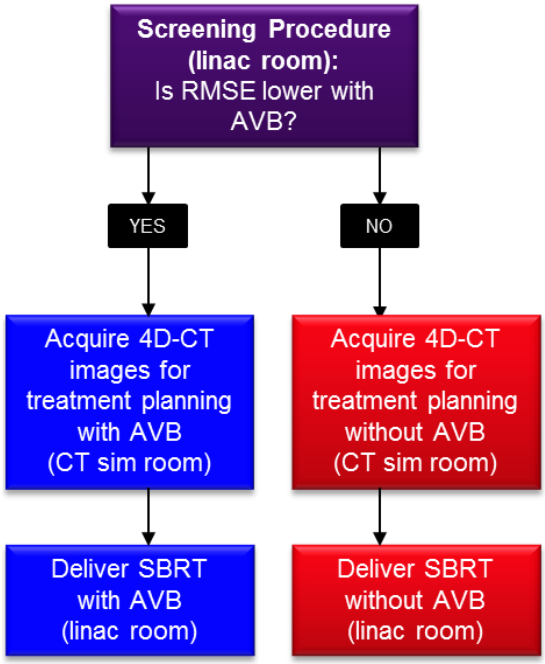


***Figure 4-2**. General flowchart of the study from screening procedure to treatment*

The study progressed much the same as per current liver SBRT standard of care with the addition of an audiovisual biofeedback screening procedure prior to the CT sim and then the implementation of audiovisual biofeedback during treatment planning and treatment delivery should that be the resultant decision yielded from the screening procedure.

4.2.3.1. Screening Procedure

A screening procedure was performed to ensure that the most regular breathing condition was utilised throughout the patient's subsequent treatment planning and treatment delivery, either (1) free breathing, or (2) audiovisual biofeedback. A training session was performed to familiarise the patient with audiovisual biofeedback. The training session involved a brief information video describing the audiovisual biofeedback system and how to follow it, followed by a one minute practice session using the audiovisual biofeedback system. After the training session, breathing motion was monitored for 4 minutes for each of the breathing conditions (1) free breathing and (2) audiovisual biofeedback. At the 2 minute mark, CBCT images were acquired. Determining which breathing condition would be selected was based on the regularity of the 4 minutes of external breathing motion (regularity quantified by the root mean square error (RMSE) in displacement);[14] the lower the RMSE value, the more regular the breathing motion. Decisions were made *in situ* using

an ‘Analyse Respiratory Session’ function within the audiovisual biofeedback software. Workflow of the screening procedure is shown in Figure 4-3. The breathing condition that was performed first, audiovisual biofeedback or free breathing, alternated between patients.

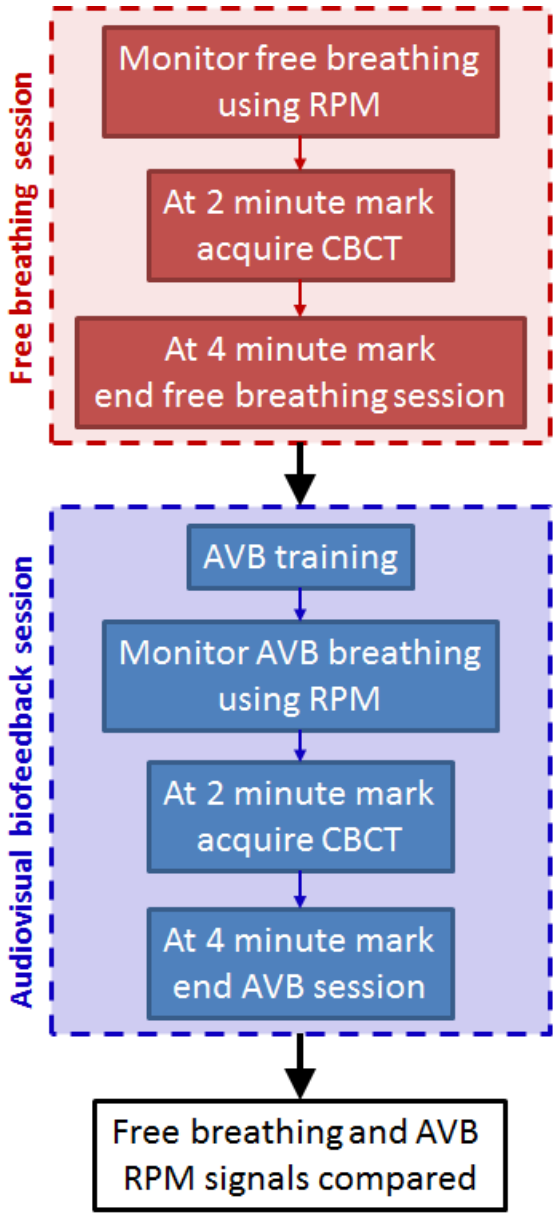


Figure 4-3. *Workflow of the screening procedure. 4 minutes of breathing was recorded from the Varian RPM, with a CBCT acquired at the 2 minute mark, providing 1 minute of internal motion information. The audiovisual biofeedback training included an information video and 1 minute practice with audiovisual biofeedback to determine whether any modifications to the guiding wave were necessary.*

4.2.3.2. Treatment Planning and Treatment Delivery

Treatment planning and treatment delivery proceeded as per the currently implemented clinical liver SBRT protocol with the addition of the audiovisual biofeedback setup, as shown in Figure 4-1, should that be the resultant decision from the screening procedure.

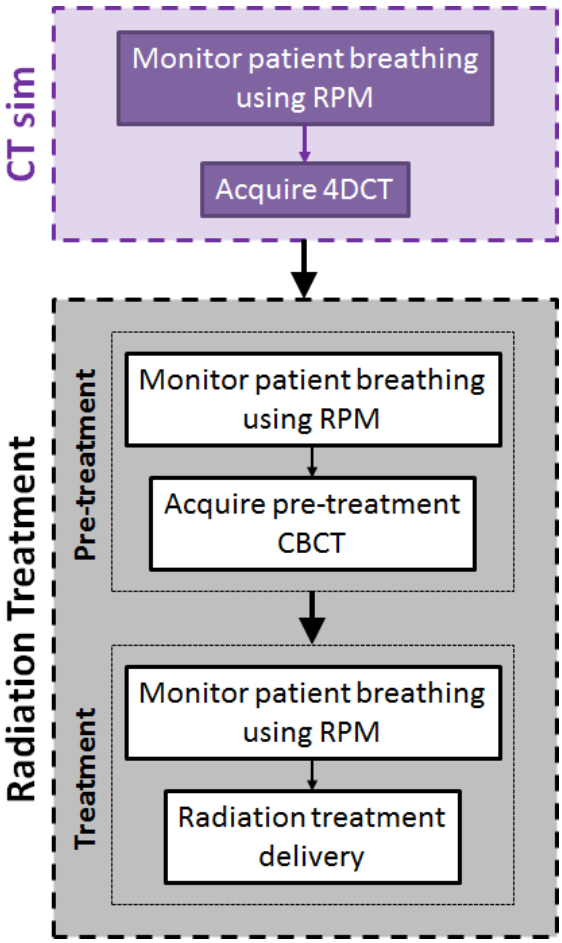


Figure 4-4. *Workflow of treatment planning and treatment delivery. Only the RPM signal was acquired during 4DCT imaging. During radiation treatment, pre-treatment CBCTs are acquired before treatment delivery. Hence, during actual treatment delivery, only external RPM signal was acquired. For each patient, one CT sim session was performed and 6 treatment fractions were performed.*

As evident from Figure 4-4, during radiation treatment, internal breathing motion was acquired in the pre-treatment CBCTs, not during treatment delivery. In reporting the radiation treatment results, the external RPM breathing signal during treatment delivery is reported on, and the internal breathing signal from the CBCTs during pre-treatment are reported on.

4.2.3.3. Data Analysis

To satisfy the primary and secondary objectives, intrafraction and interfraction breathing motion was assessed in addition to the internal-external motion correlation, and reporting on the survey results. External breathing motion was extracted from the RPM text files. Internal breathing motion of implanted radio-opaque markers was extracted from the CBCT projections images utilising a method developed by Poulsen, *et al*,[19, 20] and illustrated in Figure 4-5.

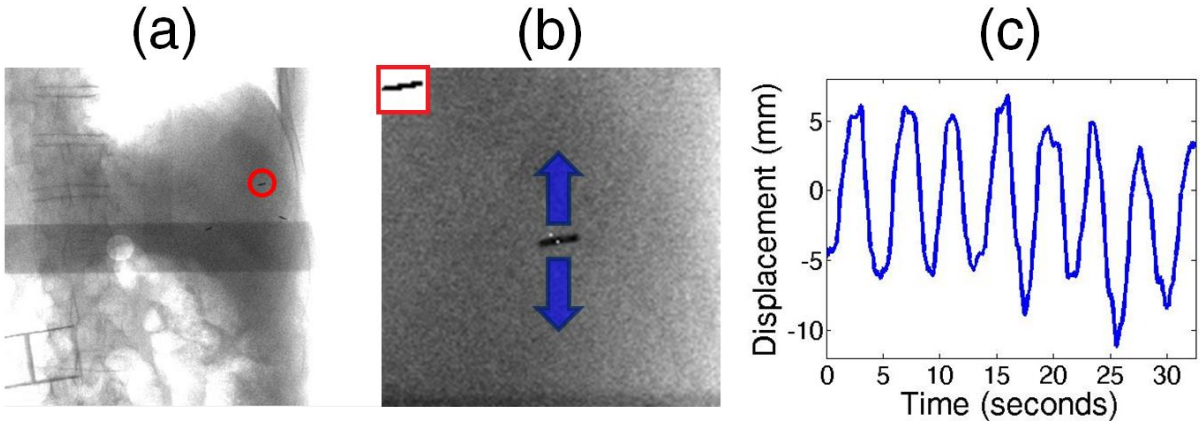


Figure 4-5*. (a) CBCT projection image with marker to be tracked circled in red. (b) Segmented marker highlighted in red square, with the marker being tracked as it moves. (c) Motion of the tracked fiducial marker. Data analysis was performed for the screening procedure and SBRT treatment separately. The screening procedure allowed a direct comparison between free breathing and audiovisual biofeedback for all patients as they underwent both breathing conditions in the screening procedure. Whereas for the CT sim and treatment delivery the patient underwent these procedures under one breathing condition only.*

It should be noted that while Figure 4-5 illustrates the one dimensional superior-inferior breathing motion of the implanted radio-opaque marker, the method developed by Poulsen, *et al*[19, 20] obtains three dimensional information of the marker. The method developed by Poulsen, *et al*[19, 20] utilises the two dimensional rotating coordinate system from the CBCT images to estimate the 3D marker trajectory. Figure 4-5 illustrates the superior-inferior motion as this is the dominant direction of breathing motion due to its proximity to the thoracic diaphragm, and is what was analysed in the results section.

4.2.3.3.1. Breathing Motion Regularity

External and internal breathing motion were analysed by assessing the regularity of breathing motion, quantified as the root mean square error (RMSE) of displacement and period.[13-15, 21, 22]

RMSE was calculated was described by equations 1 and 2. For a breathing pattern comprised of n individual breathing cycles, where each cycle in the phase domain can be written as $X = \{x_1, x_2, \dots, x_{360}\}$ and the average waveform of these cycles can be written as $Y = \{y_1, y_2, \dots, y_{360}\}$, the RMSE in displacement is calculated as:

$$RMSE\ in\ displacement = \frac{\sum_{All\ Cycles} \sqrt{\sum_{i=1\dots360} \frac{(x_i - y_i)^2}{360}}}{n} \quad (1)$$

The period of each of the n breathing cycles, in seconds, can be written as $P = \{p_1, p_2, \dots, p_n\}$, with the period of the average waveform expressed as $Period_{mean}$, the RMSE in period is calculated as:

$$RMSE\ in\ period = \sqrt{\frac{\sum_{i=1\dots n}(p_i - Period_{mean})^2}{n}} \quad (2)$$

4.2.3.3.2. Interfraction Motion Consistency

External respiratory displacement data was also sorted into phase bins from 0% to 90% in 10% increments, as per standard for 4DCT imaging.[23-25] The mean difference of the displacement in each phase bin was compared for each fraction of treatment to the CT sim, normalised by CT sim amplitude, to determine the relative difference between what was planned to motion during treatment, as illustrated by Figure 4-6.

$$\frac{\frac{1}{n}\sum_{i=1}^{n}\left|CT - Fx_n\right|}{Amp_{CT}}$$

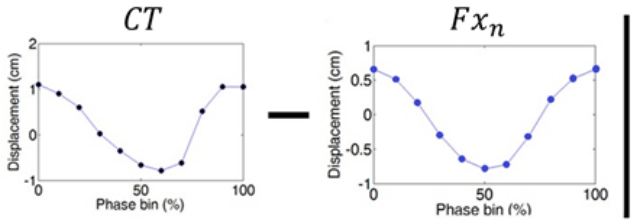


Figure 4-6*. Relative difference between CT bins and treatment bins averaged over all treatment fractions ($n = 6, Fx_1, \dots, Fx_6$). Amp_{CT} refers to the peak-to-peak amplitude of CT sim motion.*

4.2.3.3.3. Internal-External Motion Correlation

The internal-external motion correlation was assessed using the Pearson's correlation coefficient (r), which has been utilised as the correlation test in previous intern-external respiratory motion studies.[26, 27] The Pearson's correlation coefficient was selected as the statistical test of choice because: (1) Pearsons' correlation coefficient is a common test for bivariate data,[28] (2) a scatterplot of the internal-external displacements was plotted to visually inspect the relationship between the two datasets; the relationship clearly appeared to be linear and therefore adequately described by Pearson's correlation coefficient,[28] and (3) also from the visual inspection of the scatterplot, no outlier data was evident (which the Pearson's correlation coefficient is sensitive to), and therefore Pearson's correlation coefficient was still an adequate test.[28] Motion utilised here was from the pre-treatment external and internal breathing motion as indicated in Figure 4-3. It should be noted that the external breathing motion from the Varian RPM was not saved during CBCT

imaging for Patient 1, as such, only Patients 2 – 5 are reported on for the internal-external correlation results.

4.2.3.3.4. Patient and staff survey

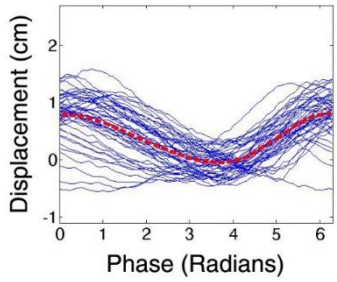
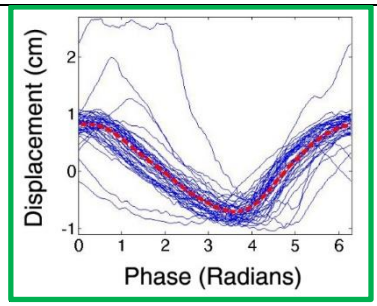
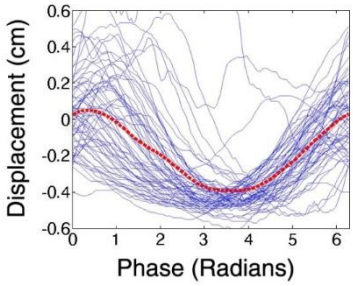
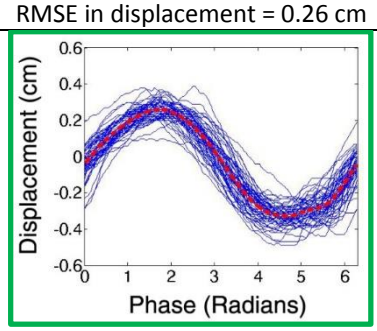
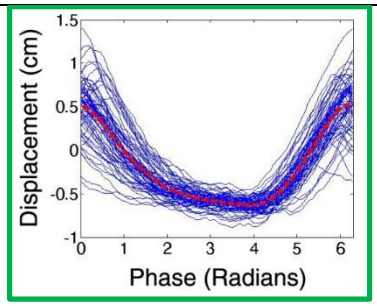
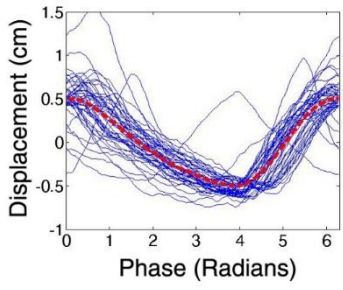
An evaluation of the patient and radiation therapist experience with the audiovisual biofeedback was also assessed though a survey, which can be found in Appendix II. Radiation therapists completed the survey because they were the hospital staff responsible for setting up and audiovisual biofeedback hardware and operating the audiovisual biofeedback software during the study. Surveys were taken by all patients and radiation therapists immediately after the Screening Procedure, and once more on the final fraction of treatment for those patients who had been utilising audiovisual biofeedback during treatment. These surveys involved responding to questions on a scale of 0 to 5 (required), in addition to inviting further comments (optional).

4.3. Results

A Case Report published in the Journal of Medical Imaging and Radiation Oncology (see Appendix III) details the first patient recruited into the study.

4.3.1. Screening Procedure

The screening procedure yielded the decision to utilise audiovisual biofeedback over a course of SBRT with 3 of the 5 recruited liver cancer patients; hence, 2 patients underwent SBRT free breathing. Figure 4-7 compares the individual patient breathing cycles for free breathing and audiovisual biofeedback. Breathing condition outcome of the screening procedure highlighted in green.

Patient	Free Breathing	Audiovisual Biofeedback
1	 RMSE in displacement = 0.31 cm	 RMSE in displacement = 0.26 cm
2	 RMSE in displacement = 0.18 cm	 RMSE in displacement = 0.07 cm
3	 RMSE in displacement = 0.18 cm	 RMSE in displacement = 0.19 cm

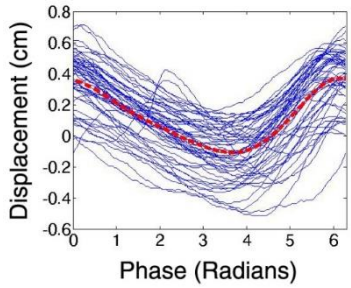
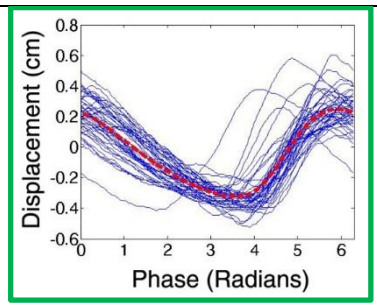
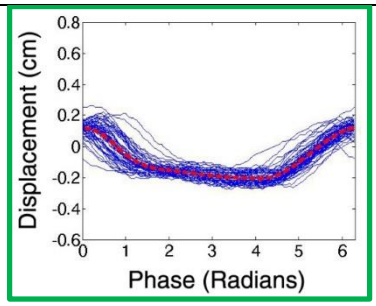
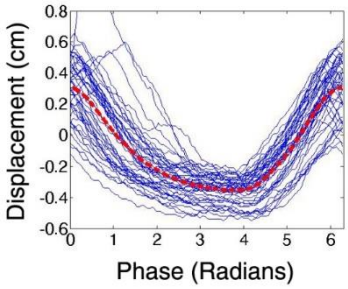
4	 RMSE in displacement = 0.15 cm	 RMSE in displacement = 0.10 cm
5	 RMSE in displacement = 0.05 cm	 RMSE in displacement = 0.15 cm

***Figure 4-7**. Patient breathing cycles for free breathing (left) and audiovisual biofeedback (right). Solid blue lines are each individual breathing cycle, dashed red lines are the average of all breathing cycles. Plots outlined in green indicate the breathing condition that yielded more regular breathing in the screening procedure.*

The average RMSE in displacement values across all patients in the screening procedure are given in Table 4-2.

***Table 4-2.** Screening procedure average ± STD RMSE values for audiovisual biofeedback and free breathing across all patients for external and internal breathing motion.*

RMSE in Displacement			
	Free breathing (cm)	**Audiovisual biofeedback (cm)**	**Improvement due to audiovisual biofeedback**
External motion	0.17 ± 0.09	0.15 ± 0.08	11% (p = 0.6)
Internal motion	0.14 ± 0.06	0.18 ± 0.07	-24% (p = 0.2)
RMSE in period			
	Free breathing (s)	**Audiovisual biofeedback (s)**	**Improvement due to audiovisual biofeedback**
External motion	0.85 ± 0.46	0.56 ± 0.22	34% (p = 0.2)
Internal motion	0.62 ± 0.32	0.42 ± 0.09	33% (p = 0.2)

Audiovisual biofeedback improved the regularity of external breathing period for 4 patients, and improved the regularity of internal breathing period for 3 patients, these 3 patients then utilised audiovisual biofeedback for their subsequent CT sim and treatment deliverry procedures.

4.3.2. CT sim and Treatment Delivery

For the 5 recruited liver cancer patients, 3 utilised audiovisual biofeedback and 2 were free breathing during their CT sim and 6 treatment fractions. Data presented here is organised into each individual patient's course of SBRT (CT sim → fraction 6) in the figures, and mean ± standard deviation values for all audiovisual biofeedback and free breathing patients, respectively. For the data presented as boxplots, the horizontal edges of each box represent the 25^{th}, 50^{th} and 75^{th} percentile values (bottom, middle, and top lines of box, respectively). Whiskers represent other points extending out to 1.5 times the interquartile range. Any points beyond the whiskers ('+') are considered outliers.

4.3.2.1. Motion Regularity

Intrafraction motion regularity of displacement was quantified by equation (1). The screening procedure identified the most regular breathing condition, either free breathing or audiovisual biofeedback, for each patient. Over their courses of SBRT, Patients 1, 2, and 4 utilised audiovisual biofeedback, and Patients 3 and 5 were free breathing, based on the decision made in the screening procedure. Figure 4-8 shows the RMSE in displacement results of external and internal breathing motion across the course of the SBRT. Internal breathing motion was acquired from CBCT projection images, and as such, internal motion was acquired for fractions of treatment only, and not from the CT sim session.

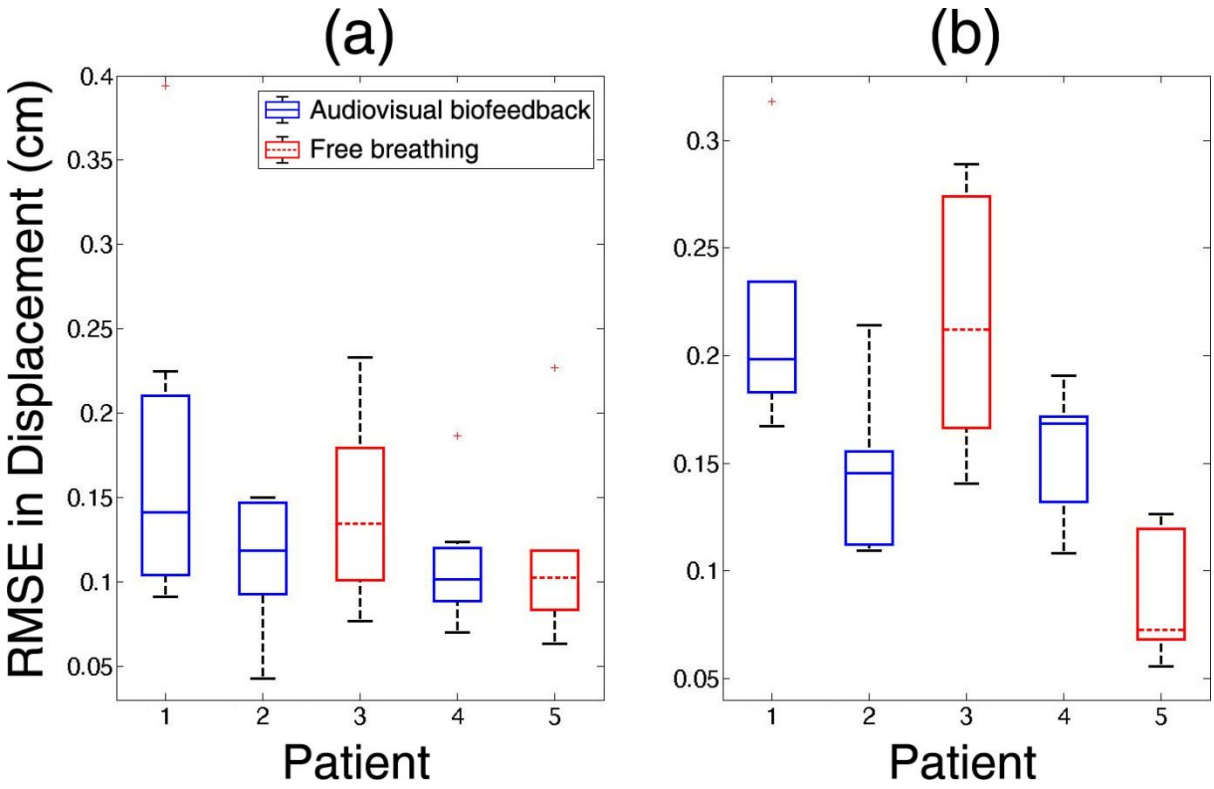


***Figure 4-8**. Average RMSE in displacement values for each patient over the course of SBRT from CT sim to fraction 6 for (a) external motion, and (b) internal motion. Free breathing patients shown as red, audiovisual biofeedback patients shown as blue.*

Intrafraction motion regularity of period was quantified by equation (2). Figure 4-9 shows the RMSE in period results of external and internal breathing motion across the course of the SBRT.

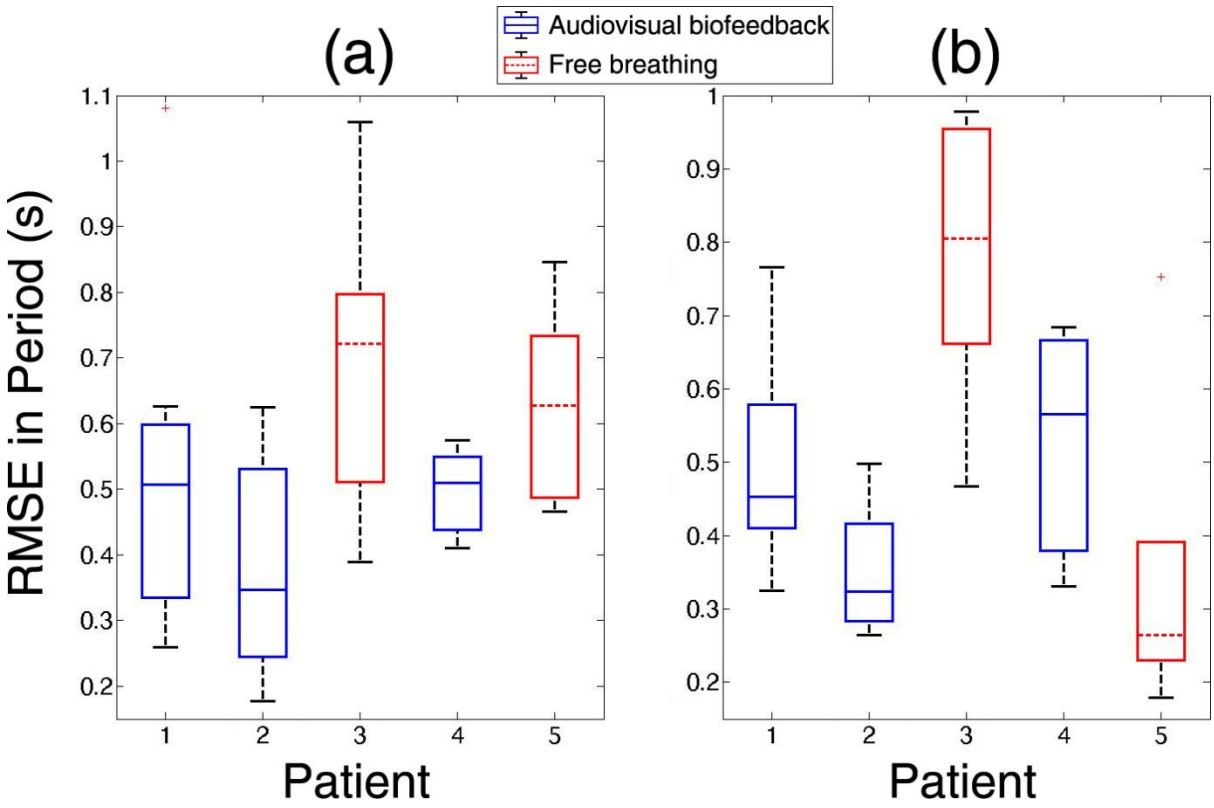


***Figure 4-9**. Average RMSE in period values for each patient over the course of SBRT from CT sim to fraction 6 for (a) external motion, and (b) internal motion. Free breathing patients shown as red, audiovisual biofeedback patients shown as blue.*

***Table 4-3.** Average ± STD RMSE values for audiovisual biofeedback and free breathing for all patients across all treatment fractions for external and internal breathing motion.*			
RMSE in Displacement (cm)			
	Free breathing	**Audiovisual biofeedback**	**Improvement due to audiovisual biofeedback**
External motion	0.13 ± 0.06	0.13 ± 0.07	-2% (p = 0.9) (no improvement)
Internal motion	0.16 ± 0.08	0.17 ± 0.05	-8% (p = 0.7) (no improvement)
RMSE in period (seconds)			
	Free breathing	**Audiovisual biofeedback**	**Improvement due to audiovisual biofeedback**

External motion	0.66 ± 0.19	0.47 ± 0.19	28% (p = 0.01)
Internal motion	0.59 ± 0.29	0.46 ± 0.15	23% (p = 0.2)

In terms of RMSE in displacement, audiovisual biofeedback and free breathing patients demonstrated comparable breathing motion regularity. For external breathing motion, Patient 2 (audiovisual biofeedback) demonstrated the most regular breathing over their course of SBRT with an average RMSE in displacement of 0.11 cm; the next most regular breathing was Patient 4 (audiovisual biofeedback) with an RMSE in displacement of 0.11 cm, followed by Patient 5 (free breathing) with an RMSE in displacement of 0.12 cm, followed by Patient 3 (free breathing) with an RMSE in displacement of 0.15 cm, followed by Patient 1 (audiovisual biofeedback) with an RMSE in displacement of 0.19 cm. For internal breathing motion, Patient 5 (free breathing) demonstrated the most regular breathing over their course of SBRT with an average RMSE in displacement of 0.08 cm; the next most regular breathing was Patient 4 (audiovisual biofeedback) with an RMSE in displacement of 0.15 cm, followed by Patient 2 (audiovisual biofeedback) with an RMSE in displacement of 0.16 cm, followed by Patient 3 (free breathing) with an RMSE in displacement of 0.21 cm, followed by Patient 1 (audiovisual biofeedback) with an RMSE in displacement of 0.22 cm.

4.3.2.2. External Interfraction Motion Consistency

Interfraction motion consistency is described by Figure 4-6, the breathing signal was organised into 10 phase bins, from 0% to 90% in 10% increments. The phase bins from CT sim were compared to the phase bins from each treatment fraction. Figure 4-10 shows the breathing signals from the CT sim and each treatment fraction organised into 10 phase bins for patients 1 to 5 for the CT sim and each fraction of treatment.

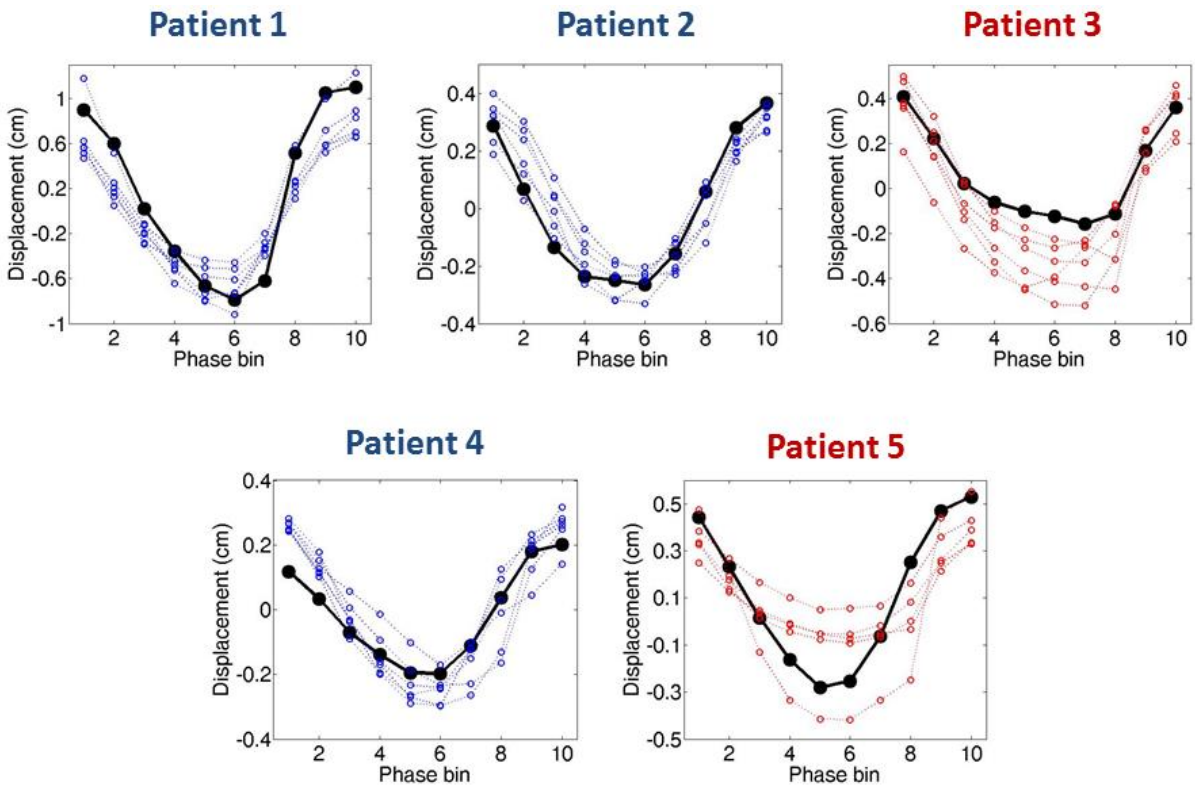


***Figure 4-10**. Breathing displacements organised into 10 phase bins for breathing motion during CT sim (black line, filled markers), and each fraction of treatment (coloured line, hollow markers) for free breathing (red) and audiovisual biofeedback (blue) patients.*

The difference of each fraction of treatment to the CT sim are shown in Figure-14.

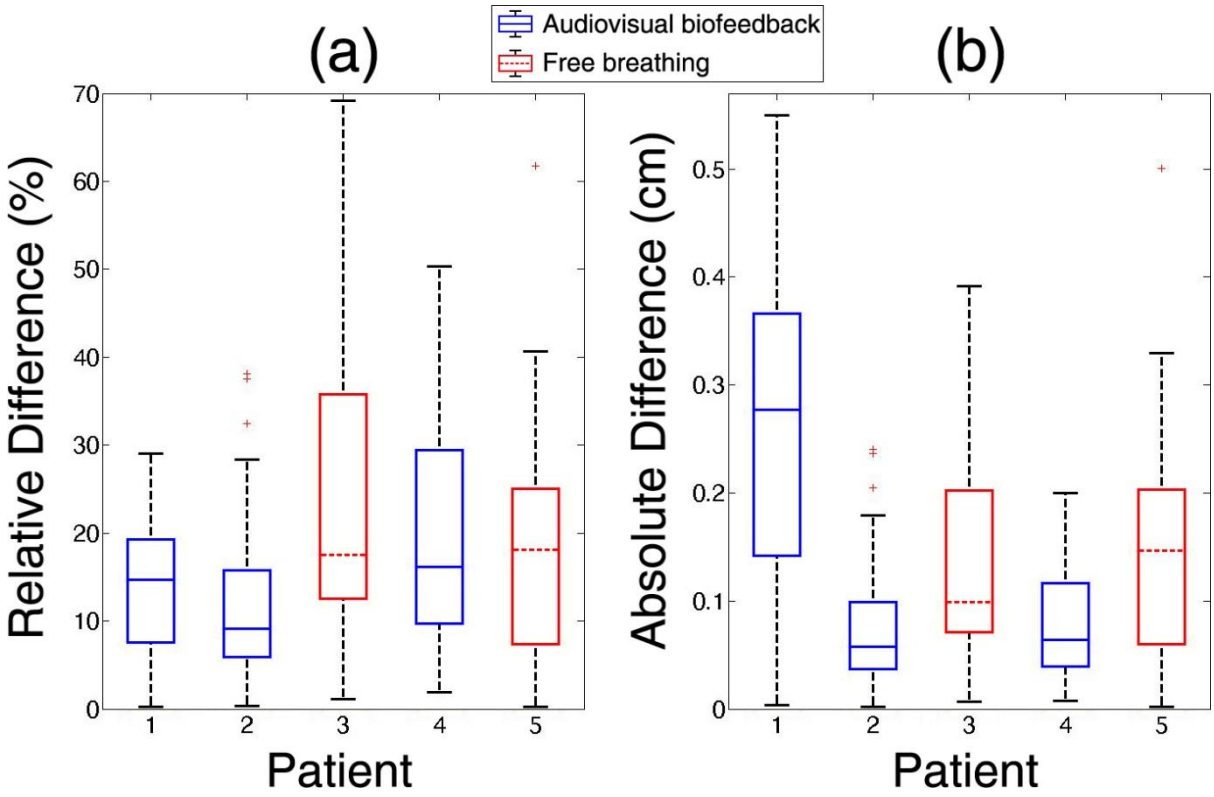


Figure 4-11. *Average (a) relative difference, and (b) absolute difference between CT sim phase bins and the each fraction of treatment phase bins. Free breathing patients shown as red, audiovisual biofeedback patients shown as blue.*

Table 4-4. *Average ± STD Inter-fraction motion consistency values for audiovisual biofeedback and free breathing.*			
Relative Difference			
	Free breathing	**Audiovisual biofeedback**	**Improvement due to audiovisual biofeedback**
Inter-fraction motion consistency (%)	22.0 ± 16.3	14.9 ± 10.0	32% ($p < 0.001$)
Absolute Difference			
	Free breathing	**Audiovisual biofeedback**	**Improvement due to audiovisual biofeedback**
Inter-fraction motion consistency (cm)	0.15 ± 0.10	0.14 ± 0.13	4% ($p = 0.6$)

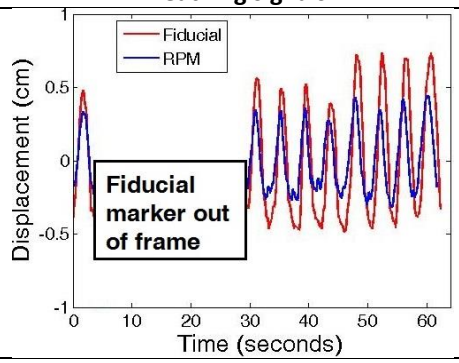
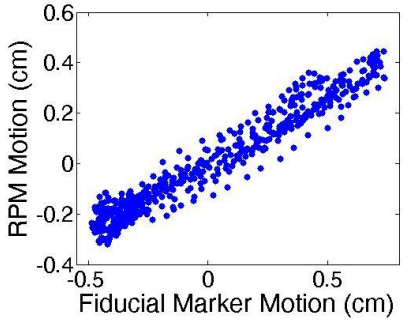
In terms of relative difference, Patient 2 (audiovisual biofeedback) demonstrated the most consistent interfraction motion with an average relative difference of 12% over their course of SBRT. Patient 1 (audiovisual biofeedback) demonstrated the next most consistent interfraction motion with an average relative difference of 14%, followed by Patient 5 (free breathing) with an average relative difference of 18%, followed by Patient 4 (audiovisual biofeedback) with an average relative difference of 19%, followed by Patient 3 (free breathing) with an average relative difference of 25%. In terms of absolute difference, Patient 2 (audiovisual biofeedback) demonstrated the most consistent interfraction motion with an average absolute difference of 0.07 cm over their course of SBRT. Patient 4 (audiovisual biofeedback) demonstrated the next most consistent interfraction motion with an average absolute difference of 0.07 cm, followed by Patient 3 (free breathing) with an average absolute difference of 0.14 cm, followed by Patient 5 (free breathing) with an average absolute difference of 0.15 cm, followed by Patient 1 (audiovisual biofeedback) with an average absolute difference of 0.27 cm.

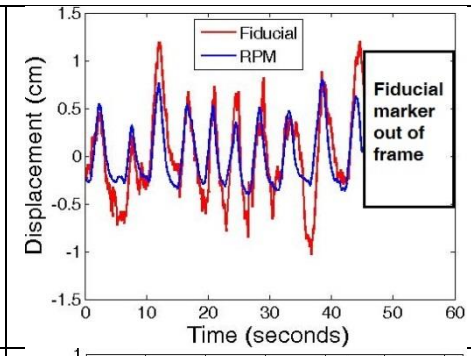
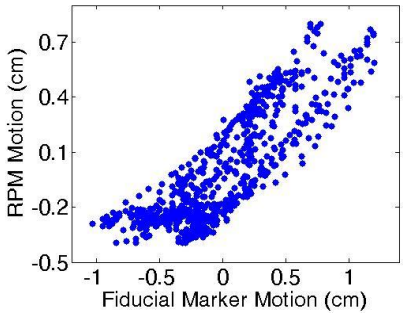
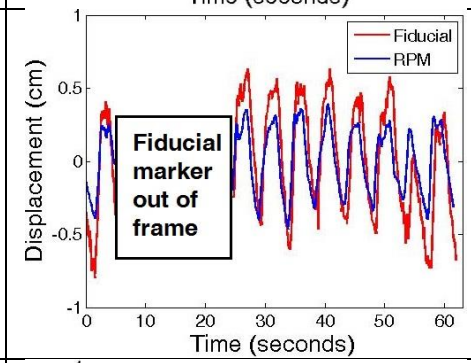
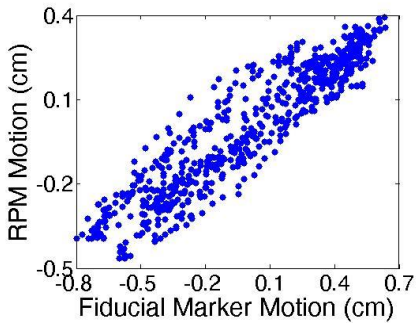
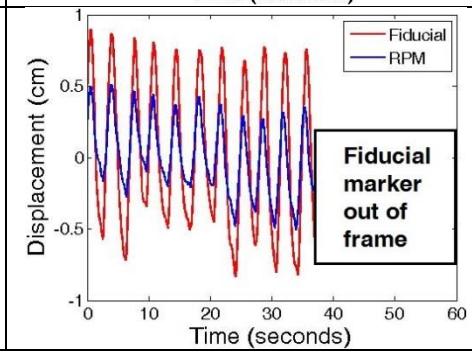
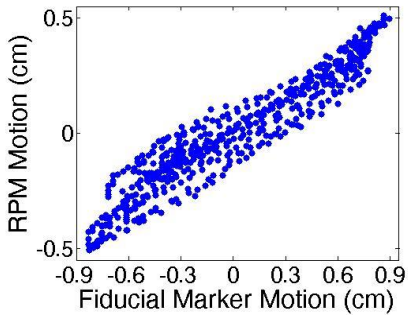
As shown in Figure 4-11(b), for two patients audiovisual biofeedback largely produced sub-millimetre interfraction motion consistency. While Patient 1 demonstrated low inter-fraction motion consistency in terms of relative difference, it had a considerably larger inter-fraction motion consistency in terms of the absolute difference. This is because Patient 1 had the largest amplitude of the 5 patients (see Figure 4-10), and therefore, by normalising the respiratory signal by its amplitude, the larger absolute differences (in cm) corresponded to a lower relative difference.

4.3.2.3. Internal-External Motion Correlation

Examples of the median R value for each patient are shown in Figure 4-12.

Table 4-5. *Median R values for patients 2 to 5 and their corresponding breathing signals and correlation plots.*

Patient	Breathing signals	Correlation plot	r
2 (AV)			0.96

3 (FB)			0.84
4 (AV)			0.93
5 (FB)			0.96

In the screening procedure a stronger r-value was yielded for two audiovisual biofeedback patients, and stronger for free breathing for the other two patients. It should be noted that Patient 1 was not included in this analysis due to external motion data loss during CBCT imaging. *Figure 4-12* shows the Pearson's correlation coefficient (r) values for the internal-external motion correlation across each patient's course of SBRT and *Table 4-6* provides the average values for the two breathing conditions over the entire course of SBRT.

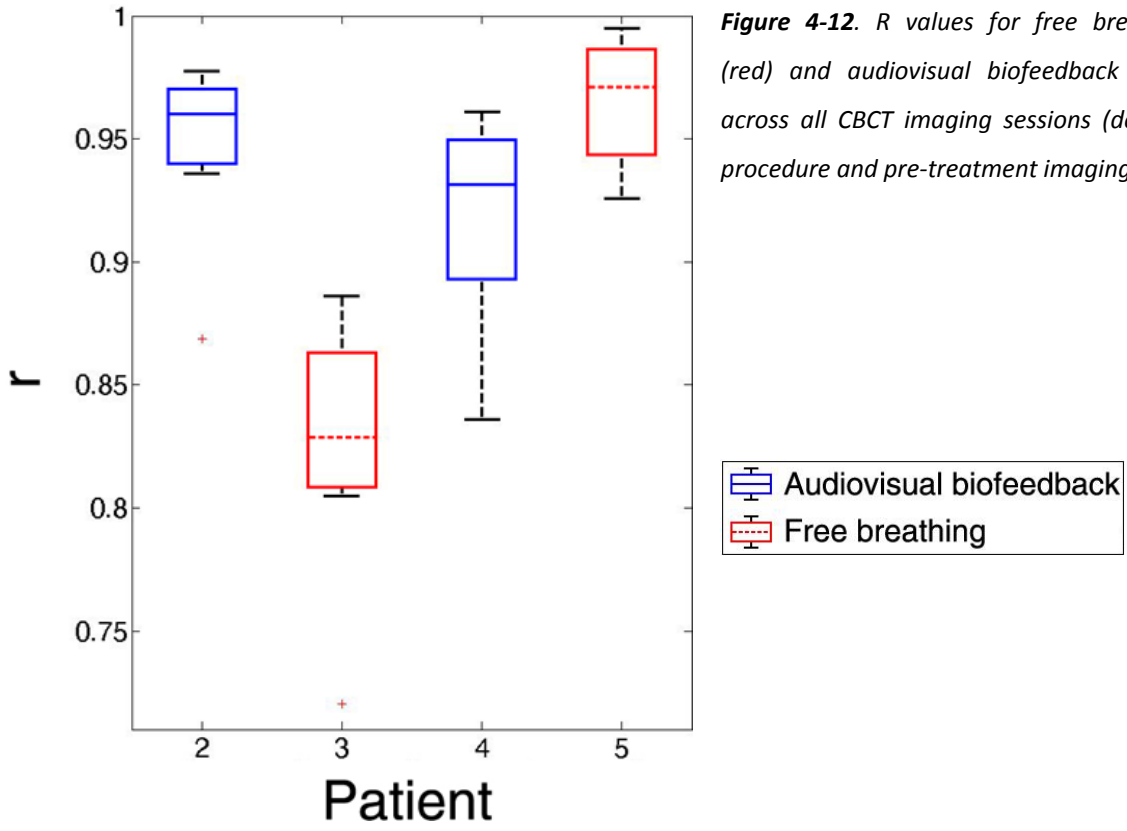


***Figure 4-12**. R values for free breathing (red) and audiovisual biofeedback (blue) across all CBCT imaging sessions (decision procedure and pre-treatment imaging).*

***Table 4-6.** Average ± STD R values for all patients' course of SBRT for Audiovisual biofeedback and free breathing.*

	Free breathing	**Audiovisual biofeedback**	**Improvement due to audiovisual biofeedback**
R	0.89 ± 0.08	0.93 ± 0.04	4% (p = 0.14)

4.3.2.4. Patient and Staff Survey

Audiovisual biofeedback surveys were taken by patients and radiation therapists on the patient's first and last use of audiovisual biofeedback, on the screening procedure and on the final fraction of treatment. The survey was taken a second time on the final fraction of treatment only for the patients and radiation therapists who utilised audiovisual biofeedback during their course of treatment. All patients completed the survey on the screening procedure. Table 4-7 and Table 4-8 details the questions and average scores given by the patients and radiation therapists, respectively.

Table 4-7. *Questions and average responses from all patients*		
Question	**Response options**	**Average patient response**
Do you feel your breathing was more consistent using audiovisual biofeedback?	0 (no) , moderately (3), to 5 (yes)	3.75
Was the training session that you had prior to this session helpful?	0 (no) , moderately (3), to 5 (yes)	4.67
Did you feel physically comfortable with the audiovisual biofeedback system?	0 (no) , moderately (3), to 5 (yes)	4.5
Did you feel the audiovisual biofeedback visual guide (white curve) was too fast or too slow?	0 (too slow) , just right (3), to 5 (too fast)	3.13
Did you feel the audiovisual biofeedback visual guide (white curve) was too shallow or deep?	0 (too shallow) , just right (3), to 5 (too deep)	2.38
Did you like having the music?	0 (no) , moderately (3), to 5 (yes)	3.14
Did the music help you breathe more consistently?	0 (no) , moderately (3), to 5 (yes)	2.33
Did you feel anxious during the session?	0 (no) , moderately (3), to 5 (yes)	1.25

Table 4-7 demonstrates the importance of the training session performed in assisting patients becoming familiar and comfortable with the audiovisual biofeedback system. Further to this, the survey also demonstrates that the audiovisual biofeedback system was comfortable for the patient to use and did not make the patient anxious, with patients reporting a low level of anxiety. Patients reported that the speed and amplitude of the guiding wave were almost 'just right', with one patient commenting that the guiding wave was a little slow, and another noting that it was a little fast, and another patient noting that it seemed a little fast at one time and a little slow at another.

Table 4-8. *Questions and average responses from radiation therapists*		
Question	**Response options**	**Average patient response**
Do you think that the training session was useful for the patient?	0 (no) , moderately (3), to 5 (yes)	4
Do you think that audiovisual biofeedback helped your patient to breathe more regularly?	0 (no) , moderately (3), to 5 (yes)	4.25
Was the audiovisual biofeedback system easy to setup?	0 (no) , moderately (3), to 5 (yes)	3.75
Was the audiovisual biofeedback system easy to operate?	0 (too slow) , just right (3), to 5 (too fast)	4
Would you recommend the audiovisual biofeedback guidance to your colleagues at other centres in similar treatment?	0 (no) , 3 (moderately), to 5 (yes)	3.25

Responses from the radiation therapists support the importance of an audiovisual biofeedback training session. Radiation therapists also reported to be confident in audiovisual biofeedback facilitating regular patient breathing. In addition to providing scores, radiation therapists also commented that the multiple components involved in setting up audiovisual biofeedback could be cumbersome, initially. Radiation therapists also commented that they would hold off recommending audiovisual biofeedback to colleagues until the results from the clinical trial were disseminated and whether such results demonstrated clinical improvements.

4.4. Discussion

This was the first investigation into the use of breathing guidance during a course of liver SBRT employing an initial screening procedure to ensure the most regular breathing condition is utilised for each patient. For the five patients recruited into this study, the findings from the screening procedure yielded the decision to utilise audiovisual biofeedback during treatment planning and treatment delivery for 3 of the 5 patients.

Over the course of SBRT treatment, there was no significant difference in the average breathing regularity between free breathing and audiovisual biofeedback patients. The mean RMSE in displacement of the external RPM motion for audiovisual biofeedback patients in this study was 0.13 cm, comparable to the findings of a lung cancer patient audiovisual biofeedback study, which obtained average RMSE in displacement values of 0.14 cm for audiovisual biofeedback patients (results presented in chapter 5.). Whereas the free breathing patients in this study yielded an average RMSE in displacement values of 0.12 cm, considerably lower than the RMSE values obtained in a previous cancer patient study (0.20 cm, see chapter 5.), and either comparable to or lower than RMSE values yielded in healthy volunteer studies (0.13 cm[13] and 0.16 cm[14]). This suggests that the screening procedure initially performed is an effective method of producing regular breathing over the subsequent course of SBRT, either by providing audiovisual biofeedback guidance or by identifying naturally regular free breathing patients.

While no significant difference in terms of breathing regularity was observed between free breathing and audiovisual biofeedback patients, a significant improvement in interfraction motion consistency was observed from the use of audiovisual biofeedback, with 32% more agreement between respiratory motion during each treatment fraction and CT sim. This demonstrates that audiovisual biofeedback could be a useful tool in maintaining consistent interfraction breathing motion, minimising the deviation in respiratory motion from what was planned in CT sim to each fraction of treatment. While internal radio-opaque marker motion was not obtained during treatment delivery, the Pearson's correlation coefficient (r) results indicate a significant correlation between internal and external respiratory motion. Further to this, audiovisual biofeedback produced a 4% improvement ($p = 0.14$) in Pearson's correlation coefficient (r) values over free breathing. Previous studies have found that audiovisual biofeedback does not impact the correlation between internal and external respiratory motion in healthy volunteers; a study by Steel, et al., (2014) found that the correlation between external RPM motion and thoracic diaphragm motion was 0.96 for both free breathing and audiovisual biofeedback.[26] However, recent preliminary

findings by Lee, *et al.*, (2015) from a lung cancer patient study indicate that audiovisual biofeedback does improve the correlation between external surrogates and internal tumour motion over free breathing.[29] Lee, *et al.*, (2015) found the correlation between abdominal to thoracic diaphragm motion to be 0.91 and 0.95 for free breathing and audiovisual biofeedback, respectively. The findings reported in this chapter here appear consistent with those of Lee, *et al.*, (2015), with the average correlation between external RPM and implanted radio-opaque marker motion being 0.89 and 0.93 for free breathing and audiovisual biofeedback, respectively. This indicates that audiovisual biofeedback could be a useful tool in facilitating a more robust correlation between external respiratory surrogates and abdominal or thoracic tumours. However, further investigation is required to determine the factors responsible for the improvement in this correlation. Additionally, utilising more direct measurements of the tumour by the audiovisual biofeedback system, such as ultrasound or MR Navigator signal,[30, 31] would yield a stronger correlation between audiovisual biofeedback signal and the tumour.

Survey results also demonstrated that patients were comfortable using audiovisual biofeedback, both in terms of physical comfort and patients reporting near 'just right' responses in terms of speed (i.e. period) and amplitude of the guiding wave. Further to this, both patients and radiation therapists indicated the importance of the training session to help familiarise the patient with audiovisual biofeedback.

The results presented here demonstrate the effectiveness of an initial screening procedure in facilitating regular breathing over the course of liver cancer SBRT by either providing audiovisual biofeedback breathing guidance or identifying naturally regular free breathing. Further to this, this study indicates that audiovisual biofeedback can improve the agreement between respiratory motion during CT sim and during treatment delivery.

4.5. Conclusion

This was the first clinical implementation of audiovisual biofeedback utilising a screening procedure to ensure regular breathing is produced during the subsequent course of liver SBRT. This screening procedure yielded the decision to utilise audiovisual biofeedback over a course of SBRT in 3 / 5 patients recruited into this study, with the other 2 patients receiving their SBRT under free breathing conditions. These 5 liver cancer patients demonstrated regular breathing over the course of their SBRT regardless of whether they used audiovisual biofeedback or free breathing, with RMSE values comparable to previous audiovisual biofeedback cancer patient studies, and considerably lower than free breathing patients in previous studies. These 5 liver cancer patients demonstrated regular breathing over the course of their SBRT regardless of whether they used audiovisual biofeedback or free breathing. While respiratory regularity was comparable between the two breathing conditions, audiovisual biofeedback did improve the interfraction motion consistency over free breathing; significantly improving the agreement between CT sim and treatment fraction respiratory motion. Audiovisual biofeedback also improved the internal-external respiratory motion correlation, however these results were non-significant. These findings demonstrate the effectiveness of the screening procedure in facilitating regular respiration over the course of SBRT in addition to audiovisual biofeedback being a potentially valuable tool in producing consistent respiratory motion between CT sim and treatment delivery. However, a study with a larger patient cohort is necessary to investigate this further.

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CHAPTER 5

Designing and initialising a multi-insitutional randomisation phase II audiovisual biofeedback clinical trial

This chapter contains the study protocol titled “Audiovisual biofeedback breathing guidance for lung cancer patients receiving radiotherapy: a multi-institutional phase II randomised clinical trial” which has been published in BMC Cancer (2015; **15**(1) 526-533)

CHAPTER 5

Designing and initialising a multi-institutional randomisation phase II audiovisual biofeedback clinical trial

As evident in chapter 2, to date, there have not been any randomised clinical trials testing breathing guidance interventions. Studies to date have largely demonstrated the proof of principle that breathing guidance improves the regularity and stability of respiratory motion. This chapter will focus on the design and initiation of a multi-site, randomised audiovisual biofeedback clinical trial. This chapter is presented in two parts: 5.1. retrospective analysis of a previous lung cancer patient audiovisual biofeedback study, and 5.2. the design and initiation of the randomised clinical trial. The aim of chapter 5.1. was to yield estimates of clinically relevant outcomes based on a retrospective analysis of a previous lung cancer patient audiovisual biofeedback investigation. The aim of chapter 5.2. was to take the insights obtained in chapter 5.1. to design and then initiate a randomised audiovisual biofeedback clinical trial.

5.1. Retrospective Analysis

The previous audiovisual biofeedback study that recruited lung cancer patients was conducted at Virginia Commonwealth University by George, *et al*. (2003 – 2004).[1-3] This study recruited a total of 24 lung cancer patients who breathed both with and without audiovisual biofeedback across 5 sessions, with each session being performed on a different date. The George, *et al*. study was also the largest audiovisual biofeedback study, to date. Given that there were no completed audiovisual biofeedback clinical trials, clinical insights to go into designing a randomised clinical trial needed to be estimated based on previous investigations. Considering that the George, *et al*. study was the largest audiovisual biofeedback lung cancer study, the George, et al., study data,[1-3] was employed to estimate clinically relevant outcomes to determine the design and statistical considerations of a randomised audiovisual biofeedback clinical trial.

5.1.1. Introduction

As noted in chapter 1.3., for highly mobile tumors, such as those in the thoracic and abdominal regions,[4,5] unstable and irregular breathing motion has a deleterious impact on the accuracy of medical imaging and radiation therapy.[6-9] During radiation treatment there are two fundamental types of errors: the errors occurring during treatment preparation (systematic) and the errors occurring during treatment delivery (random); both these types of errors are exacerbated by irregular breathing-motion.

As noted in chapter 3 and chapter 4, the use of interactive breathing guidance interventions to engage with the patient, informing the patient in real-time on how to adjust their breathing to achieve stable and regular breathing motion, is one such technique to reduce systematic and random errors. The breathing guidance system audiovisual biofeedback,[10] has demonstrated to facilitate regular anatomic motion[10,11] and regular tumour motion,[12,13] in addition to achieving improved medical image quality,[14] imaging time,[15] and gating efficiency.[1] In studies that involved participants utilizing breathing guidance across multiple sessions on different dates, a trend that the participant exhibited increasingly regular breathing with increased usage of the breathing guidance intervention has been observed. A study by Kim, *et al.*, (2012) performed MR imaging on 15 healthy volunteers over two days, spaced approximately one week apart, and observed that the breathing motion of the abdominal wall and the thoracic diaphragm was, on average, more regular on the second day.[11] A study by Cossmann, *et al.*, (2012), recruiting breast cancer patients and observed a decrease in treatment duration over 16 fractions from the use of breathing guidance in examples of two patients' course of radiotherapy.[16] A study performed by Venkat, *et al.* (2008), tested two different types of breathing guidance on 10 healthy volunteers performing a total of three breathing sessions over three different days. A trend towards more regular breathing with time was observed for one of the types of breathing guidance tested, but not for the other.[10] However, the relationship between free breathing and audiovisual biofeedback guided breathing interfractionally has yet to be assessed. Given the observations of previous studies, should a training effect be determined to be a non-stochastic process, this would have valuable implications for achieving higher patient compliance with breathing guidance thereby further minimizing irregularities present in breathing motion. This would also give insights into optimising this training effect to achieve more regular breathing motion earlier in the patient's course of treatment.

Further to this, the impact of audiovisual biofeedback on systematic and random errors has also yet to be assessed. An audiovisual biofeedback study by Lu, *et al*, (2014) investigated the impact of breathing guidance on the match between ITV_{MIP} (internal target volume generated by contouring in the maximum intensity projection scan) and ITV_{10} (ITV generated by combining the gross tumor volumes contoured over the 10 phases of a 4D-CT), however, this study did not assess the impact of audiovisual biofeedback on margin size.

A study by George, *et al.* (2006), investigated the impact of audiovisual biofeedback on respiratory gating efficiency across five days of breathing sessions. George, *et al.*, (2006) assessed the standard deviation of breathing motion within a gating window and found that audiovisual biofeedback

improved gating efficiency over free breathing and audio-only guidance, however this study did not assess the contribution of this to systematic or random errors.

To address this gap in the literature, a retrospective analysis of the George data was performed to investigate the impact of audiovisual biofeedback breathing guidance on interfraction breathing regularity in addition to the respiratory-components of systematic and random errors, and the combination of these errors using the van Herk margin calculation. It should be noted that the George, *et al.*, (2006) data is the respiratory signal from the real-time position management (RPM) external surrogate, and as such, a number of limitations of this methodology are prevalent. The calculation of systematic and random errors assume no other sources of error are present, so this represents a lower bound estimate of errors. It additionally includes the assumption that the RPM motion is similar to the tumour motion, which is a reasonable assumption in some circumstances, if the tumour is located in the lower lobe of the lung for example, but may not be an accurate surrogate for upper lobe tumours.[17] However, given that a clinical evaluation of audiovisual biofeedback has not yet been performed, such an approximation is the best available option. George, *et al.*, (2006) data was utilised as the five days of breathing sessions is representative of a hypofractionated course of radiotherapy.[18]

5.1.2. Methods

331 four minute breathing signals were acquired from 24 lung cancer patients in the George, *et al.*, (2006) study.[1,2] Patients participated in five breathing sessions performed on five different days. In each of the sessions three breathing conditions were tested for 4 minutes each: (1) free breathing (no guidance), (2) audio breathing guidance, and (3) audiovisual biofeedback breathing guidance. For the purpose of this study we only considered free breathing and audiovisual biofeedback breathing sessions. Of the 24 lung cancer patients recruited, 3 did not complete all five breathing sessions. Henceforth, each breathing session will be referred to as a fraction.

5.1.2.1. Breathing motion Analysis

Breathing motion was analysed in terms of average breathing peak-to-peak amplitude and breathing regularity. The root mean square error (RMSE) of breathing displacement and period was used to quantify breathing regularity.[10,11] A lower value of RMSE is indicative of more regular motion. RMSE values were organised into the five separate breathing sessions to assess the trend of breathing regularity interfractionally.

5.1.2.2. Phase-based gating analysis for inhale, exhale and static beam

Phase-based gating was utilized. An example phase and displacement signal is shown below.

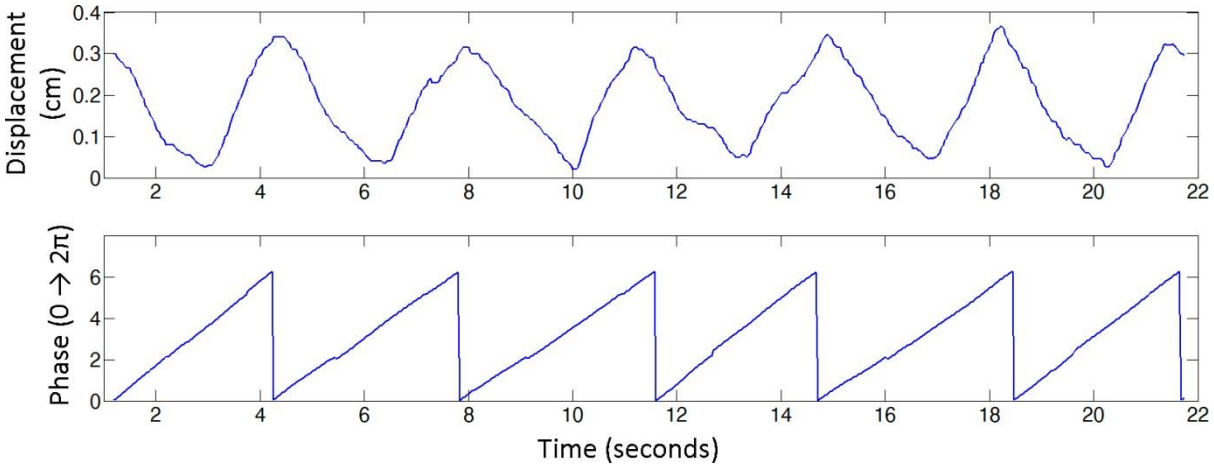

Figure 5-1. *Top: Anterior-posterior (AP) breathing motion. Bottom: Phase of the top breathing motion.*

Peak exhale corresponds to $Phase = \pi$ and peak inhale corresponds to $Phase = 0, 2\pi$. A gating window of 40% is typical for radiation therapy. So for exhale, a 40% gating window refers to the breathing signal within Phase $= \pi \pm 20\% = (1.9 \rightarrow 4.4)$. For inhale, a 40% gating window refers to the breathing signal within Phase $= \begin{cases} 0 + 20\% \\ 2\pi - 20\% \end{cases} = \begin{matrix} (0 \rightarrow 1.3) \\ (5.0 \rightarrow 2\pi) \end{matrix}$.

A static beam refers to a gating window of 100%, i.e. the entire breathing signal from Phase $= 0 \rightarrow 2\pi$. Figure 5-2 illustrates these gating windows by highlighting them on the same respiratory signal illustrated in Figure 5-1.

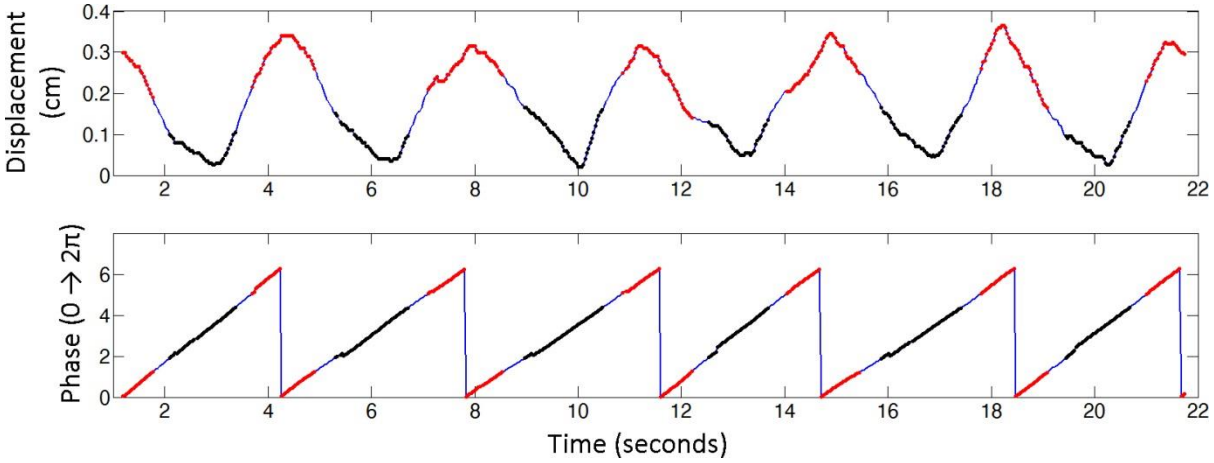

Figure 5-2. *The same respiratory signal as displayed in Figure 5-1, with phase-based gating at exhale indicated in black, and phase-based gating at inhale indicated in red.*

5.1.2.3. Margin Calculation

The systematic error (Σ) is the error between the anatomy at the time of set-up and the anatomy during treatment. A breathing signal with displacement $X = \{x_1, \dots, x_n\}$ can be expressed between times t_1 and t_2 as $X_{t_1}^{t_2} = \{x_{t_1}, \dots, x_{t_2}\}$, where t_1 and t_2 are in seconds. Assuming a setup time of 15 seconds, the systematic error for each fraction can be described as the difference in mean displacement between setup (first 15 seconds) and delivery (from 15 seconds to end of fraction (240 seconds)):

$$\Sigma_f = \overline{X_{15}^{240}} - \overline{X_o^{15}} \quad (1)$$

For each patient, the systematic error across all f fractions can be expressed as:

$$\Sigma_{pt} = \frac{1}{f}\sum_1^f \Sigma_f \quad (2)$$

The random error (σ) is the error during treatment, the random error for each fraction can be expressed as the standard deviation during treatment delivery (from 15 seconds to end of fraction (4 minutes)):

$$\sigma_f = SD\left(X_{15}^{240}\right) \quad (3)$$

For each patient, the random error across all f fractions can be expressed as:

$$\sigma_{pt} = \frac{1}{f}\sum_1^f \sigma_f \quad (4)$$

Systematic and random errors are used to estimate margin size using the van Herk formula:

$$2.5\Sigma_{pt} + 0.7\sigma_{pt} \quad (5)$$

The van Herk formula was used to calculate the respiratory component of margins for static beam, exhale phase-based gating, and inhale phase-based gating. Free breathing and audiovisual biofeedback results were compared using a paired two-tailed Student's t-test.

5.1.2.4. Correlation between margins and breathing regularity

The correlation between the calculated margins and respiratory motion regularity was assessed using the Pearson's correlation coefficient (r), and a p-value for testing the hypothesis of no correlation. Respiratory motion regularity was quantified by the mean root mean square error (RMSE) in displacement for each lung cancer patient as described in chapter 5.1.2.1.

5.1.3. Results

5.1.3.1. Interfraction Breathing Regularity

Figure 5-3 demonstrates the change in RMSE in displacement values over the five study days

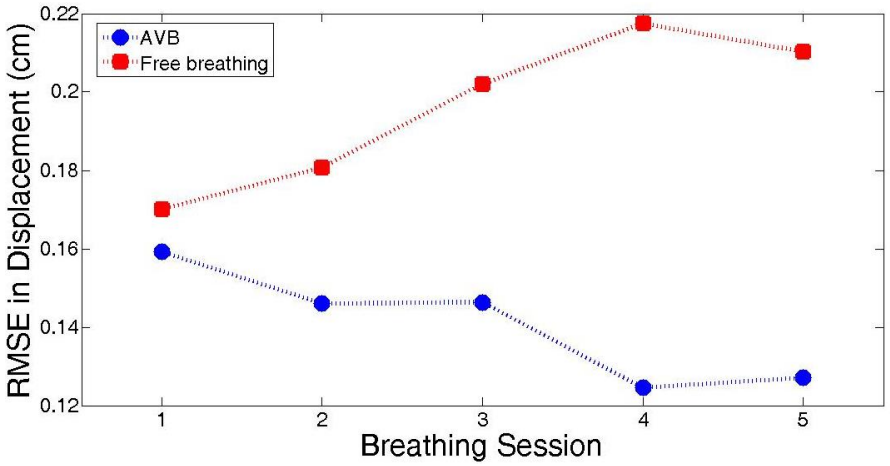

Figure 5-3. *Mean RMSE values for each study session for audiovisual biofeedback (AVB, blue) and free breathing (red)*

Mean ± standard deviation (STD) RMSE values across the five study days, in addition to how significant the improvement in breathing regularity was on each study day, are given in Table 5-1.

Table 5-1. *Mean ± STD breathing regularity (RMSE in displacement, in cm) values for each study session performed across five days.*

	Session 1	**Session 2**	**Session 3**	**Session 4**	**Session 5**	**All Sessions**
Free breathing	0.17 ± 0.06	0.18 ± 0.07	0.20 ± 0.07	0.22 ± 0.12	0.21 ± 0.08	0.20 ± 0.08
Audiovisual biofeedback	0.16 ± 0.08	0.15 ± 0.07	0.15 ± 0.08	0.12 ± 0.05	0.13 ± 0.07	0.14 ± 0.07
Reduction due to audiovisual biofeedback	6% ($p = 0.48$)	19% ($p = 0.04$)	28% ($p = 0.003$)	43% ($p < 0.001$)	40% ($p < 0.001$)	28% ($p < 0.001$)

While the improvement in breathing regularity was not significant on the patients' first breathing session, by the second day of the study the improvement in breathing regularity was significant, reaching peak disparity between audiovisual biofeedback and free breathing on day 4. The Pearson's correlation coefficient (r) between session day and RMSE value for audiovisual biofeedback was found to be -0.93 ($p = 0.02$), and 0.92 ($p = 0.02$) for free breathing. Further to this, the correlation between time and RMSE was found to be significant for audiovisual biofeedback with $r = -0.93$ ($p = 0.02$).

5.1.3.2. Margin Calculation

Results of the respiratory components of the van Herk margin calculation for static beam, exhale phase-based gating (exhale gated), and inhale phase-based gating (inhale gated) are shown in Figure 5-4 and given in Table 5-2.

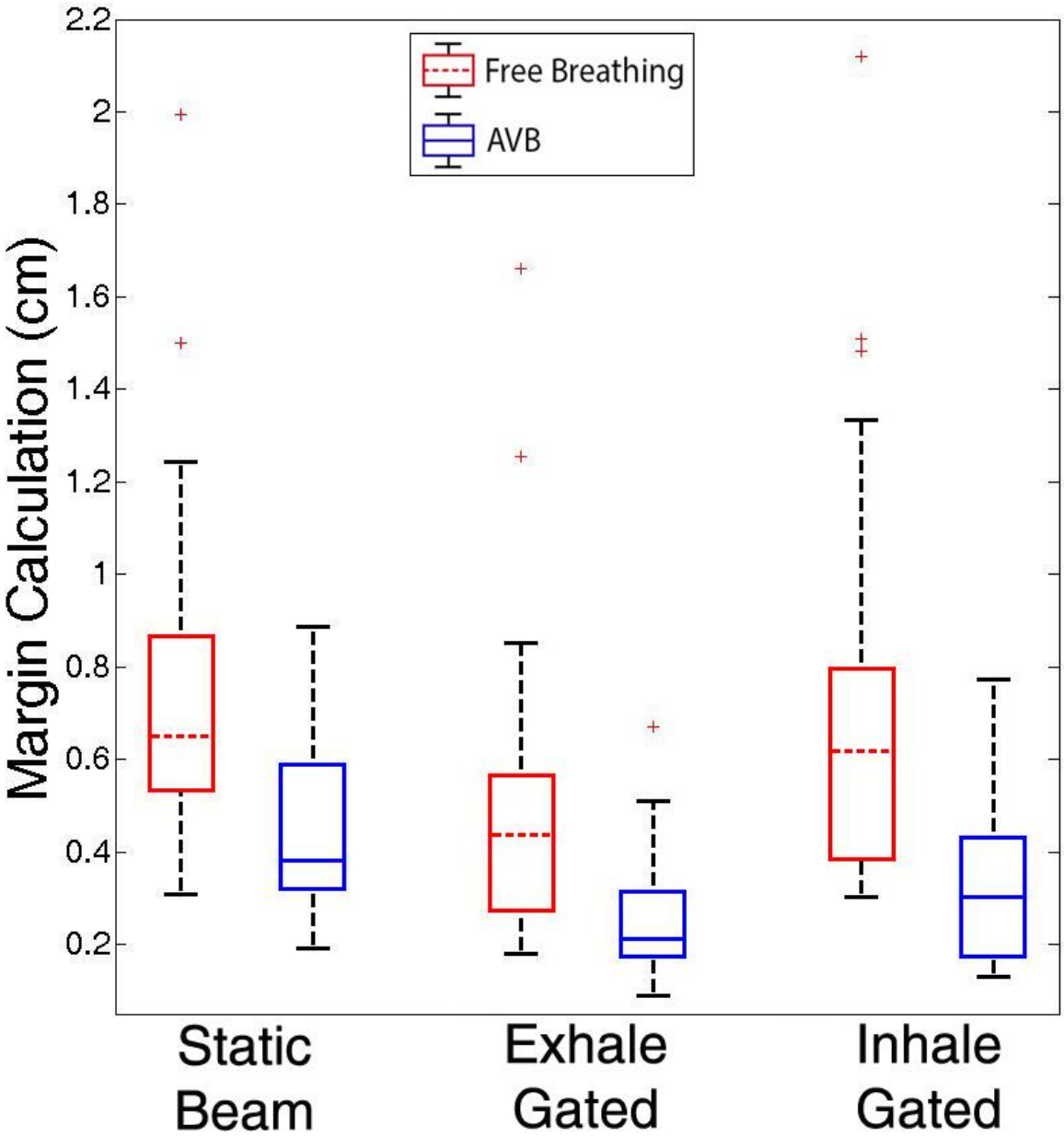

Figure 5-4. *Margin calculations for all 24 lung cancer patients for audiovisual biofeedback (AVB, blue) and free breathing (red) for static beam, exhale gated, and inhale gated.*

Table 5-2. *Margin calculations (in cm) based on the respiratory components of patient breathing motion for static beam, and phase-based gating with a duty cycle of 40% for exhale and inhale.*

	Static beam	**Exhale**	**Inhale**
Free breathing	0.75 ± 0.38 (range: 0.30 – 1.99)	0.51 ± 0.35 (range: 0.18 – 1.66)	0.73 ± 0.46 (range: 0.30 – 2.12)
Audiovisual biofeedback	0.45 ± 0.19 (range: 0.19 – 0.89)	0.09 ± 0.67 (range: 0.09 – 0.67)	0.34 ± 0.20 (range: 0.13 – 0.78)
Margin reduction due to audiovisual biofeedback	40% (p = 0.0006)	48% (p = 0.002)	54% (p = 0.0003)

Audiovisual biofeedback reduced the calculated margin size for 20 out of 24 patients for static beam, 19 out of 24 for exhale gating, and 21 out of 24 patients for inhale gating. Further to this, 14, 22, and 19 out of 24 lung cancer patients had margins less than 5 mm for audiovisual biofeedback for static beam, exhale gated, and inhale gated margins respectively; while only 5, 14, and 9 lung cancer patients had margins less than 5 mm for free breathing for static beam, exhale gated, and inhale gated margins respectively.

5.1.3.3. Correlation between margins and breathing regularity

Figure 5-5 shows the calculated margins as a function of RMSE in displacement values. Table 5-3 shows the Pearson's correlation coefficient (r) irrespective of breathing condition.

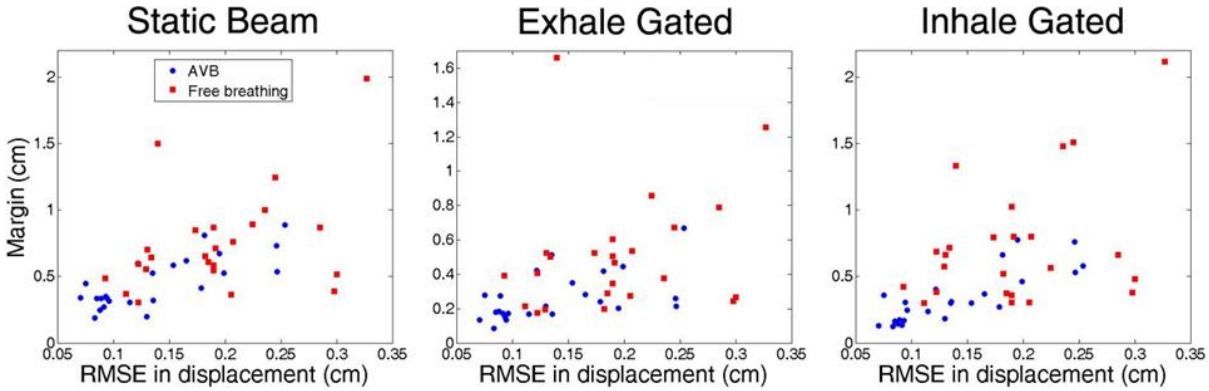

Figure 5-5. *Calculated margins as a function of RMSE in displacement for (from left to right) static beam, exhale gated, and inhale gated. Audiovisual biofeedback (AVB) indicated as blue circles, and free breathing indicated a red squares.*

Table 5-3. Pearson's correlation coefficient (r) values and their respective p-values for the correlation between respiratory motion regularity (RMSE) and calculated margins for static beam, exhale gated, and inhale gated.

	r	p-value
Static beam	0.59	< 0.001
Exhale gated	0.41	0.004
Inhale gated	0.58	< 0.001

Figure 5-5 and Table 5-3 demonstrate a significant correlation between calculated margin and respiratory motion regularity.

5.1.4. Discussion

This retrospective analysis of the George, *et al.*[1,2] data has yielded the clinically relevant insights pertaining to the impact of audiovisual biofeedback on both training effect in addition to calculated

treatment margins. The original study by George *et al.*, monitored the breathing of 24 lung cancer patients across five sessions performed over five separate days and observed an improvement in the standard deviation of breathing motion within a gating window, but observed no trend of this with respect to time.[1] In this study, the George *et al.* data was analysed utilising a metric of motion regularity (RMSE),[10-12] rather than a metric for gating efficiency, to determine the interfraction relationship between breathing regularity and time. Further to this, the respiratory-components of systematic and random errors were analysed utilising the van Herk margin calculation.[19]

On day 1 of the study, there was no significant difference in terms of breathing regularity between audiovisual biofeedback and free breathing (6% improvement, $p = 0.48$). However, by day 2 a significant difference between audiovisual biofeedback and free breathing was observed, with audiovisual reaching peak regularity by day 4, significantly more regular than free breathing (43% improvement, $p < 0.001$). The correlation between time and RMSE was found to be significant for audiovisual biofeedback with $r = -0.93$ ($p = 0.02$). Interestingly, the correlation between time and RMSE was also found to be significant for free breathing, too, with $r = 0.92$ ($p = 0.03$). The main difference between these two relationships is that the trend for audiovisual biofeedback is for RMSE to decrease with time, whereas RMSE increased with time for free breathing. The decrease in RMSE (i.e. increasing regularity) for audiovisual biofeedback is evidence for a training effect, with patients' familiarity and compliance with breathing guidance increasing with time. This increase in RMSE for free breathing may have had to do with their ongoing radiation treatment which was being performed in parallel with this study, with potential radiation toxicities compromising their respiratory function as evident as their decreasing free breathing regularity. However, as radiation toxicities were not reported in the George, *et al.*, investigation, this hypothesis is difficult to test.

Audiovisual biofeedback also facilitated an improvement in margin reduction, significantly improving static beam, exhale gated, and inhale gated margins by 40%, 48%, and 54% respectively. Furthermore, a significant correlation between breathing regularity (RMSE) and margin size was observed, providing evidence that breathing motion regularity can significantly impact clinically relevant outcomes. Audiovisual biofeedback achieved a margin size of less than 5 mm for 14, 22, and 19 out of 24 lung cancer patients for static, exhale gated, and inhale gated margins respectively; whereas free breathing achieved this for much few patients, with 5, 14, and 9 out of 24 lung cancer patients had margins less than 5 mm for static, exhale gated, and inhale gated margins respectively.

However, the margin calculation performed is not a direct measure of treatment margins, as it only takes into account the respiratory components of systematic and random errors of an external respiratory surrogates signal and assumes no other radiotherapy errors. Furthermore, the respiratory signal utilised in these margin calculations was from an external surrogate, the real-time

position management (RPM) system. It should be noted that there are several other factors that impact margin size that are independent of respiratory motion. So the results presented here should not be interpreted as the impact of audiovisual biofeedback on the PTV margin size, rather, the reduction of what the respiratory component contributes to systematic and random errors in radiation therapy.

This was the first study to investigate the impact of audiovisual biofeedback on systematic and random errors in radiation therapy in addition to the first study to investigate the training effect of audiovisual biofeedback. The results presented here provide valuable insights in terms of patient training and clinical outcomes to contribute to the design of a randomised audiovisual biofeedback clinical trial.

5.2. Clinical Trial Design and Initiation

Based on the findings from chapter 2, a randomised clinical trial investigating breathing guidance interventions has yet to be performed, further to this, investigations to date have all be single-institution studies. Using the findings presented in chapter 5.1. to drive the design and statistical considerations of a randomised clinical trial.

5.2.1. Introduction

The precision of radiotherapy can be reduced due to respiratory-related tumour motion, particularly for tumours in the thoracic region, leading to increased irradiation of healthy surrounding tissues, resulting in a significant increase in radiation-related toxicity.[20-22] This is further exacerbated when respiration is irregular in nature.[23,24] A 1Gy increase in tumour dose results in a 4% improvement in survival,[20] however, a 0.5 cm range of tumour motion can cause a 4% variation in radiation dose[22] which leads to an increase in mean dose to healthy surrounding tissues resulting in an increase in risk of pneumonitis and radiation toxicity.[21,25]

Breathing guidance is one such technique which specifically aims to facilitate regular patient breathing by showing the patient how to adjust their breathing in real-time. One such breathing guidance system is the audiovisual biofeedback system, developed by Venkat, *et al*.[10]

Audiovisual biofeedback is a real-time, interactive and personalised respiratory guide designed to facilitate regular patient breathing. However, the findings of a recent literature search, presented in chapter 2, yielded that a randomised clinical trial with any breathing guidance intervention has not yet been performed. To fill the gap in the literature, we have designed a multi-institutional, phase II, randomised clinical trial to thoroughly assess the clinical impact of the audiovisual biofeedback breathing guidance system. Based on previous findings and the results presented in chapter 5.1.3., we hypothesise that audiovisual biofeedback will significantly improve breathing regularity and reduce medical imaging errors for lung cancer patients undergoing imaging and treatment procedures during radiotherapy.

5.2.2. Study Design

The statistical considerations for this study are largely based on the analysis performed in chapter 5.1. utilising the data from a study conducted at Virginia Commonwealth University (VCU) on 24 lung cancer patients.[1,2] 26 patients were recruited for the VCU study, however, 2 patients dropped out due to not being treated with radiotherapy or rapid worsening of disease, and so their data was not collected. A clinically significant different in clinical improvement due to audiovisual biofeedback has been determined to be a margin calculation of less than 5 mm. Irregular breathing causes larger

systematic errors (Σ) from motion artefacts and variations between the planned and treated anatomy as well as random day to day variations (σ) in the treated anatomy (see chapter 5.1.3.). To combine systematic and random errors and estimate the margin contribution due to breathing irregularity we will use the van Herk method[26]: margin = 2.5Σ + 0.7σ (as described in chapter 5.1.2.3.). From this calculation, there were 14/24 patients with margins <5 mm with audiovisual biofeedback, while only 5/24 for free breathing in the static beam case. The limitations of this margin analysis have been outlined in chapter 5.1.4. in that the margin calculation performed is not a direct measure of treatment margins, as it only takes into account the respiratory components of systematic and random errors of an external respiratory surrogates signal and assumes no other radiotherapy errors. But given that a clinical evaluation of audiovisual biofeedback has not yet been performed, such an approximation is the best available option.

In this proposed study, we would like to increase the proportion of patients with reduced margins calculated using the van Herk method. This will be achieved in an exploratory phase II randomised clinical trial examining the potential impact of the audiovisual biofeedback system in facilitating regular breathing in lung cancer patients receiving radiation therapy for the treatment of lung cancer. Without this system, it is conservatively estimated that approximately 40% of patients experience regular breathing (margin component below 5mm). Increasing this proportion to 60% using the audiovisual biofeedback system would be clinically worthwhile. Based on Simon's design,[27] a sample size of 50 patients receiving the audiovisual biofeedback system will have at least 80% power with 95% confidence to rule out a regular rate of 40% in favour of a 60% rate. To minimise patient selection bias and provide an estimate of regular breathing from a contemporary control, the proposed design will be a randomized phase II with 50 patients receiving the intervention and 25 patients receiving the standard of care (no biofeedback intervention). Patients will be randomised in a 2:1 ratio, with 2/3 of the patients being recruited into the audiovisual biofeedback (intervention) arm and 1/3 in the free breathing (control) arm as shown in Figure 5-3 in chapter 5.2.3. 2:1 randomisation is appropriate as within the interventional arm there is a screening procedure where only patients whose breathing is more regular with audiovisual biofeedback use this system for their imaging and treatment procedures (Figure 5-3 in chapter 5.2.3.). Patients will be stratified by treating institution and for treatment intent (palliative vs. radical) to ensure similar balance in the arms across the sites. As the study is not powered for formal comparisons between the groups, estimates of the proportion of patients which do not experience irregular breathing will provide information as to whether further investigation is warranted.

Assuming a contamination and dropout rate of no more than 10%, this study will require that 75+8=83 patients be recruited (the 10% value was based on the 2/26 patient drop-out rate in the

VCU study). The estimated patient numbers are conservative because they are derived from the 24-lung cancer patient VCU study which used a cruder breathing training system that what will be used in this study. Further to this, from the results presented in chapter 5.1.3.1., a training effect is evident with patients using audiovisual biofeedback, with their breathing becoming increasingly regular with time. With this in mind, additional measures of patient training will be incorporated into this clinical trial to expedite this training effect, implementing a brief practice period and a patient information video to further familiarise the patient with the audiovisual biofeedback system. Providing lengthy training sessions for each patient is not feasible in a busy department, therefore the training session was designed to fit within a reasonable amount of time such that the patient could be informed and introduced to audiovisual biofeedback in a time-efficient manner. Over-training the patient through lengthy information and practice sessions that are clinically impractical may bias the results to have more audiovisual biofeedback patients in the intervention arm, compromising the secondary objective (see subsequent section 5.2.3. Study Protocol) of determining the indications and contra-indications for the use of audiovisual biofeedback.

Patients at each institution will be treated per department protocol with no additional constraints on dose, fractionation, immobilisation or image guided procedures.

5.2.3. Study Protocol

The ethics, governance, legal, and regulatory processes were completed prior to the initiation of the clinical trial. The clinical trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR), trial ID: ACTRN12613001177741. Documentation approved by the Hunter New England Human Research Ethics Committee is presented in Appendix II.

This study's protocol was published in BioMed Central Cancer.

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BMC Cancer

STUDY PROTOCOL Open Access

Audiovisual biofeedback breathing guidance for lung cancer patients receiving radiotherapy: a multi-institutional phase II randomised clinical trial

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Abstract

Background: There is a clear link between irregular breathing and errors in medical imaging and radiation treatment. The audiovisual biofeedback system is an advanced form of respiratory guidance that has previously demonstrated to facilitate regular patient breathing. The clinical benefits of audiovisual biofeedback will be investigated in an upcoming multi-institutional, randomised, and stratified clinical trial recruiting a total of 75 lung cancer patients undergoing radiation therapy.

Methods/Design: To comprehensively perform a clinical evaluation of the audiovisual biofeedback system, a multi-institutional study will be performed. Our methodological framework will be based on the widely used Technology Acceptance Model, which gives qualitative scales for two specific variables, perceived usefulness and perceived ease of use, which are fundamental determinants for user acceptance. A total of 75 lung cancer patients will be recruited across seven radiation oncology departments across Australia. Patients will be randomised in a 2:1 ratio, with 2/3 of the patients being recruited into the intervention arm and 1/3 in the control arm. 2:1 randomisation is appropriate as within the interventional arm there is a screening procedure where only patients whose breathing is more regular with audiovisual biofeedback will continue to use this system for their imaging and treatment procedures. Patients within the intervention arm whose free breathing is more regular than audiovisual biofeedback in the screen procedure will remain in the intervention arm of the study but their imaging and treatment procedures will be performed without audiovisual biofeedback. Patients will also be stratified by treating institution and for treatment intent (palliative vs. radical) to ensure similar balance in the arms across the sites. Patients and hospital staff operating the audiovisual biofeedback system will complete questionnaires to assess their experience with audiovisual biofeedback. The objectives of this clinical trial is to assess the impact of audiovisual biofeedback on breathing motion, the patient experience and clinical confidence in the system, clinical workflow, treatment margins, and toxicity outcomes.

(Continued on next page)

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Discussion: This clinical trial marks an important milestone in breathing guidance studies as it will be the first randomised, controlled trial providing the most comprehensive evaluation of the clinical impact of breathing guidance on cancer radiation therapy to date. This study is powered to determine the impact of AV biofeedback on breathing regularity and medical image quality. Objectives such as determining the indications and contra-indications for the use of AV biofeedback, evaluation of patient experience, radiation toxicity occurrence and severity, and clinician confidence will shed light on the design of future phase III clinical trials.

Trial registration: This trial has been registered with the Australian New Zealand Clinical Trials Registry (ANZCTR), its trial ID is ACTRN12613001177741.

Keywords: Breathing guidance, Motion management, Randomised, Stratified, Phase II clinical trial, Lung cancer, Radiotherapy

Background

The precision of radiotherapy can be reduced due to respiratory-related tumour motion, particularly for tumours in the thoracic region, leading to increased irradiation of healthy surrounding tissues, resulting in a significant increase in radiation-related toxicity [1–3]. This is further exacerbated when respiration is irregular in nature (deep/shallow breaths, baseline shifts, suspended breathing, etc.) [4, 5]. A 1Gy increase in tumour dose results in a 4 % improvement in survival, [6] however, a 0.5 cm range of tumour motion can cause a 4 ~ 5 % variation in radiation dose [7] which leads to an increase in mean dose to healthy surrounding tissues resulting in an increase in risk of pneumonitis and radiation toxicity [8, 9].

Techniques such as respiratory gating, breath-holds and tumour tracking are clinically useful for tumour motion management [10, 4, 11]. However, irregular respiration can reduce the efficiency of such motion management techniques, [12, 13] irregular respiration also causes motion artefacts and anatomic errors in medical imaging [14–19].

Breathing guidance is one such technique which specifically aims to produce regular patient breathing by showing the patient how to adjust their breathing in real-time. One such breathing guidance system is the audiovisual (AV) biofeedback system (shown in Fig. 1), developed by Venkat, et al [13].

AV biofeedback is a real-time, interactive and personalised respiratory guide designed to facilitate regular patient breathing. Table 1 outlines the findings from previous AV biofeedback investigations.

However, none of the studies presented in Table 1 were randomised trials, in addition to this, the findings of a recent literature search yielded that a randomised clinical trial with any breathing guidance intervention has not yet been performed. To fill the gap in the literature, we have designed a multi-institutional, phase II, randomised clinical trial to thoroughly assess the clinical impact of the AV biofeedback breathing guidance system. Based on previous findings, we hypothesise that AV biofeedback will significantly improve breathing regularity and reduce medical imaging errors for lung cancer patients undergoing imaging and treatment procedures during radiotherapy.

This trial has been registered with the Australian New Zealand Clinical Trials Registry (ANZCTR), its trial ID is ACTRN12613001177741.

Methods/Design

This study aims to assess the clinical impact of AV biofeedback by recruiting 75 lung cancer patients across seven radiation oncology departments. What follows is an outline of the AV biofeedback setup, primary and secondary objectives, participant selection criteria, the study workflow, and statistical considerations for our study design.

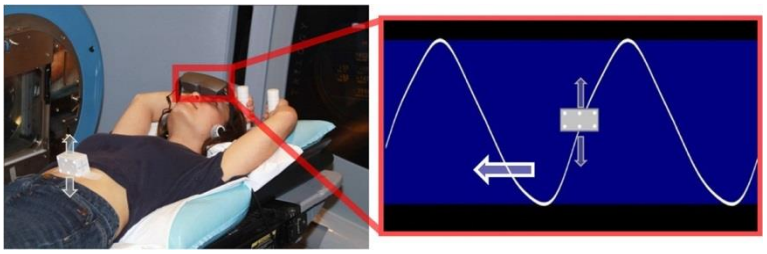

Fig. 1 AV biofeedback system (left). Display goggles and real-time position management (RPM) marker block on the abdomen shown. The visual display (right), as seen by the patient, of the AV biofeedback guiding interface shows the waveguide (white curve) and a marker position (grey marker) in real time

Table 1 Details of previous AV biofeedback investigations

Investigation author (Year)	Participants	Findings
George [23] (2006)	24 lung cancer patients	• Residual breathing motion within a gating window improved
Venkat [13] (2008)	10 healthy volunteers	• Waveguide breathing guidance produced more regular breathing than bar-model guidance and free breathing
Yang [22] (2012)	Phantom study	• 4D PET image quality improved
An [36] (2013)	Retrospective analysis of George (2006) data	• CTV coverage improved • Internal motion variation improved
Kim, [21] Pollock, [37] & Steel [38] (2012–2014)	15 healthy volunteers	• Kim (2012): Breathing regularity of thoracic diaphragm and abdominal wall improved • Pollock (2013): Accuracy of kernel density estimation motion prediction improved • Steel (2014): Strong correlation between internal and external anatomic motion for both AV biofeedback and free breathing
Lee [24] (2014)	5 healthy volunteers	• Improved 3D MR image quality • Reduced gated MRI scan time
Lu [39] (2014)	13 lung & liver cancer patients	• Breathing regularity improved • ITV_{MIP} underestimated ITV_{10}
Lee [40] (2014)	7 lung cancer patients	• Improved intrafraction lung tumour motion consistency • Improved interfraction lung tumour motion consistency

Research Ethics Committee

The protocol for this clinical trial has been reviewed and approved by the Hunter New England Human Research Ethics Committee (HREC). This Human Research Ethics Committee is constituted and operates in accordance with the National Health and Medical Research Council's 'National Statement on Ethical Conduct in Human Research (2007)' (National Statement) and the 'CPMP/ICH Note of Guidance on Good Clinical Practice'. The Hunter new England HREC has also been accredited by the New South Wales Department of Health as a lead HREC under the single ethical and scientific review. A report on the progress of this clinical trial is required to be submitted annually to the Hunter New England HREC.

Audiovisual biofeedback system

The AV biofeedback system, as shown in Fig. 1, utilises the Real-time Position Management system (RPM, Varian Medical Systems, Palo Alto, USA) to track the motion of an external marker positioned on the patient's abdomen. This real-time respiratory-motion is used by the AV biofeedback software to calculate an average cycle of respiration (using a Fourier series fit from 10 obtained respiratory cycles). This average cycle is used as the waveguide (white curve in Fig. 1) which continually moves from right-to-left across the visual display and acts as part of the visual prompt for AV biofeedback. Also on the visual display is a grey marker moving vertically up-and-down corresponding to the anterior-posterior motion of the marker block positioned on the patent's abdomen. It is the goal for the patient to keep the marker block within inhale-exhale limits (presented as the blue region in Fig. 1) and match the grey marker block over the white waveguide. The audio component of AV biofeedback is classical music playing to the patient; the music fades to silence should the marker block move outside the blue area breathing limits. AV biofeedback has been shown to be compatible in a number of imaging and treatment modalities, [20–22] as well as utilising different types of patient displays [23, 21, 24]. There are two options for patient display in this study: video goggles, or a screen mounted to the couch. Which patient display option is utilised in this study will depend on what is available at each institution.

Figure 2 illustrates the schematic of the AV biofeedback study setup, from the RPM camera monitoring patient breathing motion, to the AV biofeedback computer receiving the RPM signal and extending the AV biofeedback guiding interface to the patient display.

Objectives

This clinical trial will recruit 75 lung cancer patients across 7 radiation oncology departments testing the following objectives:

Primary objective: In a prospective multi-institutional randomised clinical trial we will test the hypothesis that AV biofeedback will significantly improve breathing regularity and reduce medical imaging errors for lung cancer patients undergoing imaging and treatment procedures during radiotherapy.

Secondary objectives will involve patient-specific and department-specific objectives:

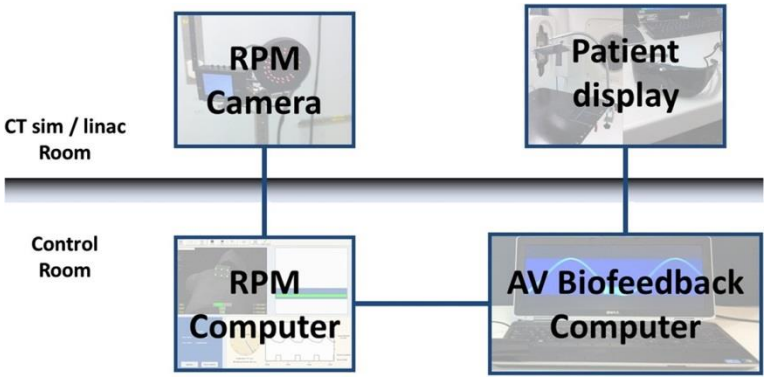

Fig. 2 Audiovisual biofeedback study setup schematic

Patient-specific objectives are to evaluate the impact of AV biofeedback by:

1) Quantifying the proportion of patients for whom breathing is more regular with AV biofeedback,
2) Quantifying the variability in breathing motion throughout a course of treatment,
3) Quantifying the improvement in image quality with AV biofeedback,
4) Evaluating the patient experience through a perception of care survey,
5) Developing indications and contra-indications for the use of AV biofeedback,
6) Quantifying the differences in image-guided radiotherapy (IGRT) shifts during treatment, and
7) Recording toxicity outcomes for up to 12 months after treatment has been completed.

Department-specific objectives are to evaluate the impact of AV biofeedback on clinical testing by:

1) Quantifying any practice changes (e.g. margin reduction),
2) Quantifying the impact on workflow using the AV biofeedback device through time-motion studies,
3) Evaluating the operator and clinician confidence in the AV biofeedback device's reliability and clinical efficacy through a technology-impact survey,
4) Quantifying the system robustness through hardware and software fault reporting, and
5) Performing system quality assurance, sharing the results through web-based uploads and provide feedback for QA improvement.

Our methodological framework will be based on the widely used Technology Acceptance Model (TAM) [25, 26]. The TAM gives qualitative scales for two specific variables, perceived usefulness and perceived ease of use, which are fundamental determinants for user acceptance.

Study participant selection criteria

This study will recruit patients with cancer of the lung receiving external beam radiation therapy. Patients fitting the eligibility criteria (see below) will be identified and introduced to this study by their treating physicians, who will participate as investigators in this study. The eligibility criteria are as follows:

1) Lung cancer patients
   i. No restrictions to type of external beam radiation therapy being received
   ii. Primary or secondary cancer
2) >18 years old
3) No gender or ethnic restrictions
4) An ECOG score in the range of 0 to 2
5) Able to give written informed consent and willingness to participate and comply with the study
6) No pregnant / lactating woman

Study workflow

Once informed consent has been obtained, the patient will be randomised into either the intervention or control arm of the study. For patients randomised into the intervention arm, prior to their planning and treatment they will undergo a breathing decision session during which they will breathe both with and without the guidance of AV biofeedback. Preceding each breathing session will be a training session to familiarise the patient with the AV biofeedback system. After the breathing decision session has been completed, the most reproducible breathing condition (AV biofeedback or free breathing) will be determined in situ by an 'Analyse Respiratory Session' function within the AV biofeedback software. It will be the most reproducible breathing condition that will continue to be used throughout the rest of that particular patient's planning and treatment. The flowchart for this study is shown in Fig. 3.

For all patients, each follow-up visitation they have with their treating physician for the first 12 months after their treatment has finished, their treating physician will

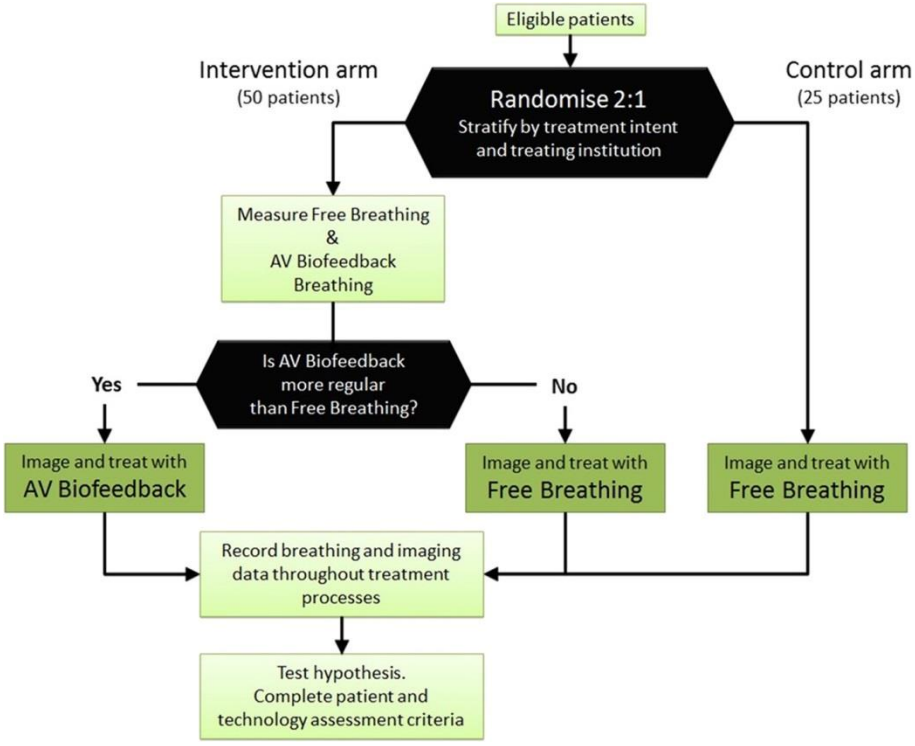

Fig. 3 Study flowchart

complete a toxicity report to satisfy the Secondary Patient-Specific Objective 7: Recording toxicity outcomes for up to 12 months after treatment has been completed by reporting the occurrence and severity of any radiation toxicities.

Patient randomisation

This trial is stratified, hence, study group random allocation will be determined by minimisation [27, 28]. Patients will be stratified by treating institution and for treatment intent (palliative vs. radical) and minimisation considerably reduces the imbalance of these stratification factors across the control and intervention groups of the study. Patients will be randomised in a 2:1 ratio, 2 out of 3 patients will be randomised into the AV biofeedback (intervention) arm and 1 out of 3 will be randomised into the free breathing (control) arm as illustrated by Fig. 3.

Sample size and power calculation

The statistical considerations for this study are largely based on a previous study conducted at Virginia Commonwealth University (VCU) on 24 lung cancer patients [23, 29]. Prior to this multi-institutional clinical trial, the VCU study was the largest AV biofeedback investigation, recruiting a total of 26 lung cancer patients, however, 2 patients dropped out due to not being treated with radiotherapy or rapid worsening of disease, and so their data was not collected. In the VCU study 109 breathing sessions were performed comparing AV biofeedback to free breathing, of which, 87 sessions (80 %) demonstrated more regular breathing with AV biofeedback. Framing this is in a more clinical relevant way: irregular breathing motion exacerbates the systematic errors (Σ) arising from motion image artefacts and variations between the planned and treated anatomy, as well as random errors (σ) from day-to-day variations in the treated anatomy [30, 15, 31]. To combine systematic and random errors and estimate the margin contribution due to breathing irregularity we will use the van Herk method [32]: margin = $2.5\Sigma + 0.7\sigma$, incorporating the respiratory components of systematic and random errors. A clinically significant difference in clinical improvement due to AV biofeedback has been determined to be a margin calculation of less than 5 mm. This magnitude of reduction was elected as clinically significant because this is the same magnitude of displacement attributed to contributing to significant artefacts and errors during radiotherapy procedures as detailed in AAPM Task Group 76 [4]. From this van Herk calculation, in the VCU study there were 14/24 patients with margins <5 mm with AV biofeedback, while only 5/24 for free breathing.

In this proposed study, to get a more accurate indication of the proportion of patients with reduced margins calculated using the van Herk method we have designed

an exploratory phase II randomised study examining the potential impact of an AV biofeedback system in regulating breathing in patients receiving radiation therapy for the treatment of lung cancer. Without the AV biofeedback system, it is conservatively estimated that approximately 40 % of patients naturally exhibit regular breathing (margin component below 5 mm). Increasing this proportion to 60 % using the AV biofeedback system would be clinically worthwhile. Based on Simon's design, [33] a sample size of 50 patients receiving the AV biofeedback system will have at least 80 % power with 95 % confidence to rule out a regular rate of 40 % in favour of a 60 % rate. To minimise patient selection bias and provide an estimate of regular breathing from a contemporary control, the proposed design will be a randomised phase II with a 50 patients receiving the intervention and 25 receiving current standard of care. Patients will be randomised in a 2:1 ratio, with 2/3 of the patients being recruited into the AV biofeedback (intervention) arm and 1/3 in the free breathing (control) arm as illustrated by Fig. 3. 2:1 ran- domisation is appropriate as within the interventional arm there is a screening procedure where only patients whose breathing is more regular with AV biofeedback
use this system for their imaging and treatment procedures. Patients will be stratified by treating institution and for treatment intent (palliative vs. radical) to ensure similar balance in the arms across the sites. As the study is not powered for formal comparisons between the groups, estimates of the proportion of patients which do not experience irregular breathing will provide information as to whether further investigation is warranted.

Assuming a contamination and dropout rate of no more than 10 %, this study will require that 75 + 8 = 83 patients be recruited (the 10 % value was based on the 2/26 patient drop-out rate in the VCU study).

Patients at each institution will be treated per department protocol with no additional constraints on dose, fractionation, immobilisation or image guided procedures. Results will be adjusted for institution (using a fixed effect) to account for differences between institutions.

Data analysis

The primary objective is to assess the impact of AV biofeedback on breathing regularity and image errors; the section that follows details the metrics to be utilised for the primary objective.

Breathing motion regularity is quantified as the root mean square error (RMSE) in displacement and period [13, 21, 24, 34]. A breathing signal is separated into its individual cycles and an 'average' waveform is calculated using a Fourier series fit. Figure 4 illustrates an example breathing trace, its separation into cycles, and its average waveform.

RMSE will be calculated as detailed by Venkat, et al., (2008),[13] but will be outlined here for clarity. For a breathing pattern comprised of n individual breathing cycles, where each cycle in the phase domain can be written as $X = \{x_1, x_2, \ldots, x_{360}\}$ and the average waveform of these cycles can be written as $Y = \{y_1, y_2, \ldots, y_{360}\}$, the RMSE in displacement is calculated as:

$$RMSE\ in\ displacement = \frac{\Sigma_{All\ Cycles}\sqrt{\Sigma_{i=1\ldots360}\frac{(x_i - y_i)^2}{360}}}{n} \quad (1)$$

The period of each of the n breathing cycles, in seconds, can be written as $P = \{p_1, p_2, \ldots, p_n\}$, with the period of the average waveform expressed as $Period_{mean}$, the RMSE in period is calculated as:

$$RMSE\ in\ period = \sqrt{\frac{\Sigma_{i=1\ldots n}(p_i - Period_{mean})^2}{n}} \quad (2)$$

The impact of AV biofeedback on 4D-CT image quality will utilise an automated method of image artefact identification developed by Cui, et al., (2012), [35] but will be outlined here for clarity. The method is based on

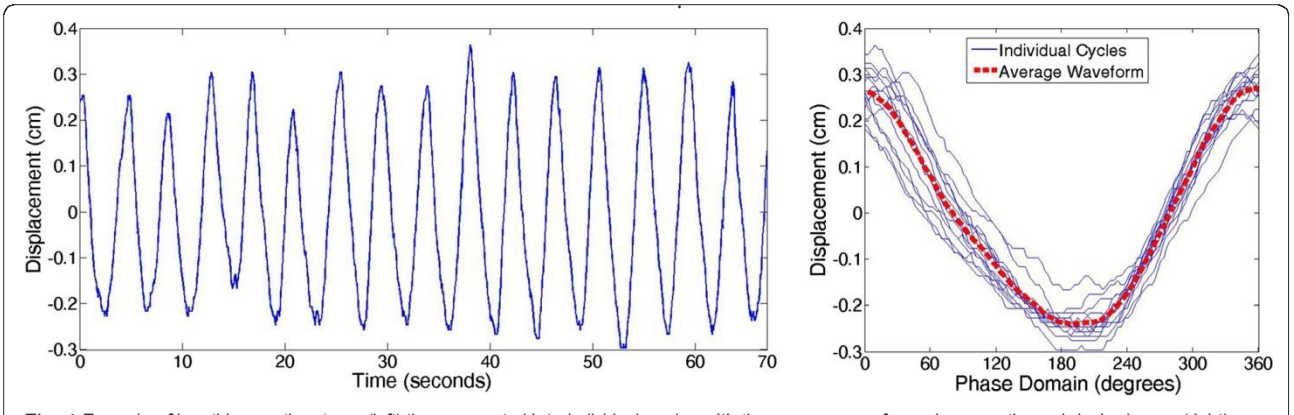

Fig. 4 Example of breathing motion trace (left) then separated into individual cycles with the average waveform shown as the red dashed curve (right)

the similarity between edge slices at adjacent couch positions A and B; the edge similarity between slice A and slice B is expressed by the normalised correlation coefficient (NCC). Deviations from standard NCC, representing normal anatomical changes between edge slices, signify the presence of an image artefact. Cui, et al., (2012) reported good agreement of their method with the assessment of two observers.

Discussion

This clinical trial marks an important milestone in breathing guidance studies as it will be the first randomised, controlled trial providing the most comprehensive evaluation of the clinical impact of breathing guidance on cancer radiation therapy to date. Based on the structure of previous investigations and taking into consideration the increase in scope of this study, the authors have designed a multi-institutional, randomised, phase II, stratified clinical trial to test the hypothesis that audiovisual biofeedback breathing guidance will significantly improve breathing regularity and reduce medical imaging errors for lung cacner patients undergoing imaging and treatment procedures during radiotherapy. While patients will be stratified by treating institution and for treatment intent, the study is not powered for formal comparisons between these stratified groups; estimates from the current proposed study of the proportion of patients which do not experience irregular breathing will provide information as to whether further investigation is warranted. Further to this, objectives such as determining the indications and contra-indications for the use of audiovisual biofeedback, evaluation of patient experience, radiation toxicity occurrence and severity, and clinician confidence will shed light on the design of future phase III clinical trials.

Abbreviations

AV biofeedback: Audiovisual biofeedback; HREC: Human Research Ethics Committee; PET: Positron Emission Tomography; MRI: Magnetic resonance imaging; ANZCTR: Australian New Zealand Clinical Trials Registry; RPM: Real-time position management; IGRT: Image-guided radiotherapy; QA: Quality assurance; TAM: Technology acceptance model; ECOG score: Eastern cooperative oncology group score; VCU: Virginia Commonwealth University.

Competing interests

This trial is funded by a National Health and Medical Research Council (NHMRC) Development Grant (application ID: 1093186). Paul Keall is one of the inventors of US patent # 7955270, and Paul Keall, Sean Pollock, Ricky O'Brien and Kuldeep Makhija are shareholders of Respiratory Innovations, an Australian company that is developing a device to improve breathing stability. No funding or support was provided by Respiratory Innovations.

Authors' contributions

SP drafted the manuscript, collects and analyses the clinical trial data. RO developed the software for the intervention used in the trial and is leading the department-specific secondary objectives (4) pertaining to system robustness and fault reporting. KM also developed the AV biofeedback software tailored for clinical use, in additional to performing fault reporting for the department specific secondary objectives (4) pertaining to system robustness and fault reporting. FHJ, JL, AR, TE, RT, and RYA are identifying and recruiting study participants as well as satisfying patient-specific secondary objective (7) pertaining to reporting patient toxicity outcomes. VG performed the power calculation and determined the sample size for the clinical trial; VG is also performing the participant randomisation of the clinical trial. PK conceived the clinical trial and participated in the design of the clinical trial. All authors read and approved the final manuscript

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5.2.4. Institution Credentialing

For an institute to become fully credentialed to recruit patients in this clinical trial it is required to:

1) Receive ethics approval from a Human Research Ethics Committee (HREC)
2) Receive ethics approval from Local Health District (LHD)
3) Receive a receipt notification from the Therapeutic Goods Administration (TGA) for the Clinical Trial Notification (CTN)
4) Perform audiovisual biofeedback daily and monthly quality assurance (QA) in CT sim and linac rooms
5) Perform clinical trial workflow, imaging, and data acquisition in CT sim and linac rooms with a motion phantom
6) Perform clinical trial workflow and data acquisition in CT sim and linac rooms with a volunteer
7) Transfer de-identified data from institution's radiation oncology department to University of Sydney

Points 4) through 7) need to be performed by investigators affiliated with the participating institution without input or assistance from investigators from the University of Sydney. This is to ensure that each institution can perform the clinical trial unsupervised, as it is not feasible for a University investigator to be present at all participating institutions during the study.

Table 5-4 details the progress of each participating institution towards full credentialing.

Nepean Cancer Centre has yet to commence training and credentialing due to not having a Varian RPM system available. Alternative motion sensors solutions are being explored; however, the absence of a current solution has limited the amount of progress of this institution towards credentialing.

Table 5-4. *Audiovisual biofeedback details for each of the seven participating institutions.*									
Institution	**HREC approval**	**LHD approval**	**TGA approval**	**QA performed**	**Phantom tests performed**	**Volunteer tests performed**	**Data transfer**	**Credentialed**	**Patient recruited**
Calvary Mater Hospital, Newcastle	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Yes	Yes (April 11th, 2016)
Canberra Hospital	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Yes	No
Royal North Shore Hospital	Complete	Complete	Complete	Complete	Complete	Complete	To be done	No	No
Gosford Hospital	Complete	Complete	To be done	Complete	Complete	Complete	To be done	No	No
Westmead Hospital	Complete	Complete	To be done	Complete	Complete	To be done	To be done	No	No
Chris O'Brien Lifehouse	To be done	To be done	To be done	Complete	Complete	Complete	To be done	No	No
Nepean Cancer Centre	Complete	To be done	To be done	To be done	To be done	To be done	To be done	No	No

5.2.4.1. Investigator Training

In order to be able to conduct the workflow of the clinical trial unsupervised, training was provided by University of Sydney investigators to institution investigators. This training involved:

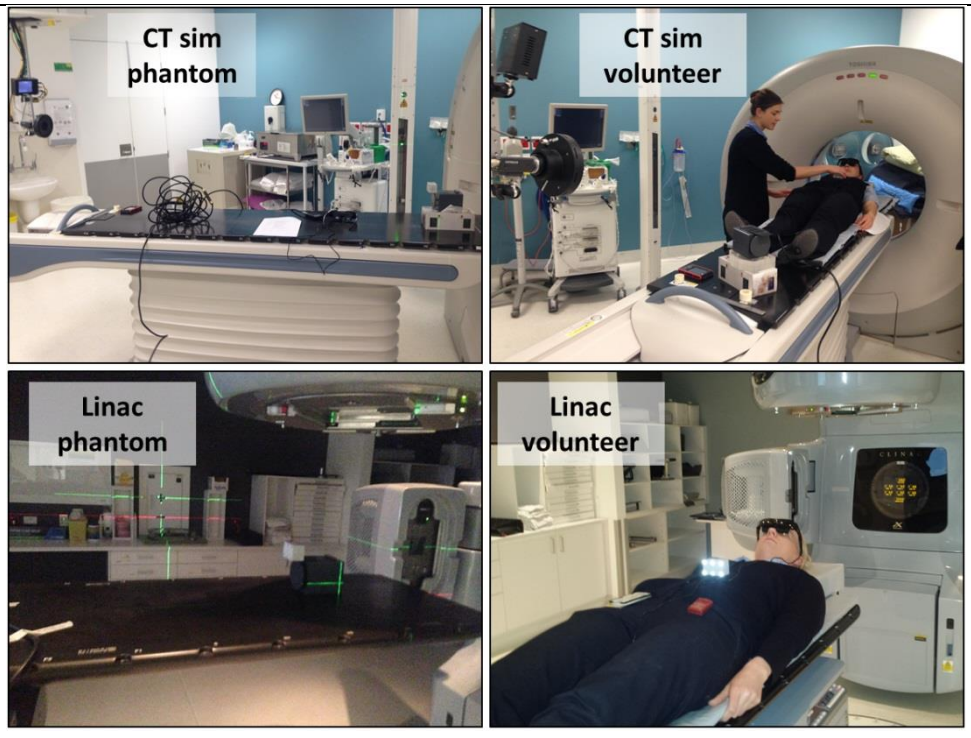
1) Clinical trial information presentation
2) Performing daily and monthly QA under supervision
3) Performing clinical trial workflow with phantom under supervision

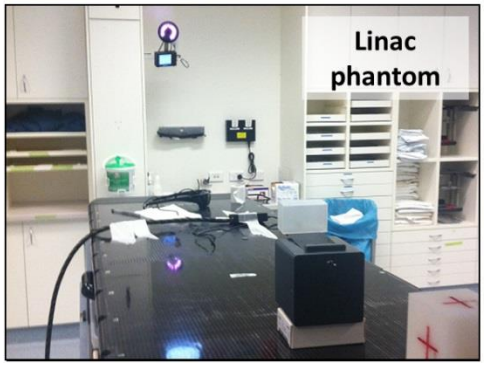
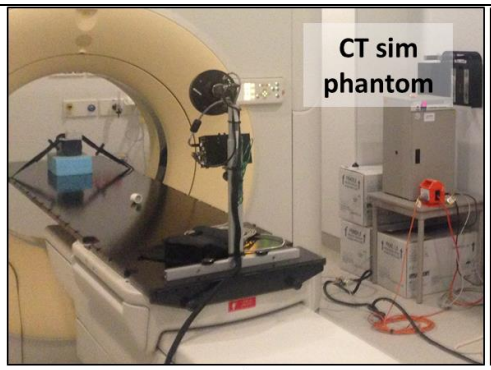
Documentation utilised to perform this investigator training is given in Appendix II.

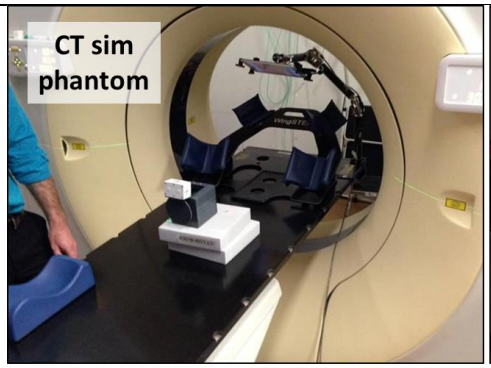
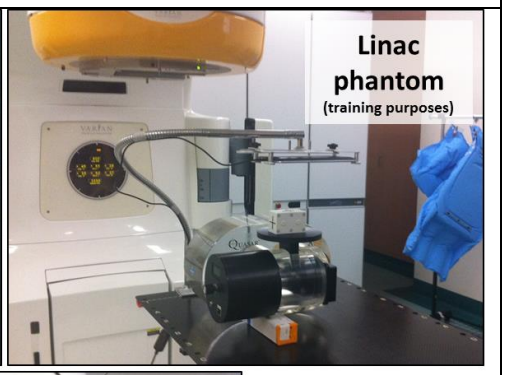
5.2.4.2. Credentialed Institutions

Once investigator training was completed, investigators at each institution performed the credentialing procedures; the credentialing form used for this clinical trial can be found in Appendix IV. Table 5-5 illustrates the credentialing performed at the clinical trial study institutions.

Table 5-5. *Photo evidence of credentialing and training performed at each of the clinical trial's participating institutions. Evidence of hospital staff training prior to credentialing is indicated with "training purposes".*

Calvary Mater Hospital, Newcastle	

Canberra Hospital	   
Royal North Shore Hospital	  

Gosford Hospital	   
Westmead Hospital	 
Chris O'Brien Lifehouse	  

Nepean Cancer Centre	Training and credentialing to be performed once motion sensor solution is implemented.

5.2.5. Discussion

This clinical trial marks an important milestone in breathing guidance studies as it will be the first randomised, controlled trial providing the most comprehensive evaluation of a breathing guidance intervention on cancer radiation therapy to date. Based on the structure of previous investigations, as detailed in chapter 5.1. and taking into consideration the increased in scope of this study, a multi-institutional, randomised, phase II, stratified clinical trial has been designed to test the hypothesis that audiovisual biofeedback breathing guidance will significantly improve breathing regularity and reduce medical imaging errors for lung cancer patients undergoing imaging and treatment procedures during radiotherapy. While patients will be stratified by treating institution and for treatment intent, the study is not powered for formal comparisons between the these stratified groups; estimates from the current proposed study of the proportion of patients which do not experience irregular breathing will provide information as to whether further investigation is warranted. Further to this, objectives such as determining the indications and contra-indications for the use of audiovisual biofeedback, evaluation of patient experience, radiation toxicity occurrence and severity, and clinician confidence will shed light on the design of future phase III clinical trials.

5.3. Conclusion

Through a retrospective analysis of a previous lung cancer patient audiovisual biofeedback study, valuable insights into patient training and the clinical impact of audiovisual biofeedback on radiation therapy were obtained to be utilised in the design of a randomised, phase II audiovisual biofeedback clinical trial. Such a clinical trial marks an important milestone in breathing guidance studies as it will be the first randomised, controlled trial providing the most comprehensive evaluation of the clinical impact of breathing guidance on cancer radiation therapy to date. Objectives such as determining the indications and contraindications for the use of audiovisual biofeedback, evaluation of patient experience, radiation toxicity occurrence and severity, and clinician confidence will shed light on the design of future phase III clinical trials.

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CHAPTER 6

Translating evidence into clinical practice through commercialisation

CHAPTER 6

Translating evidence into clinical practice through commercialisation

Translational research refers to translating research findings into medical practice, to enable broader implementation of a medical intervention outside the confines of a clinical trial to general clinical use. For audiovisual biofeedback, a medical device which has demonstrated benefits in proof-of-principle studies[1-4] has also further demonstrated more clinically relevant benefits in the translational research conducted and detailed in chapter 3, chapter 4, and chapter 5. Further to this, there is also granted patent protection[5] underpinning the audiovisual biofeedback technology. One such method to translate evidence into clinical practice is through commercialisation; this commercialisation process was explored in-house.

What follows is an analysis of the radiation oncology market in which the audiovisual biofeedback medical device will exist, the commercialisation process of audiovisual biofeedback, and how insights from these processes further developed the audiovisual biofeedback technology. The goal of the commercialisation process was to determine the feasibility of an audiovisual biofeedback medical product, to enable broader implementation of audiovisual biofeedback outside the confines of clinical trials in order to be used by more radiation oncology departments with more patients receiving radiation therapy.

6.1. Radiation Oncology Market

6.1.1. Global Market

Cancer radiotherapy is a market which generates US$5.5 billion per annum worldwide and is growing 8% each year.[6] Worldwide there are 7879 radiotherapy centres housing 11239 linear accelerators, 2275 Cobalt-60 therapy machines, and 7168 CT scanners and simulators for radiotherapy treatment planning.[7] The largest markets in the world are the United States of America (USA), China, and Japan with 2736, 1118, and 792 radiotherapy centres, respectively. Western Europe is also a large market with 1050 radiotherapy centres. Australia is home to 71 radiotherapy centres with 168 linear accelerators.[8]

Two major companies operate in the cancer radiotherapy market, with a combined 80% market share for the companies Varian and Elekta. Figure 6-1 illustrates the major companies' market share in cancer radiotherapy.[9]

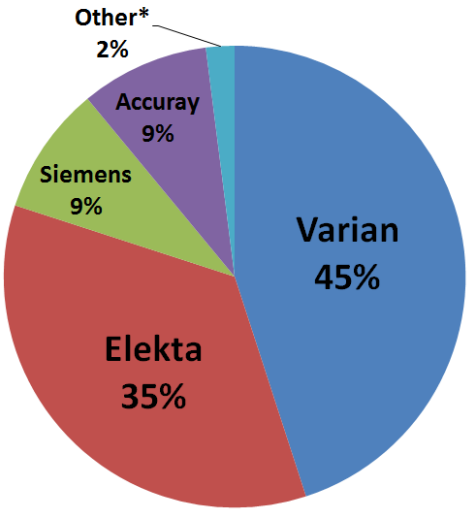


***Figure 6-1**. Cancer radiotherapy companies and their market share.*
**Tomotherapy, Brainlab, IBA, Still River Systems, ViewRay.*

It should be noted that Siemens has since left the cancer radiotherapy linear accelerator market.[10]

6.1.2. Regulatory Bodies

In cancer radiotherapy, regulatory bodies are responsible for assuring the safety, efficacy, and security of medical devices utilised for patient treatment. The Australian regulatory body is the Therapeutic Goods Administration (TGA), which follows a similar structure to the regulatory body of the European Economic Area, the Conformité Européenne (CE). The Food and Drug Administration (FDA) is the governing body over the world's single largest cancer radiotherapy market: the USA.

Medical devices are typically ranked according to classifications which indicate their risk and required controls. Risk is determined by the medical devices' intended use, the probability of harm from the use of the device and the severity of that harm; the level of risk is determined by the medical device's manufacturer. For consistency, the classifications will be outlined here in accordance with the Australian TGA, since this is where the audiovisual biofeedback technology is based and operates under. The TGA medical devices categories are detailed in Table 6-1.[11]

***Table 6-1.** Medical device classifications, in order of lowest risk to highest risk.*

Classification	**Level of risk**
Class I	Low risk medical device.
Class I (measuring / supplied sterile)	Low – medium risk medical device.
Class IIa	Low – medium risk medical device.
Class IIb	Medium – high risk medical device.
Class III	High risk medical device.
Active Implantable Medical Devices (AIMD)	High risk medical device.

With increasing risk of the medical devices' classification come increasing regulatory requirements for the medical device to satisfy, as illustrated by Figure 6-2.

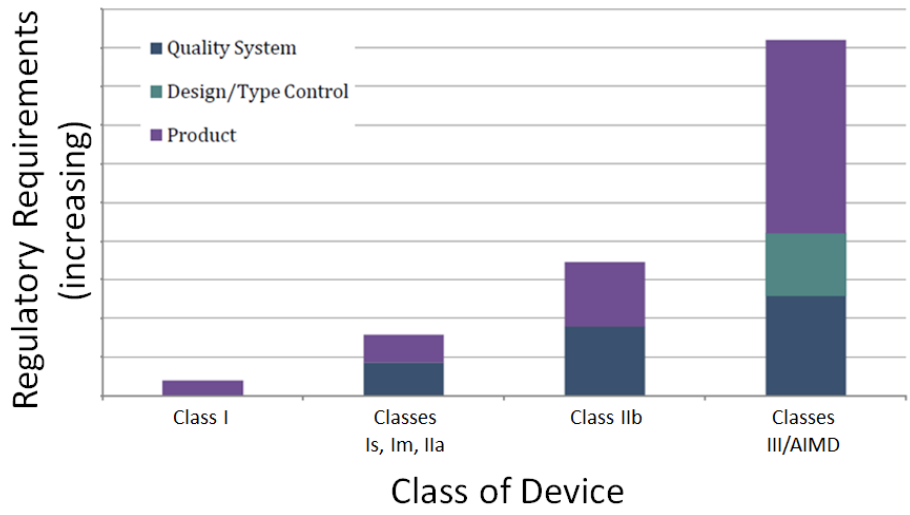


***Figure 6-2**. Risk of medical device verses regulatory requirements. Adapted from Australian regulatory guidelines for medical devices (ARGMD) Version 1.1.*[12]

6.1.3. Cancer Radiotherapy Customers

Who and what constitute a customer can be divided into three main customer segments: Users, Choosers, and Payers.[13] There can be overlap between these categories in the radiotherapy market, and it is important to map out the decision making process towards a medical device being purchased, as there may be different value propositions desired by the different customer segments.

Users are considered those who directly interact with the medical device itself. In cancer radiotherapy the users are typically the patients, radiotherapists, and medical physicist. The patients are the end recipient of the medical device designed to form part of the radiation treatment process. Radiotherapists are responsible for the setup and operation of medical devices involved in each patient's treatment. Medical physicists are responsible for conducting the quality assurance for the medical devices involved in the patients' radiation treatment.

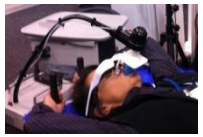
Choosers are those who strongly influence the decision of whether or not to acquire new equipment. In cancer radiotherapy the users are primarily the department heads (chief physicist, chief radiotherapist) and radiation oncologists. Department heads coordinate the activities of their respective staff (either medical physicists or radiotherapists); they will not typically use the medical devices themselves and operate in more of a managerial role. Radiation oncologists prescribe the radiation treatment for the patient and will often be there to oversee the treatment delivery process. Choosers will often attend conferences and training days to identify new techniques to implement. While Choosers are the key decision makers, they often strongly rely on the hospital Users involved in executing the patient treatments such as the radiotherapists and medical physicists.

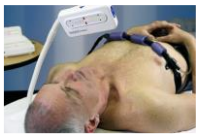
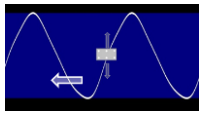
Payers are those responsible for the monetary purchase of the medical device. In cancer radiotherapy, Payers are often not involved in the patient's treatment, and occupy more of a hospital administrative role indented from the patient's treatment. In cancer radiotherapy, the Payer is typically the radiation oncology department, and unlike the Users and Choosers, is the only customer responsible for the monetary purchase of the medical device.

6.1.4. Existing respiratory motion management interventions

Table 6-2 below lists respiratory motion management medical devices currently available on the cancer radiotherapy market, their primary functionalities, their class of medical device, and their price. As indicated in chapter 2,[14] of the medical devices presented in Table 6-2 the Varian Real-time Position Management (RPM) system has been the most prominently utilised medical device in cancer radiotherapy respiratory motion management research.

Table 6-2. *Cancer radiotherapy respiratory motion management medical devices currently available. Proposed audiovisual biofeedback medical device also included for comparison.*

Medical device	Monitors patient breathing	Synchronises with treatment / imaging	Breathing guidance biofeedback	Does not touch the patient	Key components	Class of Medical device	Price (Australian dollars)
Varian Real-time Position Management (RPM)[15] 	✓ Infra-red (IR) camera	✓	✗	✓	1. IR camera 2. Marker block	Class IIb	$62,000 *
Elekta Active Breathing Coordinator (ABC)[16] 	✓ Spirometer	✓	✗ ‡	✗	1. Mouthpiece 2. Spirometer tube 3. Nose plug	Class IIb	$80,000 *
QFix SpiroDynr'X (SDX)[17] 	✓ Spirometer	✓	✓ Breathing signal and target	✗	1. Mouthpiece 2. Spirometer tube 3. Nose plug 4. Video goggles	Class IIb	$104,000 †
VisionRT AlignRT[18]	✓	✓	✗	✓	1. Camera	Class IIb	$200,000 *

	Optical surface tracking						
Medspira[19] 	✓ Chest belt	✗	✓ Light-up display panel	✗	1. Patient display 2. Chest belt	Class I	$32,000 †
Calypso[20] 	✓ Beacon	✓	✗	✗	1. Beacon 2. Panel	Class IIb	$800,000 *
Audiovisual Biofeedback 	✓	✗ ‖	✓	✓	1. All-in-one unit	Class I	$50,000

* Information obtained from customer interviews

† Information obtained from vendors

‡ Reflective mirrored prism-goggles are available to view monitor display across room

‖ Integration with the CT scanner and linac to facilitate CT sorting and beam holds respectively is a desirable feature of the AVB system, but is not planned for the initial product release

6.2. Commercialising Audiovisual Biofeedback

The following programs, shown in Figure 6-3 were utilised to explore and develop audiovisual biofeedback's commercialisation pathway: the University of Sydney offered Genesis[21] and Incubate[22] startup accelerator programs, and NSW Health's Medical Device Commercialisation Training Program (MDCTP).[23]

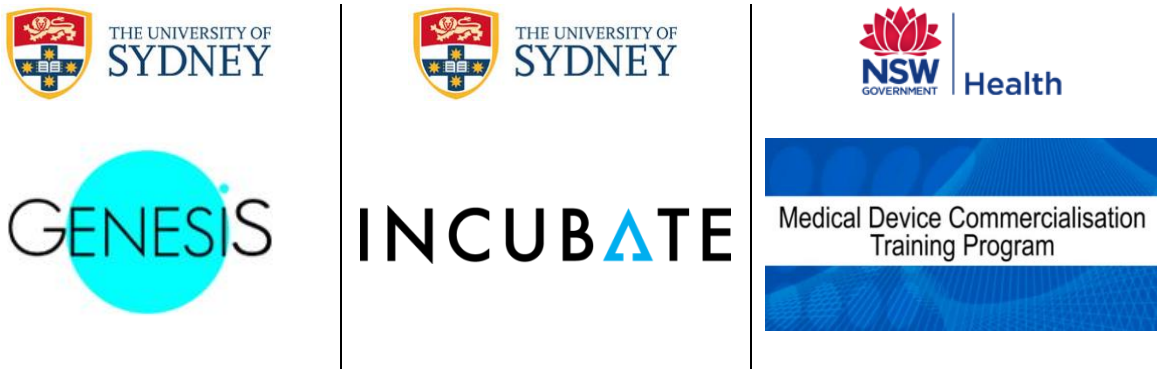


Figure 6-3. *Left to right: the University of Sydney Genesis, Incubate, and NSW Health MDCTP startup accelerator programs.*

The general approach for each of these programs was that of a startup company, typically defined by the search for the right business model,[24] which is achieved by talking to customers, investigating regulatory affairs, and determining the product-market fit.[25] For the purposes of these programs, the current research setup described in chapter 4 and chapter 5 was considered a research prototype, with the details of what the final medical product would be becoming more and more apparent through the progression through each of these commercialisation programs and with increasing customer engagement.

6.2.1. Value Proposition of Audiovisual Biofeedback

The first step is to determine what the value proposition of the medical device is. Determining what value the device creates for the proposed customers, what customer pains does it alleviate and what desired gains does it create for the customer? For audiovisual biofeedback, the proposed value propositions are the following:

1) Patient-customised breathing guidance biofeedback
    - Breathing guidance negates the errors arising from breathing motion irregularities as detailed in chapter 2, chapter 3, and chapter 4.
    - Personalised guide adds an additional element of personalised healthcare appealing to both the patient and their physicians
2) All-in-one motion sensor, patient display medical device unit

- By having all required components for the device housed in a single unit, this reduces the needed setup and calibration times compared to existing medical devices presented in Table 6-2

3) Active patient involvement in assisting accurate radiation treatment
    - Patient is no longer a passive participant in their treatment
    - Patient empowered in helping improve their own treatment

The value propositions described above were used to develop the concept for the final audiovisual biofeedback medical device, highlighted in Figure 6-4.

Figure 6-4. *Audiovisual biofeedback product concept design, highlighted on the CT couch on the left, and components indicated on the right. Images curtesy of DESIGN + INDUSTRY Sydney.*[26]

Prior to conducting customer interviews the initial value propositions are effectively hypotheses on what we think customers want. In order to effectively conduct customer interviews, the customers for audiovisual biofeedback need to be identified and mapped out.

6.2.2. Customer Segments for Audiovisual Biofeedback

As described above, customers are not only the ones responsible for the monetary purchase of the medical device but also the conceptual purchase of the device. The majority of those that will interact with the medical device, the radiotherapists, the medical physicists, the radiation oncologists, may not be responsible for the actual monetary purchase of the device, but are instrumental in recommending its use and acquisition. Table 6-3 details the Users, Choosers, and Payers and their interaction with the audiovisual biofeedback medical device.

Table 6-3. *Details of the Users, Choosers, and Payers of the audiovisual biofeedback medical device.*	
User	**Patient**. The cancer patient will directly interact with the audiovisual biofeedback device. The medical device will monitor their breathing and the patient will then follow the guiding prompts. The patient is understandably anxious about their treatment.
	Radiotherapist. Radiotherapists prepare the treatment rooms for each patient's treatment, so they will be responsible for setting up the audiovisual biofeedback device prior to the patient's arrival, controlling the software during treatment, and packing it away once the treatment is over.
	Medical Physicist. Medical physicists perform quality assurance tests on the audiovisual biofeedback device, assuring that the hardware and software components will perform robustly during patient treatment.
Chooser	**Radiation Oncologist**. The radiation oncologists will not directly interact with the audiovisual biofeedback medical device, but are crucial in recommending its use. Radiation oncologists are key decision makes in adopting new techniques and technologies.
	Department Head. Similar to the radiation oncologists, department heads are crucial in recommending the acquisition of audiovisual biofeedback. However, while radiation oncologists will be more motivated by clinical benefits of the medical device, the department head will also have more focus on the cost-benefits of the medical device.
Payer	**Radiation oncology department**. Typically from a capital budget, the radiation oncology department will represent the final stage of approving and paying for a purchase recommended by the radiation oncologist and/or department head.

The typical decision making process, highlighting the users, choosers, and payers in a radiation oncology department, is illustrated in Figure 6-5.

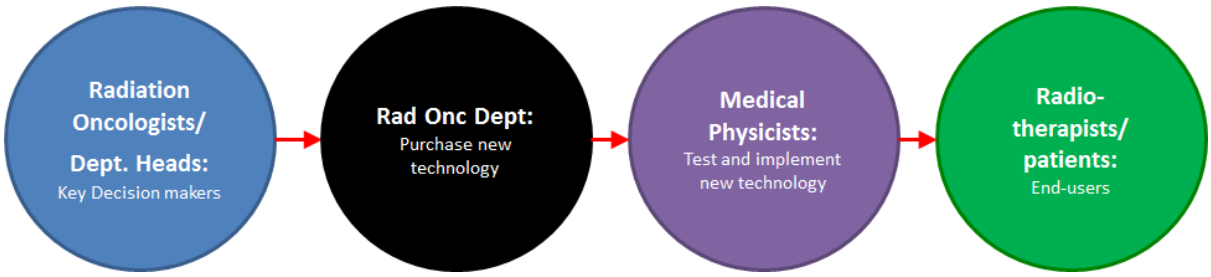


Figure 6-5. *Typical decision making process in a radiation oncology department.*

Each of the customer segments presented in Table 6-3 and Figure 6-5 prioritise the value propositions of audiovisual biofeedback differently. To best align the value propositions of audiovisual biofeedback with its customer segments, customer interviews are required to determine whether there is a product-market fit for the medical device. It should be noted that the relationships in a multi-disciplinary radiation oncology department are far more complex than

linearly indicated in Figure 6-5, with each indicated segment having influence over the others. For example, a radiation oncologist will defer to the judgement of the radiation therapist as they are the ones conducting the patient treatments every day; or a department head heeding the advice of medical physics on the technical feasibility of medical equipment.

6.2.2.1. Customer Interviews

A total of 106 customer interviews were conducted; interviewees ranged from hospital staff, medical companies and vendors, cancer patients, and business and startup mentors. Table 6-4 details the number of interviews and interviewees.

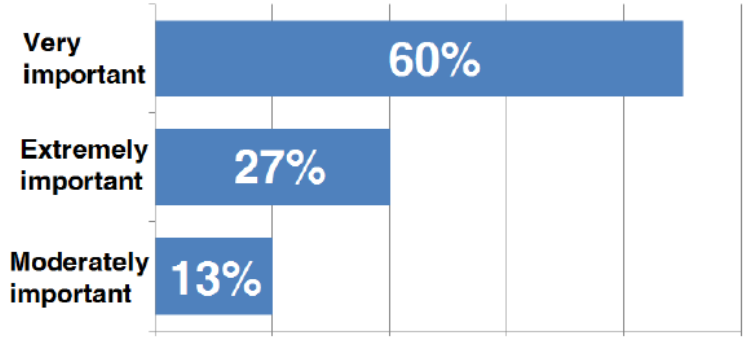
Table 6-4. *Total number of interviews conducted.*

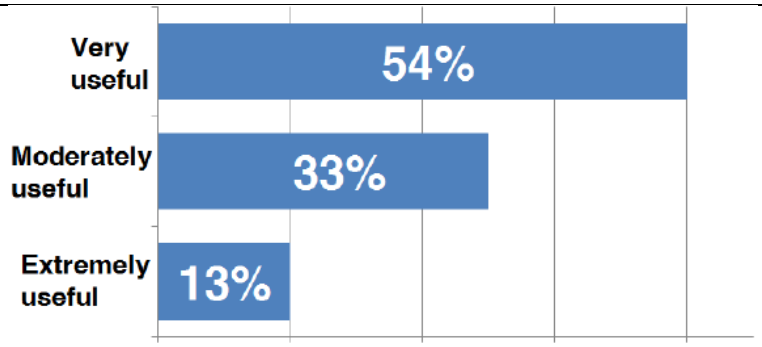
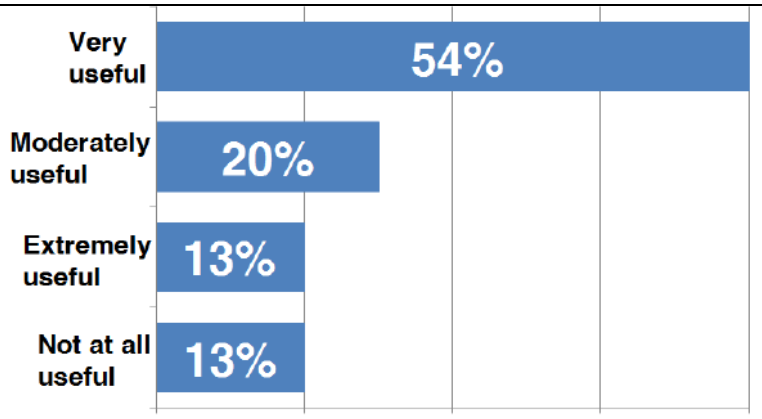
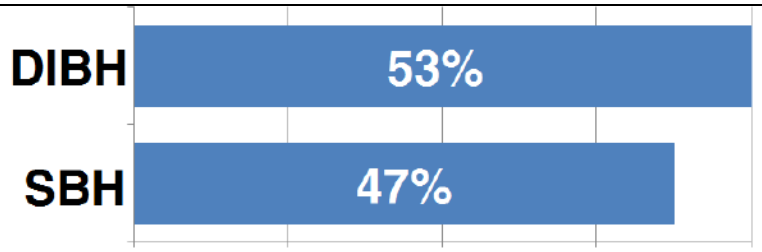
Hospital Staff	73	Radiotherapists	30
		Medical Physicist	12
		Radiation Oncologists	12
		Department Heads	11
		Other*	8
Companies/ vendors	15		
Cancer patients	6		
Business/startup mentors	12		
*Radiologists, technicians, scientists			

32 interviews were conducted during the Incubate accelerator program, and 74 were conducted during the MDCTP.

An online survey was conducted during Incubate interviews determining how important regular respiratory motion and the importance of the use of audiovisual biofeedback was in the facilitation of this. The questions provided in the online survey and the overall responses are given in Table 6-5.

Table 6-5. *Responses to interview questions conducted in the Sydney Incubate program.*

(1) How important do you consider regular and stable patient breathing-motion to be during imaging and/or radiation treatment?	

(2) How useful would audiovisual biofeedback be for patients' imaging and/or treatment?	
(3) How likely is it that you would recommend audiovisual biofeedback's use in patient imaging and/or radiation treatment	
(4) How useful would breath-hold guidance be for patients' imaging and/or treatment?	
(5) Which function do you consider more useful: standard breath holds (SBH) or deep-inspiration breath holds (DIBH)?	
(6) How likely is it that you would recommend audiovisual biofeedback to a colleague?	

(7) For which patients / conditions do you consider audiovisual biofeedback to be useful? (Multiple answers possible)

Lung cancer	87%
Liver cancer	73%
Breast cancer	60%
Stress/anxiety	53%
Kidney cancer	40%
Pancreas cancer	33%
Hypertension	27%
Pneumonitis	20%

Interviews conducted throughout the MDCTP, rather than focusing on what customers thought about audiovisual biofeedback, focused on what customers thought about what they currently implemented in cancer radiotherapy. Information gathered from these interviews provided insights into what the customers' main frustrations and desired improvements were and whether the value propositions offered by audiovisual biofeedback aligned with, or could be adapted to, addressing these problems encountered by customers. Also, given the interest expressed from previous interviews in breath hold guidance, MDCTP interviews also perused this functionality of audiovisual biofeedback.

From the 74 interviews conducted in the MDCTP, Table 6-6 details the main frustrations and desires expressed by cancer radiotherapy hospital staff.

Table 6-6. *Key insights from hospital staff on current medical devices used in cancer radiotherapy.*

Radiation Oncologists	**Medical Physicists**	**Radiotherapists**
Reproducibility of medical device	Extra time is needed to implement new technologies	Poor patient communication
Cost-effectiveness of medical device	Software interface of current medical devices (see Table 6-2) often frustrating to use	Poor patient compliance

A total of 37 Australian radiation oncology departments (52% of the Australian market) participated in these interviews. Clinically in Australia, there are no hospitals with a solution to facilitate regular patient breathing, and there are 20 hospitals that are not performing DIBH with their breast cancer patients. A key element of the commercialisation process is establishing a product-market fit, ensuring the product offering matches your customers' wants and needs, pivoting if need be to ensure that it does. A key element that customers communicated during the interview process is that there is a strong desire for biofeedback methods for deep inspiration breath holds with breast cancer patients. As such, DIBH for breast cancer patients was also considered in the commercialisation process.

Patients who were interviewed indicated that had there been an option for them to help assist with improving their radiation therapy, they would have wanted to contribute.

Customer interviews yielded that there is not an equivalent breathing guidance solution on the market to audiovisual biofeedback, and that the key insights from hospital staff highlighted the need for an effective and simple to use solution to maximise communication efficiency between patients and radiotherapists and minimise setup time. This higher efficiency would lead to faster treatments

times per patient, allowing more patients to be treated per day, increasing the cost-effectiveness of the medical device.

6.2.3. Regulatory Approval

While audiovisual biofeedback does monitor patient breathing motion, but these measurements are not used to diagnose, prescribe, or guide treatment, and as such audiovisual biofeedback is considered a non-measuring device. For the cancer radiotherapy procedures it will be used for, audiovisual biofeedback is not required to be kept sterile. Therefore, audiovisual biofeedback is a Class I medical device. Table 6-7 details the regulatory requirements of audiovisual biofeedback for the regulatory bodies TGA, CE, and FDA.

Table 6-7. *Regulatory approval classification and details for the regulatory bodies of Australia, the USA, and Europe.*

	Australia	**Europe**	**USA**
Regulatory Admin	TGA	CE	FDA
Classification	Class I	Class I	Class I
Quality Management System	Not needed[27]	Not needed[28]	Not likely needed[29]
Risk Analysis	Low risk[30]	Low risk[31]	No risk analysis needed[32]
Regulatory body intervention	Incidence reporting to TGA[33]	Notify local government authorities of adverse event[34]	Incidence reporting to FDA[35]

It should be noted that should audiovisual biofeedback be synchronised with the radiation treatment beam, this would increase the class of medical device to Class IIb, because then the measurements taken by audiovisual biofeedback are being used to guide treatment.

6.2.4. Intellectual Property & Freedom to Operate

Current intellectual property (IP) is primarily in the form of United States patent US 7955270 B2 protecting the methodology of producing a customised patient-specific interface for biofeedback breathing guidance.[5]

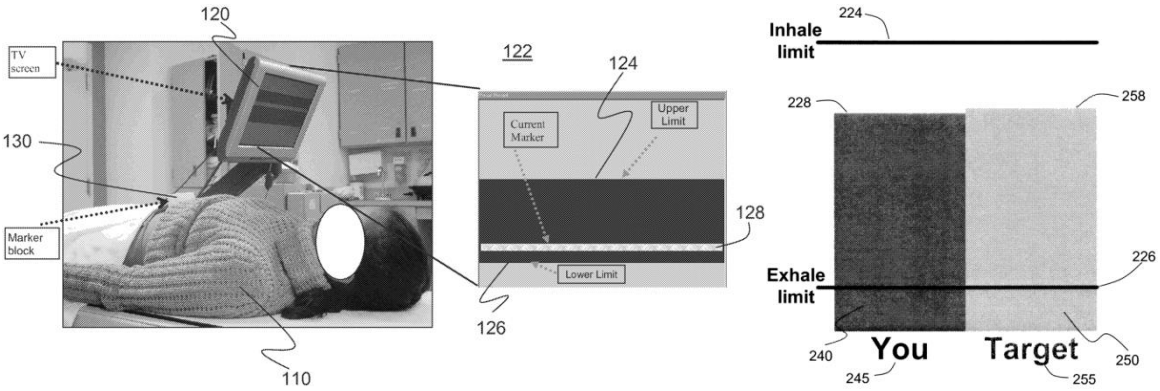


Figure 6-6. *US 7955270 B2 figures demonstrating the audiovisual biofeedback setup (left) and guiding interface (right).*[5]

This patent protects the world's single largest radiation oncology market, the United States of America, which is also where the largest radiation oncology company, Varian, is based. Personalised medicine is becoming increasingly of interest,[36, 37] so producing a customised patient-specific breathing guide to further tailor radiation treatment to the patient is one of audiovisual biofeedback's competitive advantages. This patent details claims pertaining to a respiratory audio-visual biofeedback device for medical imaging and radiotherapy treatment procedures incorporating a target position and the patient's position and presenting them in such a way such that the difference between the target position and patient position is readily apparent. Subsequent claims relate back to this core claim further incorporating elements of learning patient breathing and producing target position via mathematical algorithms. This protects the audiovisual biofeedback IP by protecting the use of audio and visual prompts to guide patient respiration, in addition to producing a customised guiding interface by learning the patient breathing through mathematical algorithms.

Table 6-8 details the findings of a freedom to operate search, detailing similar patents to patent US 7955270 B2 protecting audiovisual biofeedback and their relative risk to US 7955270 B2. For reference, audiovisual biofeedback's patent US 7955270 B2 was filed on 04/10/2006 and granted on 07/06/2011.

Table 6-8. *Findings of freedom to operate search.*

Patent	Summary of claims	Relative risk of IP
Patent number: US 6,937,696 B1 **Title**: Method and system for predictive physiological gating **Filed**: 26/06/2001	• Method of detecting / estimating regular cycles of physiological activity • Gating of radiation treatment based on the phase of physiological	Low. Patient guidance / feedback not considered.

Date of patent: 30/08/2005	activity	
Patent number: US 7,393,329 B1 **Title**: Method and apparatus for delivering radiation therapy during suspended ventilation **Filed**: 22/05/1998 **Date of patent**: 01/07/2008	• Apparatus: ventilator controlling inhalation and exhalation • Valves in ventilator shut to suspend patient breathing • Display apparatus of lung volume and target • Apparatus of mirror-glasses to view display	Low-Medium. Apparatus described is decidedly different from audiovisual biofeedback. Claims detailing a 'target' and 'display' relate it back to lung volume and mirror-glasses. Infringement between audiovisual biofeedback and this unlikely.
Patent number: US 7,869,562 **Title**: Automatic patient positioning system **Filed**: 18/03/2009 **Date of patent**: 11/01/2011	• 3D optical imaging system for positioning patient relative to radiographic equipment • 3D optical system produces positional signal • Used to reposition the couch relative to various scanners	Low. Filing date is later than audiovisual biofeedback's. audiovisual biofeedback utilises a 1D signal, this was focussed on 3D No details regarding displaying signal to patient
Patent number: US 7,769,430 B2 **Title**: Patient visual instruction techniques for synchronising breathing with a medical procedure **Filed**: 30/09/2004 **Date of patent**: 03/08/2010	• Continuation of 'US 6,937,696 B13' • Informing patients of the relationship between an action performed by the patient and a target result to be achieved • Focus on synchronisation with radiation source and medical device.	High. Has earlier filing date than audiovisual biofeedback's. Details relationship between patient position and the desired target position. Details synchronisation with 'radiation source' and 'medical device'.
Patent number: US 8,619,945 B2 **Title**: Prediction-based breathing control apparatus for radiation therapy **Filed**: 20/09/2011 **Date of patent**: 31/12/2013	• Method of radiation delivery based by determining a future treatment opportunity • Past observed motion is used to predict future positions	Low. Details using the breathing signal to predict future position for the radiation beam to fire upon. No details on providing feedback to the patient or breath holds.
Patent number: US 8,781,558 B2	• Ventilator used to generate respiratory manoeuvres	Medium. Patent specific to ventilation

Title: System and method of radiation dose targeting through ventilator controlled anatomical positioning **Filed**: 07/11/2011 **Date of patent**: 15/07/2014	• Closed loop with imaging / treatment machines	methods (spirometry), however, feedback to patient is mentioned in one of the claims. audiovisual biofeedback has earlier filing date.
Patent number: US 2006/0129044 A1 **Title**: Device for monitoring anatomical imaging unit or a radiotherapy unit **Filed**: 22/04/2002 **Date of patent**: 15/06/2006	• Representing ventilator level of their suspended ventilator level for inhalation and exhalation • Two valves: rest valve, triggering valve	Medium. Has earlier filing date than audiovisual biofeedback. But pertains to ventilation, i.e. measuring airflow, not anatomic motion. Potential conflict of 'suspended breathing' claims.
Patent number: US 2013/0211261 A1 **Title**: Motion compensation and patient feedback in medical imaging systems **Filed**: May 7, 2010 **Date of patent**: 15/08/2013	• An optical motion sensing system • This was confusingly worded… • Generate feedback data, providing audio and visual feedback indicative of the anatomic structure	Medium-High. Details of the feedback motion sensor descriptions seem to infringe on audiovisual biofeedback patent claims. audiovisual biofeedback's patent predates this one.
Patent number: US 2013/0261424 A1 **Title**: System for inducing respiration using biofeedback principle **Filed**: 08/03/2013 **Date of patent**: 03/10/2013	• A system for processing a biofeedback-treated, respiration-induced signal image using the biofeedback principle. • Claims focussed on image processing for segmenting an observed image into regions and extracting signal from there	Medium. While biofeedback is detailed in the application, the claims pertain to image processing. Potential conflict for how certain motion sensors can operate.

From the results of the freedom to operate search, there is one patent (US 7,769,430 B2) with an earlier priority date that poses a high risk to audiovisual biofeedback's IP. However, Varian, which owns patent US 7,769,430 B2, did not extend this patent to protect the Australian market. Therefore, audiovisual biofeedback has freedom to operate in the Australian market, with a potential risk of patent infringement in the American market.

6.2.5. Reimbursement

In order to be eligible for insurance reimbursement a medical device, under the Australian Medicare system, needs:

- TGA approval
- To lodge an application to Medical Services Advisory Committee (MSAC)
    - To demonstrate health benefit and economic benefit in terms of quality adjusted life years (QALYs) and incremental cost-effectiveness ratio (ICER), respectively.

The Medicare Benefits Schedule (MBS) doesn't usually make reference to the specific equipment used, it typically just refers to the service provided; radiation Oncology – General has the MBS Note T2.1.[38] However, there are exceptions should the medical device demonstrate a certain level of health benefits and cost-effectiveness. For example, gold fiducial markers implanted in the prostate for use in radiotherapy has the MBS item number 37217.[39]

Audiovisual biofeedback needs to demonstrate a certain level of health and economic benefits before it can be listed on the MBS for reimbursement. Outcomes of ongoing and future clinical trials will provide evidence as to whether this is achievable; otherwise, the radiation oncology department will be the sole payer of the device.

6.2.6. Market Analysis and Business Model

Based on the price of similar medical devices shown in Table 6-2, the revenue stream of the audiovisual biofeedback medical device is a capital cost of $50,000 for the audiovisual biofeedback product was determined to be both competitive and conducive to generate positive cash flow once making sales. Further to this, similar medical devices also include a service cost of 20% to cover staff training, installation, system breakages, and maintenance. As such, there will also be an annual service charge of an additional 20% ($10,000) for audiovisual biofeedback.

6.2.6.1. Audiovisual Biofeedback Market

The market for audiovisual biofeedback will be considered from three perspectives: the total addressable market, served available market, and the target market.[24] The total addressable market refers to monetary value representative of if everyone who could purchase the medical device did purchase the medical device. The served available market represents those customers in the total addressable market that can be feasibly reached through an available sales channel. The target market represents the medical device's first customers.

Audiovisual biofeedback would be used on CT scanners and simulators in addition to linacs; as detailed in chapter 6.1.1., there are 11244 linacs and 7169 CT scanners and simulators worldwide,[7]

therefore there are a total of 18413 facilities where audiovisual biofeedback can be used, representing a total addressable market size of $1,104,780,000. Note that each purchase takes into account the capital cost of $50,000 in addition to the first years' service cost ($10,000).

Since it is more likely that our serviceable markets are Australia, the USA, and Europe, where there are 6523 linacs and 2818 CT scanners and simulators,[7] this represents a served available market size of $560,460,000.

The first sales of audiovisual biofeedback will likely be made in Australia, as that is where both the technology and the team behind it are based. The first customers will most likely be those hospitals who currently no not perform breathing guidance for both regular breathing and DIBH. As detailed in chapter 6.2.2.1., this is represented by 20 hospitals. Each Australian hospital will have one CT scanner or simulator, and has an average of 2.3 linacs per radiation oncology department.[7] Taking 2 linacs per department as a conservative estimate, audiovisual biofeedback's first customers comprise of 40 linacs and 20 CT scanners and simulators, representing a target market of $3,600,000.

6.2.6.2. Business Model Canvas

A business model canvas, shown in Figure 6-7, is a tool to identify and plan out the main aspects of a company, a startup company is typically defined as the search for the business model outlining not only their first customers, but a scalable business.[24]

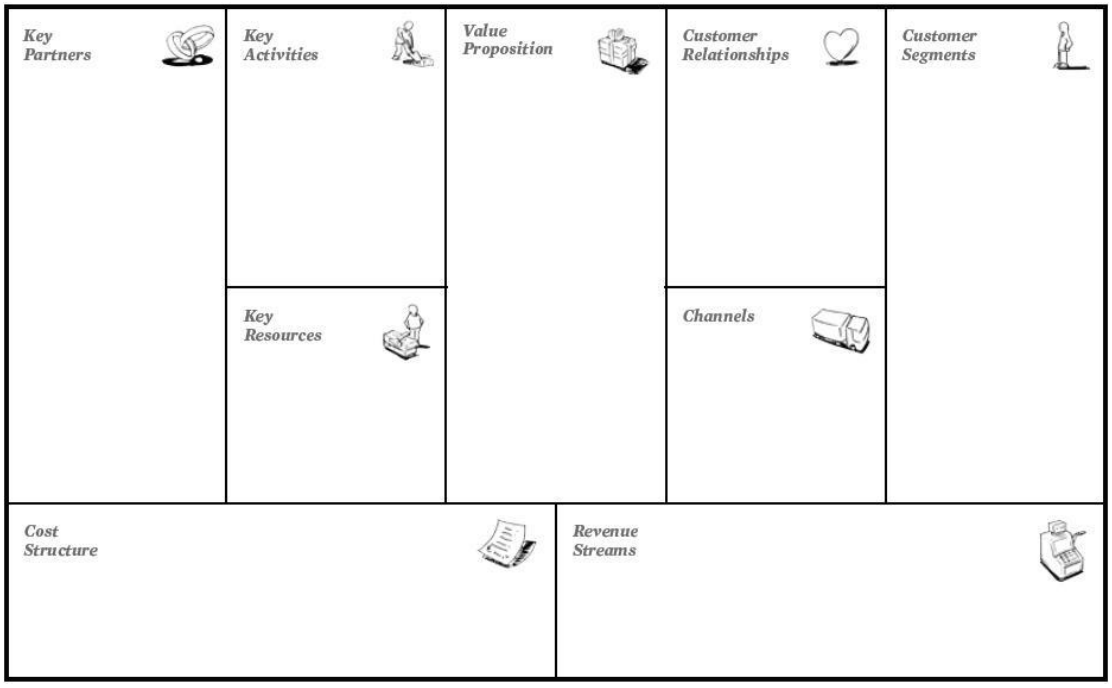


Figure 6-7. *A blank business model canvas.*[40]

The value proposition, customer segments, and revenue streams have already been described. The order in which to approach each component of the business model canvas is as follows: (1) Customer segments, (2) Value proposition, (3) Customer relationships, (4) Channels, (5) Revenue streams, (6) Key resources, (7) Key activities, (8) Key partners, (9) Cost structure.[40] When the value proposition aligns with the customer segments, this is referred to a product market fit.[25]

Customer relationships outline the different types of relationships the business has with its customer segments. These could be how first contact is made with customers and how the relationship is sustained once the customer acquires the medical device. Channels describe how the medical device and the value it delivers is provided to the customer segments.

Key resources describes business' infrastructure and what resources of are crucial for the business' success. This can involve the team itself executing the business plan and IP protection. Similarly, key activities describe what needs to be done for the business to succeed; these activities can be broadening IP protection, fund raising, and regulatory approval. Key partnerships describe those outside your business who can assist in adding value to your business. Examples of key partners include clinical trial partners, manufacturing partners, and distribution partners.

Once components (1) through (8) on the business model canvas are well understood will reveal how much each of these components will cost. If the cost structure is appropriately less than the revenue stream, then there is a viable business model.

Initially, the business model canvas for audiovisual biofeedback was filled in with assumptions about what we thought its model model should be. Over time, the business model canvas for audiovisual biofeedback was continuously refined over the 106 performed customer and mentor interviews. Figure 6-8 details the current business model canvas for audiovisual biofeedback after all the customer interviews.

Through the customer interviews, the decision making process for acquiring new equipment of radiation oncology departments was determined, as such, key relationships with customers and the channel to customers was determined to best utilise existing relationships through clinical trials, demonstrate the technology at hospital research meetings, providing the technology to customers via distributions channels provided by the manufacturers.

Also throughout the interview process, component providers, designers, and manufacturers were identified and enganged to produce the final audiovisual biofeedback product.[41-43] The audiovisual biofeedback product concept design shown in Figure 6-4 is a result of these engagements.

This business model canvas details the not only audiovisual biofeedback's first customers (the target market) but is scalable and so describes customers for when audiovisual biofeedback enters the international market (the served available market).

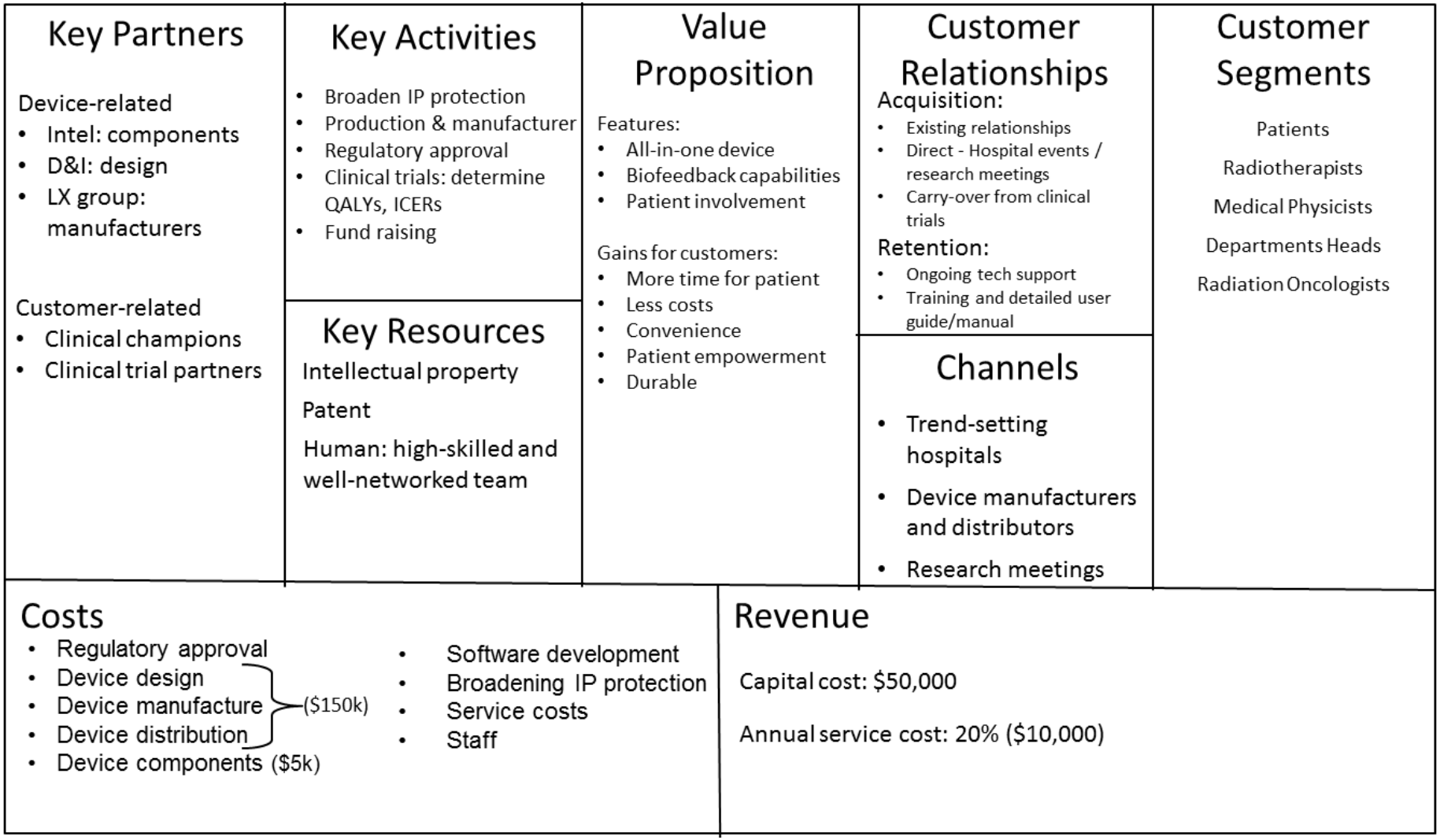


***Figure 6-8**. Business model canvas for audiovisual biofeedback.*

6.2.6.3. Cost-effectiveness of audiovisual biofeedback

In addition to determining a product-market fit, a key element to be demonstrated by medical devices is the cost-effectiveness, especially for it to be eligible for insurance reimbursement, as detailed in chapter 6.2.5.. The primary health benefit of audiovisual biofeedback will present itself in terms of reducing the occurance and severity of radiation toxicities, and therefore, the primary cost-effectiveness of audiovisual biofeedback will be in terms of reducing the costs associated with managing these toxicities.

As shown in Table 6-5, the patients for whom audiovisual biofeedback was considered most useful were lung, liver, and breast cancer patients; lung and breast cancer are also the two most common forms of cancer. The most common radiation toxicities for such patients include esophagitis, pneumonitis, pulmonary fibrosis, and cardiovascular complications such as ischemic heart disease. For the purpose of this analysis, cost-effectiveness for lung cancer patients was considered from the perspective of regular breathing audiovisual biofeedback, and cost-effectiveness for breast cancer patients was considered from the perspective of deep inspiration breath hold (DIBH) audiovisual biofeedback. Table 6-9 details the costs involved in managing radiation toxicities.

Table 6-9. Costs involved in managing radiation toxicities. Values given are in Australian dollars.

Cardiac toxicities	
Event	**Cost**
Coronary Artery Grafts-Bypass surgery	$38,100[44]
Insertion of a Cardiac Stent	$7,800[44]
Coronary Angiogram	$9,100[44]
Pulmonary toxicities	
Esophagitis	$1,754.24[45]
Pneumonitis	$5,672.52[45]
Pulmonary fibrosis	$1,502.61[45]
Miscellaneous costs	
Hospital bed per day	$325.91[46]
Economic cost of one sick day	$375[47]

Table 6-10 details the occurrence and length of recovery for lung and breast cancer patients with such aforementioned toxicities. It has been reported that for patients presenting with cardiac toxicities 1/3rd of these patients require an angiogram and stents and 10% are treated with coronary

artery bypass surgery.[48] Based on this and the values presented in Table 6-9, the average cost of cardiac toxicities per patient was calculated to be $9,443.33.

Table 6-10. Occurance and recovery time of raidation toxicities for free breathing lung and breast cancer patients.

Breast cancer patients	
Occurrence of serious cardiac event (no radiotherapy)	19.2%[49]
Increase of risk due to the use of radiotherapy	43%[50]
Relationship between risk of cardiac event and radiation dose to the heart	Increases by 7.4% with each Gy of mean heart dose[51]
Hospital days after surgery (see Table 6-9)	Up to 8[52]
Sick days after surgery	Up to 2 months[52] (40 business days)
Risk of pneumonitis	14%[50]
Lung cancer patients	
Risk of esophagitis	31.6%[45]
Risk of pneumonitis	30%[45]
Risk of pulmonary fibrosis	8.3%[45]
Relationship between risk of pulmonary toxicity and radiation dose to the lungs	Increases by 10% from an increase of 4.5% in mean lung dose[53]
Relationship between treatment margin size and dose to the lungs	23% reduction in PTV (~0.29cm) corresponds to 10% reduction in mean lung dose[54]

Based on the information presented in Table 6-10, radiotherapy increases the risk of a serious cardiac event by 43%, from 19.2% to 27.5%, for free breathing breast cancer patients. Further to this, for free breathing breast cancer patients receiving radiotherapy, the risk of a cardiac event increases by 7.4% with each Gy delivered to the heart. In addition to this, also taking into account the information presented in Table 6-9, the cost of an 8 days stay at the hospital equates to $2,607.28 and 40 sick days equates to $15,000. However, this would only be applicable to the 43.33% of patients requiring cardiac procedures (detailed in Table 6-9, 10% of patient receiving bypass surgery, 1/3rd receiving angiogram and stents), resulting in an average hospital stay and sick day cost of $7,629.82.

Pulmonary toxicities do not typically require surgery, as such, there are negligible additional days spent at the hospital and days spent home from work for the patient. Also, a 4.5% reduction in mean

lung dose corresponds to a 10% decrease in pulmonary toxicity, corresponding to approximately a 2.22% increase in toxicity risk with each percent increase in mean lung dose.

Table 6-11 details the benefits of providing DIBH to breast and regular breathing for lung cancer patients.

Table 6-11. Impact of DIBH and audiovisual biofeedback on mean dose and treatment margins.	
Impact of DIBH on mean heart dose	Mean heart dose is reduced by 2.5Gy[55]
Impact of DIBH on mean lung dose	Mean ipsilateral lung dose is reduced by 1 Gy[56]
Impact of regular breathing on margin size	Audiovisual biofeedback reduced margin size by 0.30 cm (see chapter 5.)*
* Assuming no other errors	

Hence, based on the information presented in Tables 6-9 to 6-11, for breast cancer patients:

- DIBH reduced mean heart dose by 2.5 Gy (Table 6-11), and therefore reduces the risk of a serious cardiac event by 2.5 × 7.4% = 18.5% (Table 6-10), reducing the risk of a cardiac event from 27.5% to 22.4%
- DIBH reduced mean lung dose by 1 Gy, which as stated earlier, corresponds to a 2.22% decrease in toxicity risk, resulting in a decrease in risk of pneumonitis from 14% to 11.78%.
- Audiovisual biofeedback reduced margins by 0.30 cm (Table 6-11), comparable to the 0.29 cm reduction achieving a 10% reduction in mean lung dose (Table 6-10), which corresponds to a 10 × 2.22 = 22.2% reduction in risk of pulmonary toxicity. Reducing the risk of esophagitis from 31.6% to 24.6%, pneumonitis from 30% to 23.34%, and pulmonary fibrosis from 8.3% to 6.5%.

The cost-effectiveness was determined to be the difference between the cost of managing toxicities (free breathing) and the cost of managing toxicities (DIBH/regular breathing) for breast and lung cancer patients. The cost of managing toxicities was determined to be:

$$Total\ Cost = [Number\ of\ patients] \times [Risk\ of\ toxicity] \times [Monetary\ cost\ of\ toxicity] \quad (1)$$

Where, in Australia, only left-sided breast cancer patients are considered since DIBH is not typically performed for right-sided breast cancer patients:

$$Total\ Cost_{free\ breathing} = ([7090] \times [27.46\%] \times [\$9443.33 + \$7629.82])_{cardiac} + ([7090] \times [14\%] \times [\$5{,}672.52])_{pneumonitis} = \$38{,}870{,}504$$

$$Total\ Cost_{DIBH} = ([7090] \times [22.38\%] \times [\$9443.33 + \$7629.82])_{cardiac} + ([7090] \times [11.78\%] \times [5{,}672.52])_{pneumonitis} = \$31{,}828{,}389$$

Yielding a cost-effectiveness of $7,042,000 from the use of DIBH for breast cancer patients, or $993 per patient. Globally, this translates to cost-effectiveness of $844,000,000 each year.

For lung cancer patients treated with radiotherapy in Australia each year:

$$Total\ Cost_{free\ breathing} = ([5000] \times [31.60\%] \times [\$1754.24])_{esophagitis} + ([5000] \times [30\%] \times [\$5672.52])_{pneumonitis} + ([5000] \times [8.60\%] \times [\$1502.61])_{fibrosis} = \$11{,}926{,}602$$

$$Total\ Cost_{regular} = ([5000] \times [24.85\%] \times [\$1754.24])_{esophagitis} + ([5000] \times [23.34] \times [\$5672.52])_{pneumonitis} + ([5000] \times [6.46\%] \times [\$1502.61])_{fibrosis} = \$9{,}284{,}817$$

Yielding a cost-effectiveness of $2,640,000 from the facilitation of regular breathing from audiovisual biofeedback for lung cancer patients, or $528 per patient. Globally, this translates to cost-effectiveness of $475,000,000 each year.

The use of audiovisual biofeedback for both DIBH and regular breathing stands to reduce the Australian health-care associated costs of lung and breast cancer patients' radiotherapy by a combined $9,684,000, and $1,319,000,000 worldwide.

Further to this, a typical radiation oncology department will treat 100 lung cancer patients and 100 breast cancer patients each year. After purchasing audiovisual biofeedback for $50,000 (see Table 6-2), the cost savings from the use of audiovisual biofeedback will make up for the cost of the device itself after 66 lung and breast cancer patients have been treated (within 8 months).

6.2.7. Market Capture Strategy and Future Projections

In keeping with a lean startup approach, the Australian go-to-market strategy is direct distribution, starting in NSW and moving across Australia, leveraging the existing NSW-focused clinical trials detailed in chapter 4 and chapter 5. Direct distribution refers to directly delivering the product to customers personally rather than through contracted distributors. Direct distribution is lower cost than going through a contracted distributor but also limits the company to a low volume of sales; however given the high gross margin of the product allows the company to be sustainable throughout early low-volume customer sales. The proximity to our customer base through direct distribution will enable close company-customer feedback and interaction, with rapid product

improvement to meet user needs. As of August 2016, two NSW radiotherapy centres have signed an intent-to-purchase letter to secure the audiovisual biofeedback device once it becomes TGA-approved. Early adopters in Australia will help us establish a viable business model, determine its multipliers and generate funds for international growth. Contracted distributors will be engaged for international sales and service. Figure 6-9 illustrates projected sales revenue and company growth in terms of full time equivalent (FTE) employees over the next 3 years until end of financial year (EOFY) 2018/2019.

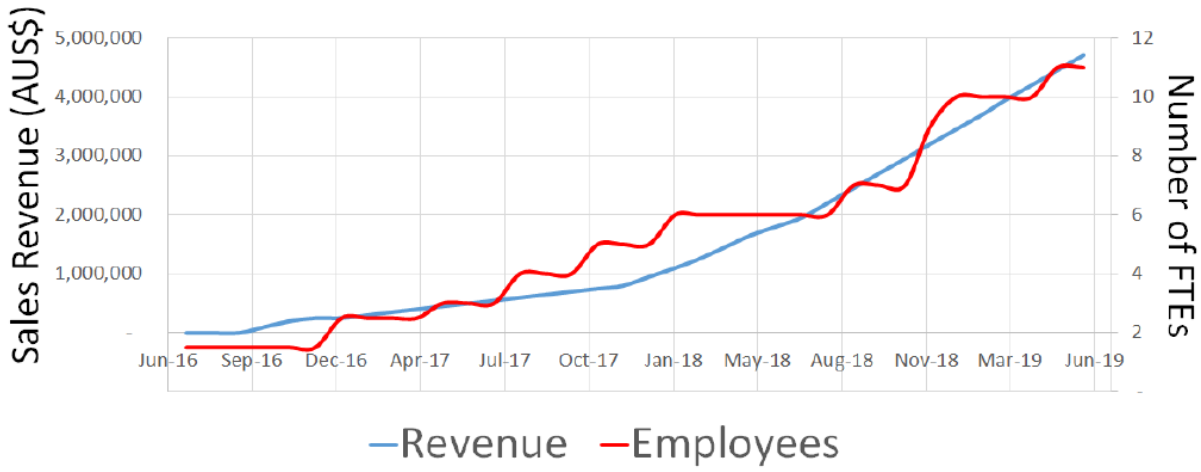


Figure 6-9. *Projections of sales revenue (blue) and number of FTE employees (red) by EOFY 2018/19.*

Projections indicate revenue from sales to be $4.8M by EOFY 2018/19, with 11 new jobs created by EOFY 2018/19. Assumptions made in regards to the projections illustrated in Figure 6-10 include:

- TGA approval and first sales in Australia in November, 2016
- FDA approval and first sales in the USA in November, 2017
- New employees are recruited when (i) an additional 20 products are in service, and (ii) company demonstrates continuous growth 3 months in a row
- Direct sales implemented in Australia, distributor channels utilised in the USA with a 40% distributor margin.

6.3. Feeding Customer Insights back into research approach

From the interviews conducted, both with hospital staff currently using audiovisual biofeedback for the clinical trials described in chapter 3 and chapter 4 and with hospital stuff who have never used audiovisual biofeedback, a number of insights were garnered in terms of what desired features for the audiovisual biofeedback system in addition to currently used motion management technologies (see chapter 1.2.1.5.).

6.3.1. Development of the audiovisual biofeedback hardware

From the insights garnered by talking with radiation oncology hospital staff, the most cumbersome element of the current research setup of the audiovisual biofeedback system is interfacing with and receiving the respiratory signal from the Varian RPM motion sensor. This requires:

1) "Enabling Serial Protocol" in the RPM software to enable the real-time output of respiratory information
2) Installing the required cable drivers on the research computer with audiovisual biofeedback installed

Various firewalls and limitations to internet access can greatly inhibit the two critical steps detailed above which are necessary to simply adequately connect the research computer with audiovisual biofeedback installed to the Varian RPM. Once connectivity between audiovisual biofeedback and the RPM is enabled, there is still the need to connect all the components together; the schematic shown in Figure 6-10(a) is from a clinical trial workflow guide (included in Appendix IV) illustrates the current audiovisual biofeedback setup. Figure 6-10(b) illustrates the schematic setup of a condensed audiovisual biofeedback system setup, housing the motion sensor, patient display, and software in a single unit.

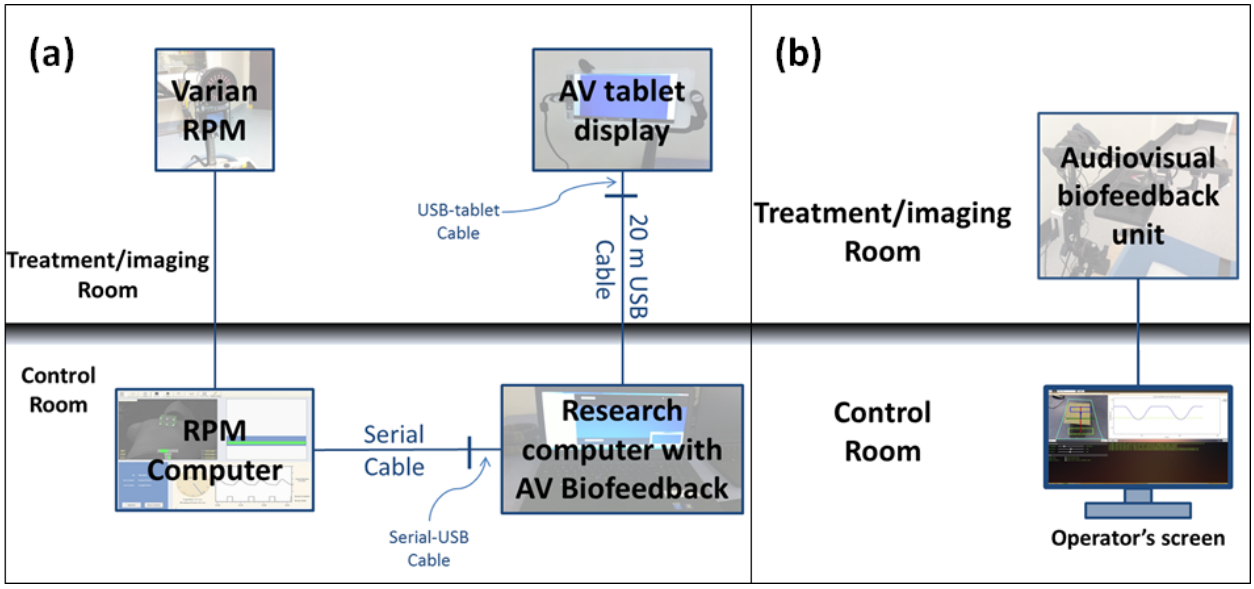


Figure 6-10. *Audiovisual biofeedback system components and connectivity, with (a) the current research setup and (b) the proposed condensed setup on the right.*

6.3.1.1. Development of stand-alone motion sensor

The first major hurdle to house the necessary audiovisual biofeedback components in a single unit was to identify and test a physiologically-accurate respiratory sensor alternative to the current sensor: the Varian RPM.

6.3.1.1.1. Microsoft Kinect

One such respiratory sensor was the Microsoft Kinect, which monitors respiratory motion as a depth sensor.[57, 58] Figure 6-11 illustrates the Microsoft Kinect operating as a depth sensor.

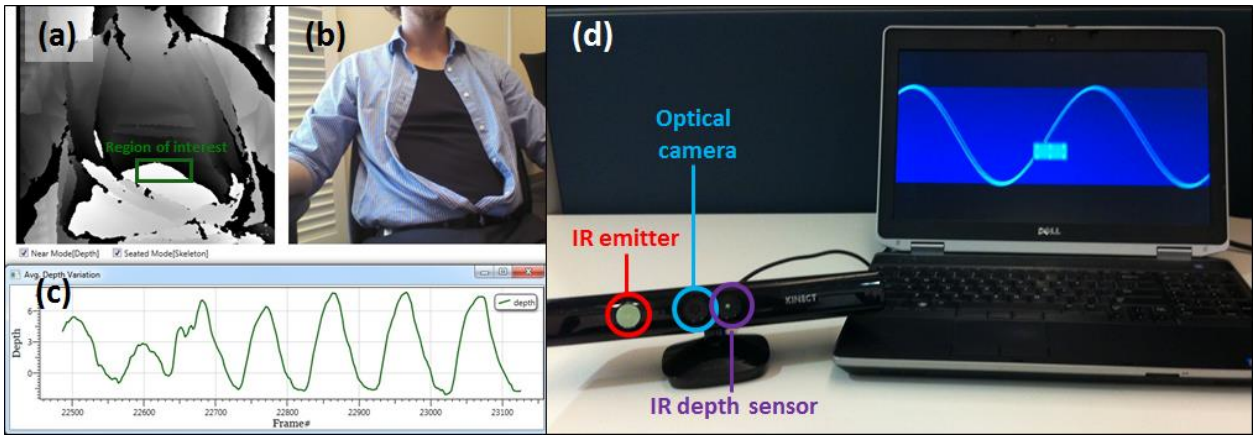


Figure 6-11. *Screenshot of the Microsoft Kinect's motion tracking software developed in-house, demonstrating (a) depth image, (b) optical image, (c) depth signal of the determined region of interest, and (d) the Microsoft Kinect interfaced with the audiovisual biofeedback software.*

Figure 6-12 demonstrates a volunteer Microsoft Kinect test performed at the Seattle Cancer Care Alliance Proton Therapy Center on August 7th, 2015.

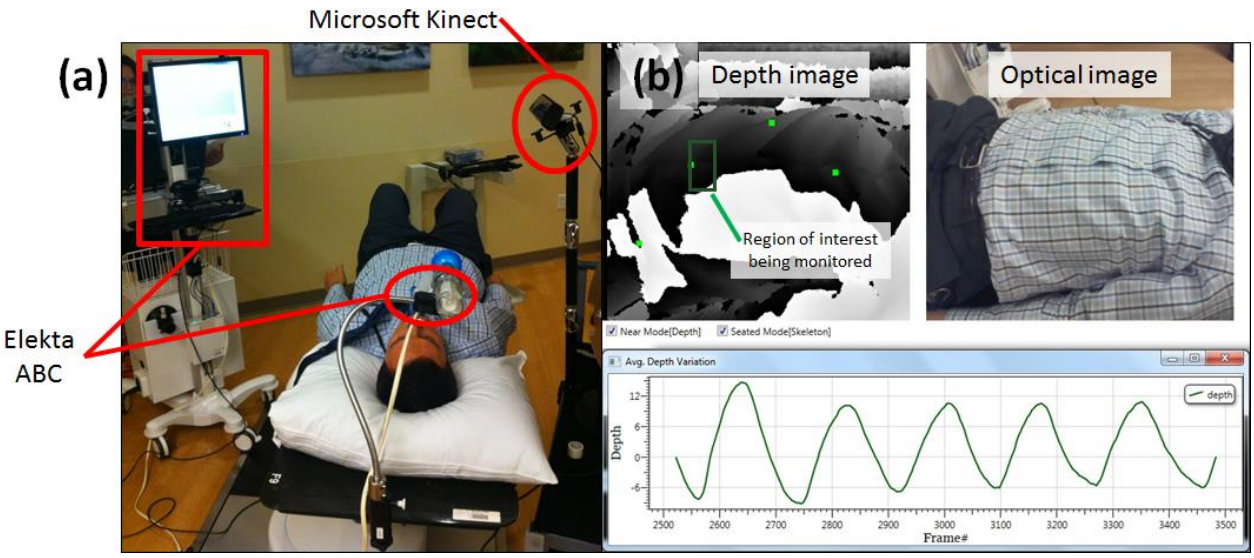


Figure 6-12. *Volunteer testing with the Microsoft Kinect and the Elekta ABC. (a) Volunteer test setup. (b) Screenshot of the Microsoft Kinect depth sensor tracking volunteer abdominal respiratory motion.*

As shown in Figure 6-12, an Elekta ABC (see chapter 1.2.1.5.2.) was also used in this volunteer testing; the signals of the Elekta ABC and the Microsoft Kinect were compared, as shown in Figure 6-13. Correlation between the two respiratory signals was assessed using Pearson's correlation coefficient (r).

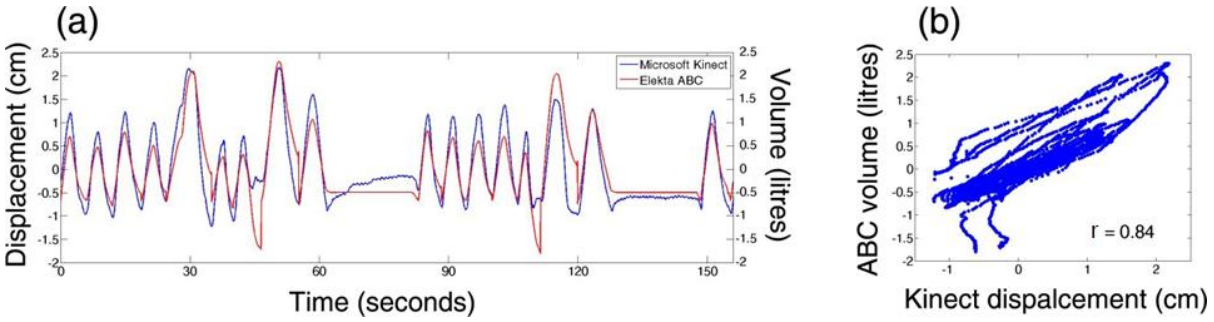


Figure 6-13. *(a) Respiratory signals obtained from the Microsoft Kinect (blue) and Elekta ABC (red); two exhale breath holds were performed. (b) Correlation plot between the Microsoft Kinect and Elekta ABC respiratory signals.*

Validation tests of the Microsoft Kinect were also performed with the AlignRT (see chapter 1.2.1.5.3.); volunteer setup shown in Figure 6-14, performed July 22nd at the University of Texas SouthWestern.

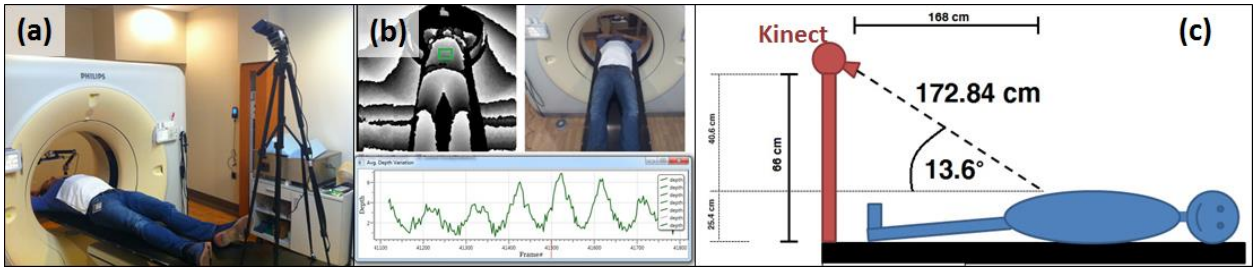


Figure 6-14. *(a) Volunteer test setup in the CT sim room with the Kinect mounted on a tripod fixed to the end of the patient couch. (b) Depth image, optical image, and respiratory signal from the region of interest on the volunteer's abdomen. (c) Schematic of the setup with distance from Microsoft Kinect to monitored region of interest included.*

The region of interest monitored by the Microsoft Kinect was created to be as close as possible to the region being tracked by the ceiling-mounted AlignRT, shown in Figure 6-15.

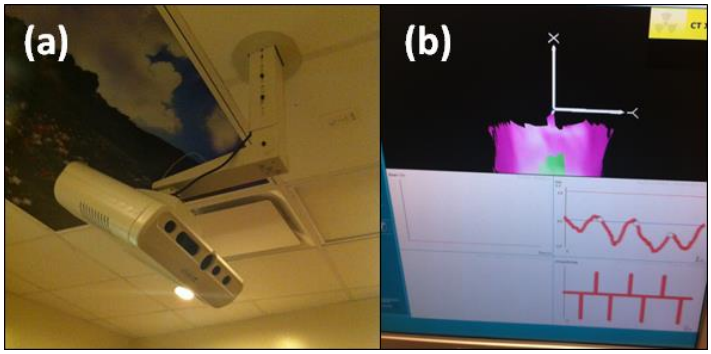


Figure 6-15. *(a) Ceiling-mounted AlignRT monitoring volunteer abdominal motion. (b) Screenshot of AlignRT software, pink region indicates registered abdominal surface, green region indicates the area of the abdominal surface being tracked.*

The signals of the AlignRT and the Microsoft Kinect were compared, as shown in Figure 6-16. Correlation between the two respiratory signals was assessed using Spearman's rank correlation coefficient (rho).

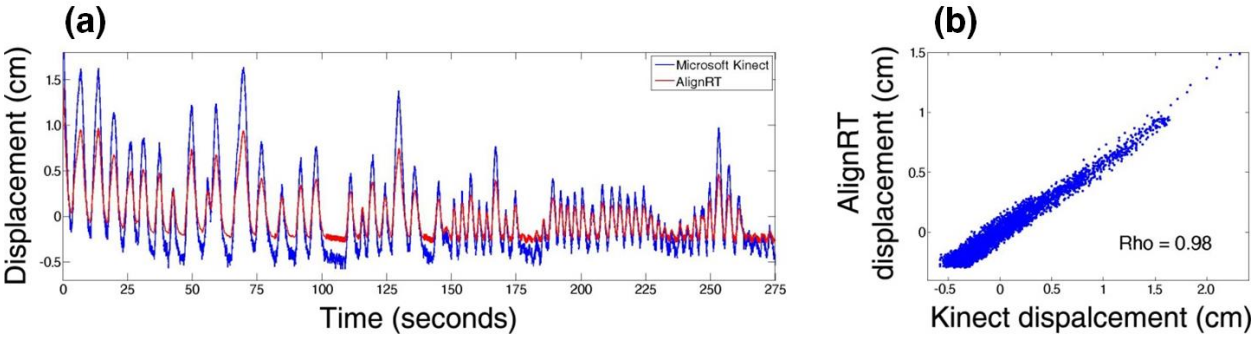


Figure 6-16. *(a) Respiratory signals obtained from the Microsoft Kinect (blue) and AlignRT (red). (b) Correlation plot between the Microsoft Kinect and AlignRT respiratory signals.*

While the correlation between the Microsoft Kinect and AlignRT was considerably higher than that between the Microsoft Kinect and the Elekta ABC, as evident from Figure 6-14(b) and Figure 6-16(a), more noise was evident in the Microsoft Kinect signal in the AlignRT tests. This was largely due to

the greater distance between the Microsoft Kinect and the region being monitored in the AlignRT test compared to the Elekta ABC test, where the Microsoft Kinect was directly next to the volunteer as shown in Figure 6-12(a). Microsoft reports that the Microsoft Kinect depth sensor range is from 80 cm to 400 cm;[59] however, studies have reported depth sensor ranges of 75 cm to 250 cm.[60]

6.3.1.1.2. Intel RealSense

Another depth sensor that was identified was the Intel RealSense,[61] which can also be utilised as a depth sensor.[62, 63] Figure 6-17 illustrates the Intel RealSense operating as a depth sensor. The operational distance of the Intel RealSense depth sensor is 20cm to 120 cm.[61]

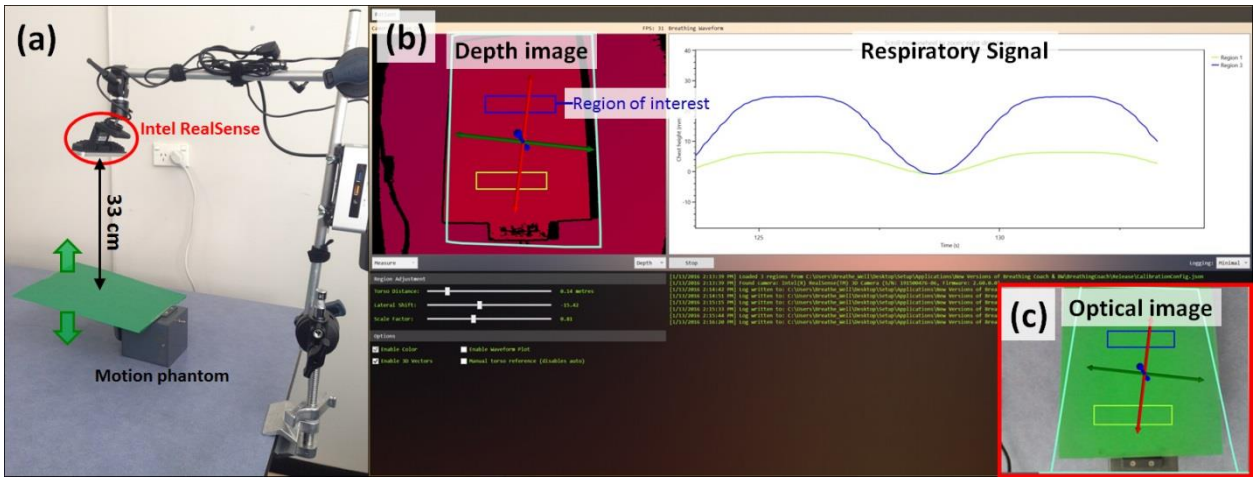


Figure 6-17. *(a) Setup with a motion phantom as a surrogate for respiratory motion with the Intel RealSense positioned above the phantom by a table frame. (b) Screenshot of Intel RealSense motion depth sensor software, highlighting the region of interest and its corresponding respiratory motion signal. (c) It's possible to switch the depth image display with an optical image display.*

Volunteer testing was performed at the University of Sydney on January 14th, 2016. The Varian RPM system (see chapter 1.2.1.5.1.) was also used to compare the respiratory signals of the two motion sensors. The setup for this test is shown in Figure 6-18. The region being monitored was selected to be the surface of the RPM marker block, therefore, the two respiratory signals should have the same amplitude.

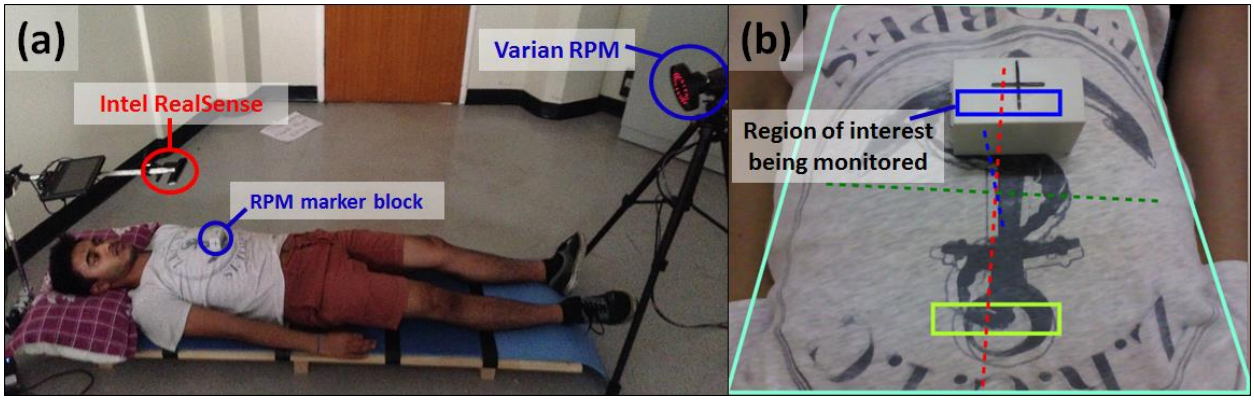


Figure 6-18. *(a) Volunteer study setup indicating the position of the Intel RealSense, Varian RPM, and RPM marker block. (b) Optical view of the Intel RealSense, indicating that the region of interest being monitored was the anterior surface of the RPM marker block.*

The signals of the Varian RPM and the Intel RealSense were compared; the sampling frequency of the Varian RPM was found to be 29.9 ± 1.2 Hz, the sampling frequency of the Intel RealSense was found to be 23.5 ± 7.4 Hz. Figure 6-19 shows the respiratory signals and correlation between the Varian RPM and Intel RealSense.

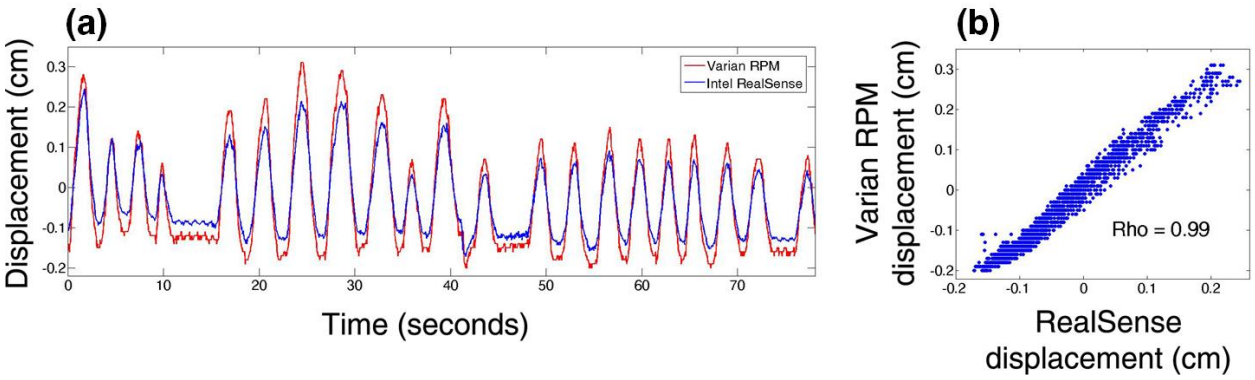


Figure 6-19. *(a) Respiratory signals obtained from the Intel RealSense (blue) and Varian RPM (red). (b) Correlation plot between the Intel RealSense and Varian RPM respiratory signals.*

6.3.1.2. Logistics of single unit audiovisual biofeedback

A wooden prototype frame was built to test the logistics of dimensions for how future audiovisual biofeedback systems would fit in imaging and treatment rooms; this frame is shown in Figure 6-20.

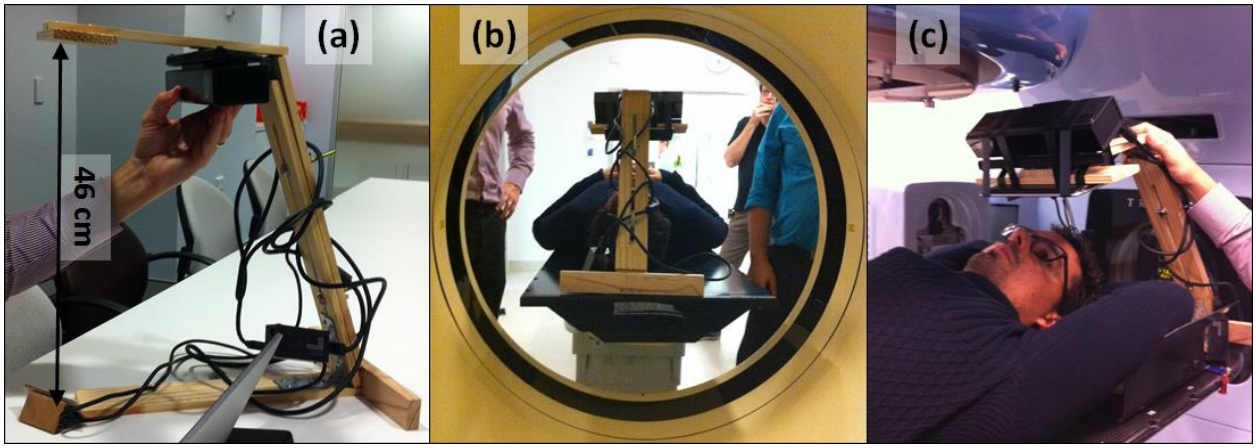


Figure 6-20. *(a) Wooden frame prototype, (b) in the CT sim bore, and (c) on the treatment couch.*

Measurements were taken in order to ensure the frame will fit within the CT imaging bore as well as avoiding any potential collisions with the linac's gantry. The dimensions for the frame are illustrated in Figure 6-21.

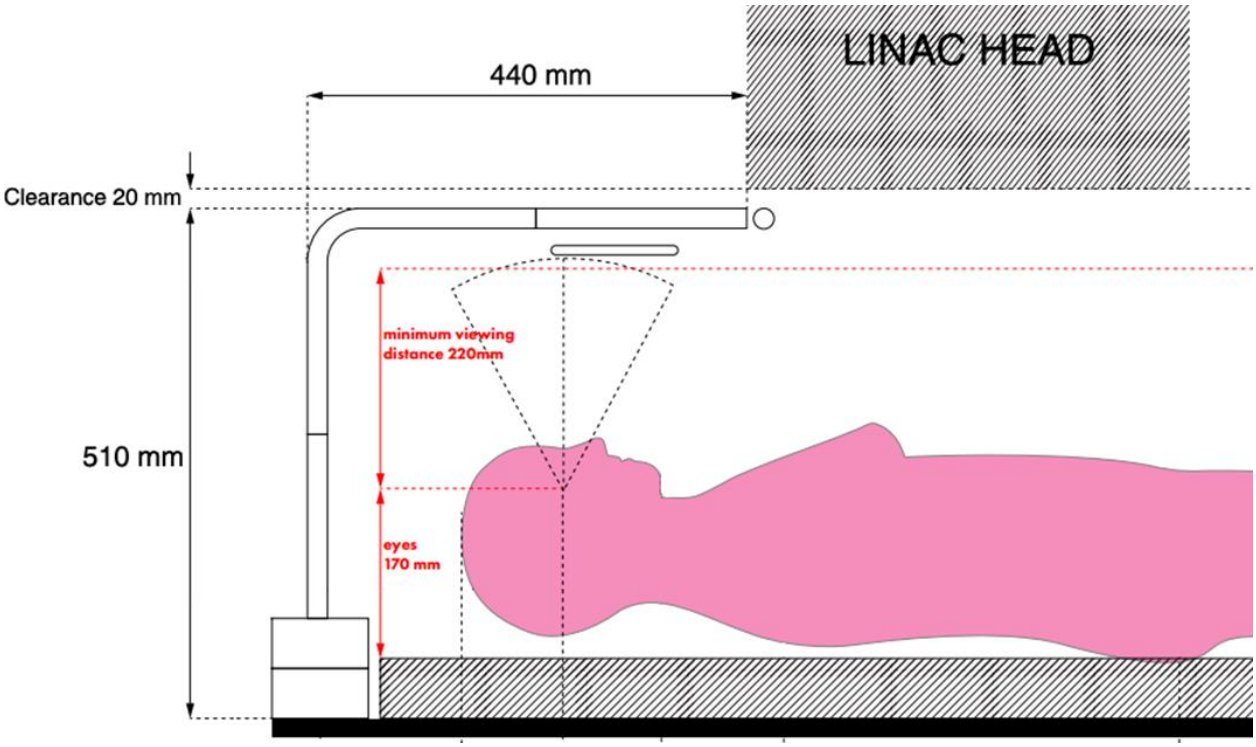


Figure 6-21. *Dimensions and design considerations for the audiovisual biofeedback frame to be positioned on the linac treatment couch without risk of gantry collision. Image provided by Design + Industry Sydney.*[26]

As shown in Figure 6-21, the minimum distance between the subject and the frame is 22 cm, as such, it will be required of the motion sensor to produce a physiologically accurate signal for distances as low as 22 cm. This eliminates the Microsoft Kinect as a viable motion sensor as the minimum achievable distance for the Microsoft Kinect is 75 cm.[60] The Intel RealSense achieves the desired distance from frame to subject by having an operational distance of 20cm to 120 cm,[61] and the distance from the Intel RealSense sensor to the region being monitored, as shown in Figure 6-18, was 25 cm. Further to this, the Intel RealSense achieved a strong correlation with the clinically implemented Varian RPM system.

6.3.2. Development of Audiovisual Biofeedback for Deep Inspiration Breath Holds

While audiovisual biofeedback has been utilised to facilitate regular respiration and anatomic motion,[1-4] inhale and exhale breath holds,[64, 65] and quasi-breath holds,[66] it has yet to be utilised to assist with deep inspiration breath holds (DIBH). Further to this, many of the interviewees described respiratory guidance biofeedback for DIBH to be a highly desirable feature.

6.3.2.1. Deep Inspiration Breath Holds for Breast Cancer Radiation Therapy

DIBH is performed with breast cancer patients because by taking a deep breath in, lung volume increases and the heart position moves inferiorly in the thorax, this reduces the pulmonary and cardiac dose during radiation therapy,[56, 67, 68] illustrated by Figure 6-22.

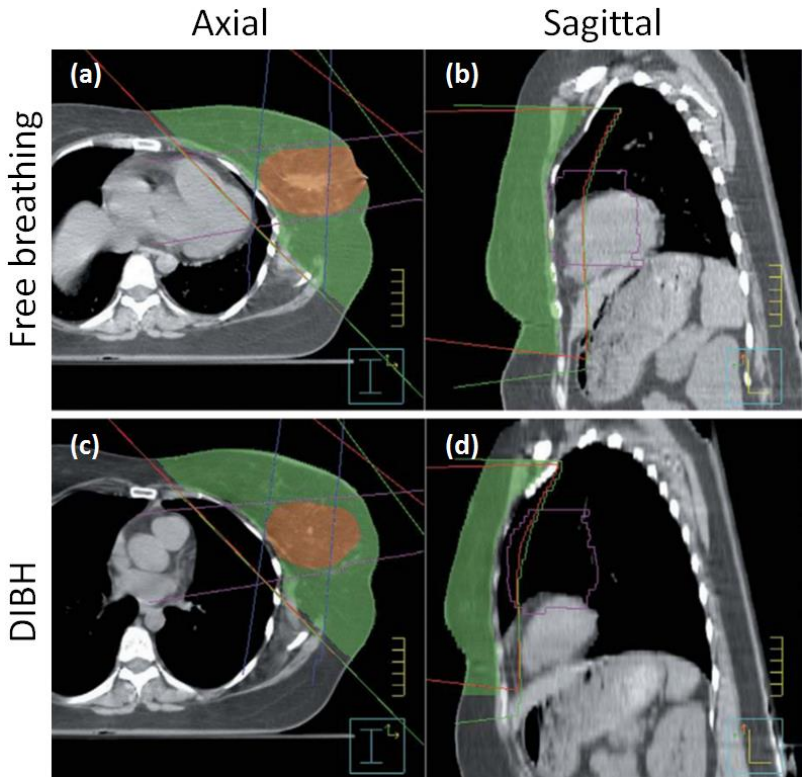


Figure 6-22. *Axial and sagittal CT scans of a breast cancer patient free breathing: (a) and (b), and performing DIBH: (c) and (d). PTV indicated as the green area, and boost PTV indicated by the orange area. Adapted from Hayden, et al. (2012).*[69]

As shown in Figure 6-22(a), for the free breathing case the heart is proximal to the PTV and boost PTV areas in addition to partially being in the path of the planned tangential radiation beam. Whereas, as shown in Figure 6-22(c), the heart is now more distal to the PTV and boost PTV areas in addition to being outside of the planned tangential radiation beam. Figure 6-22(d) demonstrates the heart in a more inferior position during DIBH compared to free breathing.

Previous findings have demonstrated the advantages of treating their left-sided breast cancer patients with DIBH over free breathing.[56, 70, 71] The Vikström, *et al*. (2011) study noted a reduction in mean heart dose of 54% from the use of DIBH compared to free breathing (from 3.7 Gy to 1.7 Gy with DIBH). Vikström, *et al*. (2011) also found that the ipsilateral lung volume receiving at least 20 Gy (V_{20}) was reduced by 18%.[56]

Further to this, utilising visual feedback to assist patients perform DIBH has demonstrated to further improve upon unguided DIBH procedures.[72, 73] Cerviño noted an improvement in breath hold reproducibility and stability of 76% and 53%, respectively from the use of visual feedback DIBH compared to DIBH without feedback. Figure 6-23 illustrates examples of DIBH from the use of DIBH with visual feedback and DIBH without feedback.

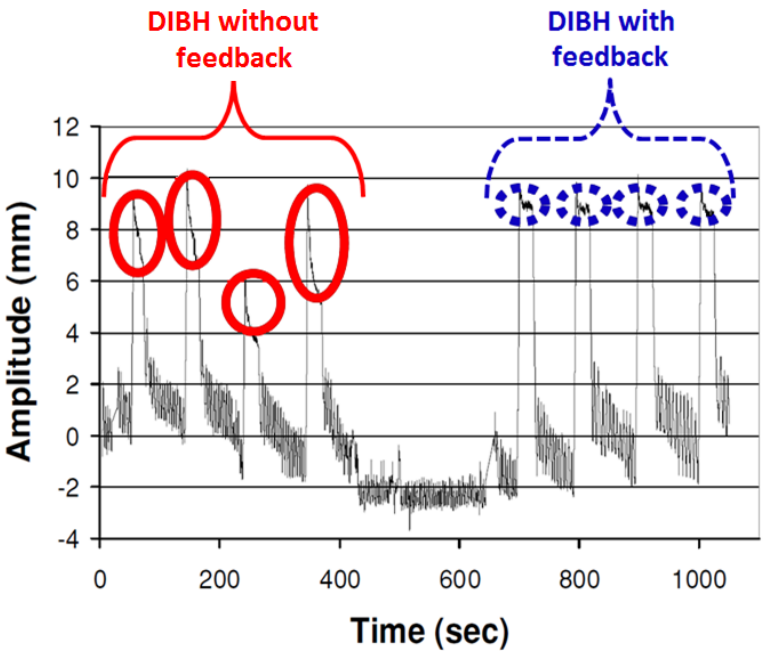


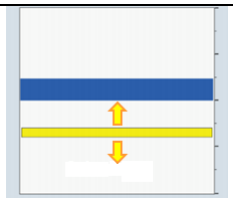
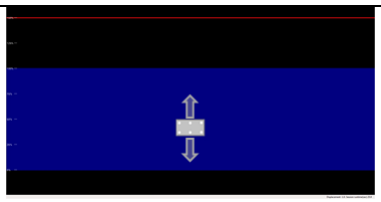
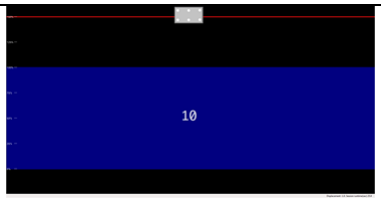
Figure 6-23. *Examples of DIBHs performed by a volunteer. The first four DIBHs (red, solid lines) are without visual feedback, the second four (blue, dashed lines) are with visual feedback. Adapted from Cerviño, et al. (2009).*[73]

Figure 6-23 demonstrates that through the use of visual feedback, volunteers were able to reproduce the same DIBH each time in addition to sustaining a stable breath-hold level compared to DIBH without visual feedback, where DIBH amplitude varied in addition to the respiratory signal drifting downwards mid-breath hold. Damkjær, *et al.* (2013) compared gated breath holds to DIBH with visual feedback and found that V_{20} was significantly reduced by 9% from the use of visual feedback.[72]

6.3.2.2. Audiovisual biofeedback for Deep Inspiration Breath Holds

Given the positive findings of both DIBH over free breathing and the use of visual feedback in assisting patients perform DIBH over DIBH with no feedback in addition to customer interview feedback, the functionalities of audiovisual biofeedback have been extended to assist patients to perform DIBH. In the Damkjær, *et al.* (2013) study, they extended the display of the Varian RPM to show the patient their respiration and the gating window to hold their breath at. Audiovisual biofeedback will utilise an automated method of producing a customised breath hold guide for each patient. Table 6-12 details the main differences between the two methods.

Table 6-12. *Comparison of DIBH used in Damkjær, et al. (2013) study to the proposed audiovisual biofeedback DIBH.*

		Damkjær, *et al.* (2013) DIBH[72]	Audiovisual Biofeedback DIBH
Visual display	Before DIBH		
	During DIBH		
Breath hold level		Set manually	Automatically detected and loaded
Miscellaneous		• Synchronised with Varian RPM gating	• Save and load patient-specific breath hold guides • Breath hold countdown shown to patient • Markerless

6.4. Conclusion

Given the proof of principle research detailed in chapter 1.4.2. and chapter 2., the translational research conducted and detailed in chapter 3., chapter 4., and chapter 5., and the granted patent protection[5] underpinning the audiovisual biofeedback technology, this positions audiovisual biofeedback towards the commercialisation pathway. This commercialisation pathway was explored utilising a variety of commercialisation accelerator programs paired with extensive customer interviews to map out the market, regulatory, and intellectual property landscape of the audiovisual biofeedback technology and search for the best business model to address the customer's unmet need, ultimately yielding commitments from NSW radiotherapy centres to purchase the audiovisual biofeedback device. Extensive customer engagement also yielded the expansion of audiovisual biofeedback functionalities to deep inspiration breath holds for use with breast cancer patients. Learnings from these customer interviews were then applied back into the research component to further develop the audiovisual biofeedback technology and functionalities. Further to this, the cost-effectiveness of audiovisual biofeedback for both lung and breast cancer patients can potentially reduce the health-care burden by almost $10 million a year in Australia alone, and over $1.3 billion worldwide.

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CHAPTER 7

Summary, Conclusions, and Future Work

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Summary, Conclusions, and Future Work

7.1. Summary and Conclusions

This thesis has identified the gaps in the literature by performing the first systematic review of breathing guidance interventions in radiation treatment and imaging procedures (chapter 2), and then utilised these insights to perform experiments and design clinical trials to address these gaps in the literature. By initiating the first randomised, phase II clinical trial for a breathing guidance intervention, this thesis also explored the next steps in determining the pathway to broaden the audiovisual biofeedback's use beyond the current limited number of hospitals under clinical trial conditions to widespread clinical implementation through commercialisation.

This thesis has given evidence that audiovisual biofeedback significantly improves 4DCT image quality (chapter 3), interfraction motion consistency with liver cancer patients (chapter 4), and the respiratory-components of treatment margin calculation (chapter 5.1.). There was also an observed training effect where audiovisual biofeedback became more regular interfractionally which demonstrated a significant correlation between time and RMSE values (chapter 5.1.). These insights went towards the design and workflow of the largest respiratory guidance intervention investigation study, to date (chapter 5.2.), which recruited its first patient on April 11th, 2016. This clinical trial demonstrates a number of firsts for respiratory guidance investigations: it is the first (1) randomised, (2) multi-site, (3) stratified, (4) phase II, (5) lung cancer radiotherapy audiovisual biofeedback clinical trial.

With the proof of principle of respiratory guidance interventions explored (chapter 1, chapter 2), and the more clinically relevant metrics of 4DCT image quality (chapter 3), interfraction consistency (chapter 4), and margin size (chapter 5.1.), coupled with its patent protection, warranted the exploration of the commercialisation of the audiovisual biofeedback technology in order for cancer patients to benefit from this technology. This was done through an extensive evaluation of the radiation oncology field and over one hundred interviews to determine the product-market fit of audiovisual biofeedback.

The culminations of these findings demonstrate the clinical benefit of the audiovisual biofeedback

respiratory guidance system, and the need to make breathing guidance systems more widely available to patients.

7.2. Future Work

While a number of the results presented in this thesis address the gaps in the literature as detailed in chapter 1 in addition to the systematic review presented in chapter 2, as detailed in chapter 2 there still areas of research to fill these gaps further. As detailed in Table VI in chapter 2, prospective studies focussing on the impact of breathing guidance on radiation dose to healthy tissue, tumour tracking, target coverage, and treatment margins would be valuable future work. Further to this, as noted in chapter 4, it is recommended that the clinical impact of audiovisual biofeedback on liver cancer patients is evaluated with a larger patient cohort.

In addition to future studies further addressing the identified gaps in the literature, future work of audiovisual biofeedback will also pertain to building upon the results presented in this thesis. Building upon the results in chapter 3 with a prospective 4DCT patient study, for example. The clinical trials detailed in chapter 4 and chapter 5 will provide insight into the design of a phase III audiovisual biofeedback clinical trial. Clinical studies will also need to be conducted to test the hardware and software updates detailed in chapter 6. In the subsequent sections, such studies that are being prepared to build upon this thesis are detailed.

7.2.1. Audiovisual biofeedback with tumour tracking

Further to this, a clinical trial tracking and adapting to prostate motion during cancer radiation therapy in real-time utilising multi-leaf collimator (MLC) tracking[1-3] and the Calypso electromagnetic transponder tracking system[4-6] was recently completed at Northern Sydney Cancer Centre, Royal North Shore Hospital. This clinical trial demonstrated that utilising tracking significantly improved the agreement between delivered and planned doses compared to no tracking.[7]

Given the positive findings from this prostate tracking clinical trial, a follow up tumour tracking clinical trial recruiting lung cancer patients has been developed. However, the system latency of the tumour tracking software and hardware has been demonstrated to be 350 ms.[8] The use of the Calypso transponders will also provide further insights into the correlation between external respiratory surrogates and internal respiratory motion.

7.2.2. Audiovisual biofeedback during breast cancer DIBH

The audiovisual biofeedback setup with the Intel RealSense described in chapter 6.3.1.1.2., coupled

with the functionality for DIBH, as described in chapter 6.3.2.2., will be utilised in an upcoming breast cancer patient clinical trial to be performed at Royal North Shore Hospital. This study will recruit a total of 40 breast cancer patients and its primary objective is to test the efficacy of audiovisual biofeedback to assist DIBH during breast cancer radiotherapy compared with the current treatment standard, the Varian RPM. The primary hypothesis is that accuracy of audiovisual biofeedback is non-inferior to the RPM system.

7.2.3. Audiovisual biofeedback during proton therapy

The audiovisual biofeedback setup with the Intel RealSense described in chapter 6.3.1.1.2., has been provided to the University of Washington, Seattle, to be used to guide regular respiration during lung cancer patient proton therapy. This study represents a landmark in the field as it will be the first study to investigate the use of a breathing guidance intervention over the course of proton therapy. It was noted by Figure 1-15 in chapter 1.3. (shown here for clarity) that the size of the ITV can vary not only over the course of treatment but also during treatment delivery. The University of Washington will be testing the hypothesis that audiovisual biofeedback will reduce the variations in ITV size, compared to free breathing, over the course of lung cancer patient proton therapy. Interest was also indicated for the use of audiovisual biofeedback for guided exhale breath holds for liver cancer patients receiving proton therapy.

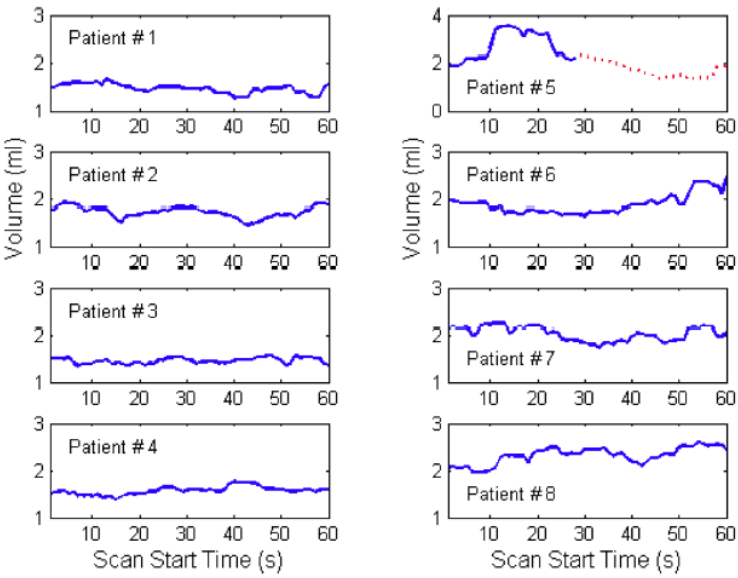

Figure 1-15. *Variations of the volume of ITV over a fraction of treatment for 8 lung cancer patients. From St James, et al. (2012).*[9]

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Appendix I

Signed statements from co-authors of the published manuscripts included in this thesis

Publication Statement (for thesis chapter 2)

Statement from co-authors confirming the authorship contribution of the PhD candidate:

As co-authors of the paper 'Breathing guidance in radiation oncology and radiology: A systematic review of patient and healthy volunteer studies', we confirm that Sean Pollock's contribution to the paper is consistent with him being named first author. In particular, the candidate's contribution to the following items should be noted:

- Conception and research of the review
- Writing and critical appraisal of the content

Signed:  Date: 18/4/2016

(Robyn Keall)

Signed:  Date: 18 April 2016

(Paul Keall)

Publication Statement (for thesis chapter 3)

Statement from co-authors confirming the authorship contribution of the PhD candidate:
As co-authors of the submitted for publication paper 'The impact of breathing guidance and prospective gating during thoracic 4DCT imaging: an XCAT study utilizing lung cancer patient motion', we confirm that Sean Pollock's contribution to the paper is consistent with him being named first author. In particular, the candidate's contribution to the following items should be noted:

- Conception and design of the research
- Analysis and interpretation of the findings
- Writing of the paper and critical appraisal of the content

Signed:  Date: 7/3/2016
(John Kipritidis)

Signed:  Date: 3/3/2016
(Danny Lee)

Signed:  Date: 26.02.2016
(Kinga Bernatowicz)

Signed:  Date: 18 April 2016
(Paul Keall)

Publication Statement (for thesis chapter 5.2.3)

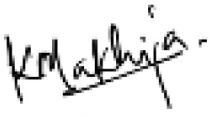
Statement from co-authors confirming the authorship contribution of the PhD candidate:

As co-authors of the paper 'Audiovisual biofeedback breathing guidance for lung cancer patients receiving radiotherapy: a multi-institutional phase II randomized clinical trial', we confirm that Sean Pollock's contribution to the paper is consistent with him being named first author. In particular, the candidate's contribution to the following items should be noted:

- Conception and implementation of the research project
- Writing of the paper and critical appraisal of the content

Signed:  Date: 7/3/2016

(Ricky O'Brien)

Signed:  Date: **7/3/2016**

(Kuldeep Makhija)

Signed:  Date: 26/10/2016

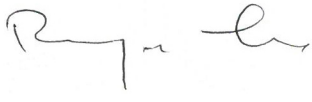
(Fiona Hegi-Johnson)

Signed: 

(Jane Ludbrook) Date: 27.10.2016

Signed:  Date: 27/10/16

(Angela Rezo)

Signed:  Date: 26/10/2016

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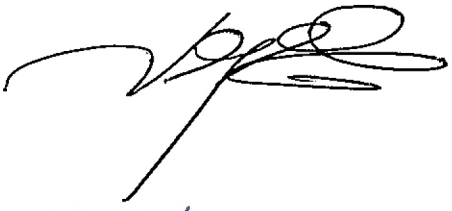
Signed: 

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Date: 18 April 2016

Publication Statement (for Appendix III)

Statement from co-authors confirming the authorship contribution of the PhD candidate:

As co-authors of the paper 'First clinical implementation of audiovisual biofeedback in liver cancer stereotactic body radiation therapy', we confirm that Sean Pollock's contribution to the paper is consistent with him being named first author. In particular, the candidate's contribution to the following items should be noted:

- Conception and implementation of the research project
- Analysis and interpretation of the findings
- Writing of the paper and critical appraisal of the content

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Signed: (Darren Martin) Date: 27/10/2016.

Signed: (Lisa McLean) Date: 09/03/2016

Signed: (Gwi Cho) Date: 10/3/2016

Signed: (Robin Hill) Date: 9/3/16

Signed: (Sheila Pickard) Date: 9.3.2016

Signed: (Paul Aston) Date: 9.3.16

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Signed: 

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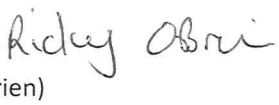
Date: 7/3/2016

Signed: 

(Ricky O'Brien)

Date: 7/3/16

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(Paul Keall)

Date: 18 April 2016

APPENDIX II

Documentation submitted to the human research ethics committees (HREC) for the two clinical trials presented Chapter 4 and Chapter 5

RADIATION ONCOLOGY DEPARTMENT
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CLINICAL TRIAL PROTOCOL

Investigation of respiratory-related tumour motion in liver cancer patients undergoing stereotactic body radiotherapy treatment (SBRT) using audiovisual (AV) biofeedback

Version Number: V4.0

Date of Protocol: 29/06/2015

SYNOPSIS

Protocol title: Investigation of respiratory-related tumour motion in liver cancer patients undergoing stereotactic body radiotherapy treatment (SBRT) using audiovisual (AV) biofeedback

Protocol version: V4.0

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Summary

Study Title:	Investigation of respiratory-related tumour motion in liver cancer patients undergoing stereotactic body radiotherapy treatment (SBRT) using audiovisual (AV) biofeedback.
Protocol version:	V4.0
Objectives	*Primary objective*: Evaluate the improvement in reproducibility of respiratory-related tumour motion (via fiducial maker surrogacy) for liver cancer patients with the AV biofeedback respiratory guidance system. *Secondary objectives*: Assess the potential clinical benefit of AV biofeedback. Analysis of obtained data will involve: (1) Based on the respiratory motion analysis, the proportion of patients with improved reproducibility of respiratory motion from AV biofeedback will be obtained (2) Quantification of the improvement in dose distributions and treatment margins with and without AV biofeedback by reconstructing the delivered dose using a method developed for liver SBRT (3) Quantification of the reduction in 4D CT errors with and without AV biofeedback by programming the Quasar phantom with the AV biofeedback and free breathing respiratory traces (4) Reconstruction of cone beam CT (CBCT) images into 4D CBCT using the respiratory signal and comparing the image quality with and without AV biofeedback (5) Evaluation of the correlation between internal fiducial marker and external marker motion. (6) An evaluation of the patient and operator experience with the AV biofeedback system through a questionnaire will also be performed.
Study design	The reproducibility (i.e. the consistency of respiratory amplitude and period) of liver fiducial-marker motion due to respiration will be assessed with AV biofeedback and for free breathing using CBCT imaging. To improve the image quality and radiation targeting for the patient, all subsequent imaging and treatment sessions will use the most reproducible breathing condition, AV or free breathing.

	Planned sample size This study will involve the participation of 30 liver cancer patients. Selection criteria The following patients are eligible for this study: 1) Liver cancer patients, either primary hepatocellular carcinoma or liver metastases, eligible for stereotactic radiotherapy. 2) >18 years old 3) No gender or ethnic restrictions 4) Radio-opaque markers implanted (fiducials and/or surgical clips previously implanted in the liver) 5) Able to give written informed consent and willingness to participate and comply with the study 6) No pregnant / lactating woman
Study procedure	The AV biofeedback system is simple and easy to implement. It is comprised of a screen or AV goggles that the patient views to receive their audio and visual guiding prompts. As a part of their clinical treatment plan, the patients will already be having 18 CBCT scans; by participating in this study, they will have only two additional CBCT scans. Eligible patients that have agreed to participate in the study and have given informed consent will undergo routine radiotherapy planning in preparation for their SBRT treatment. During the planning procedure, as part of this study, the following will also be performed in addition to standard procedure: Two additional CBCT scans will be obtained, one while the patient undergoes AV biofeedback and the other with the patient during free breathing. The reproducibility of liver tumour motion due to respiration will be assessed with AV biofeedback and for free breathing using cone beam CT imaging. To improve the image quality and radiation targeting for the patient, all subsequent imaging and treatment sessions will be undertaken with the best and most reproducible breathing condition, either AV feedback or free breathing (signed off by radiation oncologist, see *Figure 14*: Proposed Patient Report). Patient time commitment Each session will take a total of 1 hour inclusive of setting and packing up the AV biofeedback system in addition to the CBCT scans, but it may be completed in

	less time than this. After each initial study session (during planning) the patient will be asked to complete a questionnaire regarding the AV biofeedback system; each questionnaire is designed to only take 2 minutes to complete. In the event that AV biofeedback is the more reproducible breathing condition, it will be continued to be used as a part of their treatment in the remainder of their 18 CBCT scans and treatment. Should AV biofeedback remain in the patient's treatment, a single follow-up questionnaire will be performed towards the end of their treatment to gauge any change in opinion towards the AV biofeedback system. <u>Data analysis</u> For each patient the acquired internal motion (from CBCT images) and respiratory data (from the TGA-approved real-time position management (RPM) system) will be analysed in order to quantify the clinical impact of AV biofeedback through the following measurements: 1) Quantify the proportion of patients for whom respiration is more regular with the guidance of AV biofeedback. 2) Quantify the respiratory reproducibility with AV biofeedback and free breathing. Respiratory results will be evaluated using the root mean squared error (RMSE) method and compared using statistical analysis methods such as the Student t-test. 3) Quantify the improvement in treatment margins and dose distributions with and without AV biofeedback by reconstructing the delivered dose using a method developed for liver SBRT. 4) Quantify the reduction in 4D CT errors with/without AV biofeedback by programming the Quasar phantom with the AV and free-breathing respiratory traces. 5) Reconstruct the CBCT into the 4D CBCT using the respiratory signal and compare the image quality with and without AV biofeedback. (6) The correlation between internal and external motion
Estimate the clinical benefit	To estimate the improvement in treatment margins and dose distributions, dose reconstruction using the method of Poulsen *et al* (Med Phys 2012)[1,2]will be performed using the tumour motion extracted from AV biofeedback-guided CBCT images and free breathing CBCT images. Using radiobiological response models

	from QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) we will assess the impact of the change in radiation dose delivered to healthy tissues with and without AV biofeedback respiratory guidance. 4D CBCT image quality will also be investigated. CBCT images will be reconstructed into 4D CBCT using the obtained respiratory signals and the image quality will be compared for with and without AV biofeedback.
Statistical considerations	According to preliminary results from 15 healthy human subjects, assuming a type I error rate of 5%, 80% power and a moderate effect size of 0.34σ for the paired differences between free breathing and AV biofeedback, a sample size of 30 patients will be required. If we assume that the standard deviations of these differences in the patient population will be approximately double that of the healthy volunteers then the minimal detectable difference will be 0.068, ($\sigma = 0.2$).
Duration of the Study	2 years

Contents

1.BACKGROUND

In Australia, 115,000 cancer patients are newly diagnosed each year and 40% of cancer patients receive radiotherapy as part of their treatment plan[3] with radiotherapy being an effective anti-cancer treatment by delivering high-energy radiation directly to tumours to destroy cancer cells.[4] Stereotactic body radiotherapy (SBRT) in particular has recently been incorporated into the treatment of liver cancer due to its demonstrated effectiveness in clinical studies as well as improving survival rate,[5,6] with over 54% of American liver cancer patients being treated with SBRT.[7] SBRT is a high-precision, high-dose irradiation of a lesion in a small number of fractions (typically 1 – 6).[8]In 2008, there were 1304 new cases of liver cancer diagnosis across Australia,[9] with NSW having a higher rate of diagnosis than the national average.[9,10] Liver tumours are considered highly mobile due to their proximity to the thoracic diaphragm, which is a dominant factor in inducing respiratory motion in the thoracic and abdominal regions.[11,12]

Such respiratory motion reduces the precision of radiation therapy resulting in poor radiation targeting and tumour control.[12,13] A key problem to be solved in this study is inadequate respiratory-related tumour motion management, especially for irregular respiratory-related tumour motion which further negatively affects the clinical outcome.[14,15] A 1Gy increase in tumour dose results in a 4% improvement in survival,[16] however, a 0.5cm tumour motion leads to a 4~5% variation in radiation dose[17] which can lead to an increase in mean dose to healthy surrounding tissues. In previous reports, tumours subject to respiratory motion have been shown to move up to 5 cm,[12] and rotate up to 45° during respiration.[18] Given that average liver motion in the superior-inferior (SI) direction has been shown to be 9 ± 5 mm,[19] this can exacerbate the variation in radiation dose by up to 10%, leading to a further increase in mean radiation dose to the healthy liver tissue.

During radiotherapy, in order to irradiate the tumour at all times, the treatment volume must be increased to cover the entire range of tumour motion; this increases the dose delivered to the surrounding healthy tissue.[16,17,20,21] Without respiratory motion management, patients can receive an underdose of radiation to the tumour and overdose to the surrounding healthy tissues, which can lead to cancer recurrence and severe radiation side effects. For example: a 1Gy increase in mean lung dose results in on average a 1% reduction in pulmonary function[22] and a 2% increase in risk of pneumonitis(28% of patients were suspected of having radiation pneumonitis in a previous study).[20,23]We hypothesise that the more reproducible respiratory motion as a result of AV biofeedback will result in reduced treatment margins leading to improved radiation sparing of the surrounding healthy tissue.

Techniques such as respiratory gating, breath-holds and tumour tracking are clinically useful for tumour motion management;[24-26] abdominal compression is also used to reduce the magnitude of liver tumour motion.[27] However, irregular respiration (such as deep/shallow breaths, baseline shifts, inconsistent amplitude, etc) can reduce the efficiency of such motion techniques[28,29] as well as causing motion artefacts and anatomic errors in medical imaging.[30-35]

Respiratory guidance is one such technique which specifically aims to produce regular patient breathing. At the forefront of respiratory guidance is the **audiovisual (AV) biofeedback** system. The AV biofeedback system (*Figure 1*) developed by Venkat, *et al*[29] is one such management technique to minimise irregular respiration. AV biofeedback uses a non-invasive external marker to measure abdominal motion and guides the patient to produce regular respiration. This system has demonstrated a reduction in average cycle-to-cycle variations in respiratory amplitude and period by up to 50% and 70% respectively,[29] which has also shown to be beneficial in improving motion reproducibility for respiratory-gated radiotherapy[36] in addition to reducing blurring artefacts in 4D PET[37] and CT.[38]

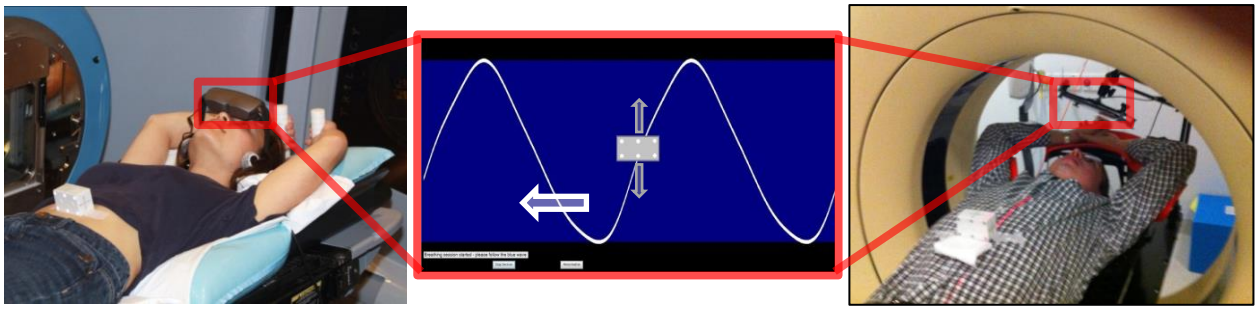


Figure 1. *AV biofeedback system. AV goggles (left) and screen (right) setups; marker block on the abdomen shown (IR camera not shown, see section 5.1: Study Equipment). The visual display (centre) as seen by the subject (sans arrows) of the AV biofeedback system shows the guiding wave (white curve) and a marker position (marker image) in real time.*

Additionally, this system can be employed for real-time tumour tracking and respiratory gating. In this case, tumour motion can be indirectly managed by regularising respiratory motion based on the correlation between the external abdominal position and the internal tumour position during regular breathing.[39,40]

Despite the positive results of AV biofeedback studies to date, the participants have thus far been healthy volunteers, which are sufficient when investigating tumour surrogates. However, to determine the true clinical value of the AV biofeedback system a study involving the monitoring of tumours themselves needs to be undertaken; that is the purpose of this study.

2.PRELIMINARY RESULTS

2.1. IRREGULAR RESPIRATION LEADS TO MEDICAL IMAGE AND ANATOMIC ERRORS

There is a clear link between respiratory irregularity and anatomic errors on 4D CT images.[30-35] The irregularity of breathing is shown in *Figure 2*; the impact of this irregularity on medical images is shown in *Figure 3*.

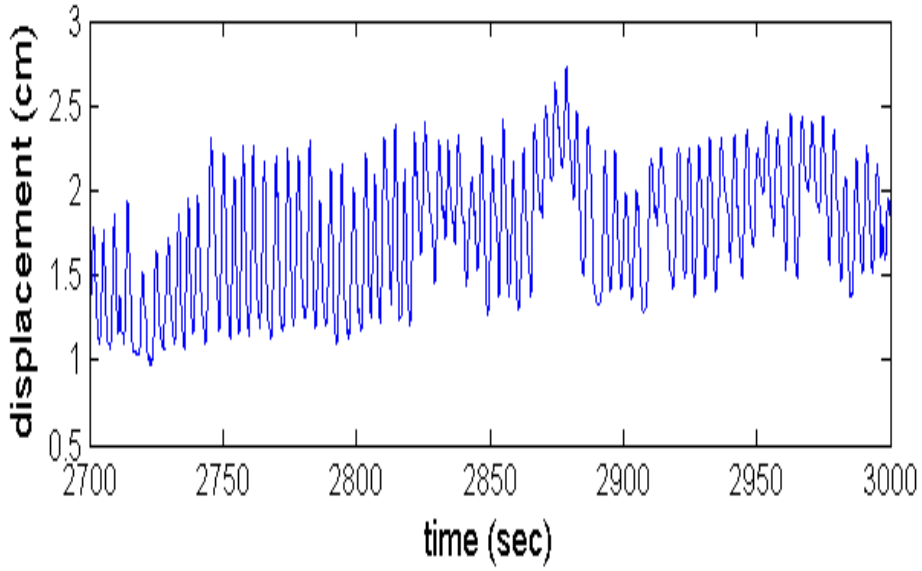


Figure 2. *Example lung tumour motion (superior-inferior) with time showing the variation in breathing period, shape, magnitude and baseline position. From Suh et al.*[12]

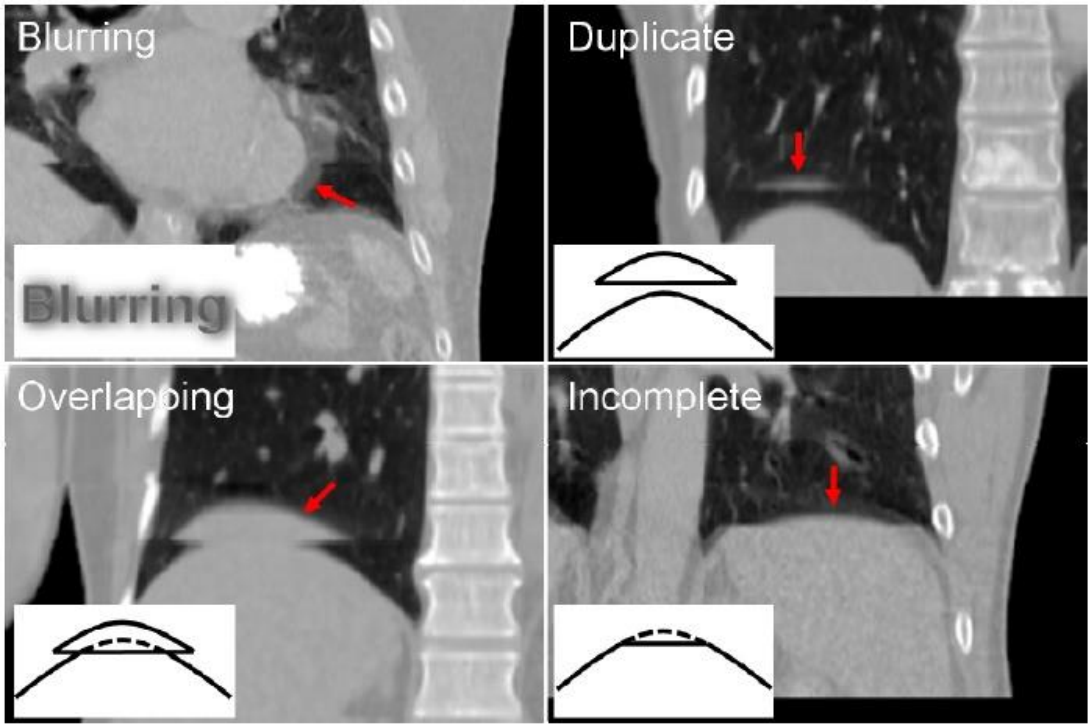


Figure 3. *Irregular breathing causes four different types of errors in 4D CT images: 46 of 50 patients had scans with an on average 11mm error. From Yamamoto et al.*[31]

2.2. LIMITATIONS OF PRIOR STUDIES OF BREATHING TRAINING IN RADIATION ONCOLOGY

To address the problem of respiratory irregularity, various methods of patient respiratory guidance have been applied by other groups, as summarised in *Table 1*. However there are a number of limitations: none of the studies used audio biofeedback, only a single measurement point was used for the respiratory signal and none of these systems are commercially available. Despite these limitations, improvements in the respiratory signal reproducibility was observed, indicating the potential for breathing training to improve image quality and radiation targeting.

This will be the first study to implement AV biofeedback in liver cancer patients undergoing radiation therapy.

Table 1. *Summary of breathing training studies in radiation oncology*

Author, year	Sensor	Subjects	Comments
Wang 1995[41]	Bellows belt	6	Audio prompt for breath-hold MRI
Wang 1995[42]	MR navigator	6	Visual prompt for multiple breath-hold MRIs
Wong 1999[24]	Flow monitor	12	Immobilizing breathing motion
Vedam 2003[28]	RPM	5	Visual motion wave with two motion limits (inhale and exhale limits)
George 2005,[43] 2006[36,44]	RPM	24	Visual motion bar with two motion limits with audio instruction
Lim 2007[45]	Thermocouple	10	Visual guidance with audio prompt. Baseline drift not observed using the thermocouple
Locklin 2007[46]	Bellows belt	16	Visual biofeedback only for breath-hold CT scans
Ono 2011[47]	Accelerometer	Phantom	Used cheap, available equipment. No patient studies.

This study will involve the recruitment of 30 participants, which is considerably greater than the participants involved in the vast majority of previous respiratory guidance studies as shown in *Table 1*. Such a number of participants in this study would make it the most comprehensive AV biofeedback study to date. The inclusion of more participants would also produce more accurate and significant results.

Unlike previous studies that tested the effect of AV biofeedback on respiration,[29] CT image quality,[38] or treatment margins, such studies involved the participation of healthy volunteers,[28] this study involves the recruitment and imaging of cancer patients.

2.3. RESPIRATORY REPRODUCIBILITY

Respiratory reproducibility refers to how consistent a breathing signal's amplitude and period are. The commonly used quantification of respiratory reproducibility used throughout the literature is the root mean square error (RMSE).[5,29,48] A low value of RMSE is indicative of a highly reproducibly respiratory signal. *Figure 4(c & f)* exemplifies the difference in respiratory reproducibility; the respiratory signal shown in *Figure 4f* would have a much lower RMSE value (in both amplitude and period) that the signal presented in *Figure 4c,* and is therefore the more reproducible signal of the two. Even though the two respiratory signals presented in *Figure 4c & f* have similar ranges of motion, a lower value of RMSE has been demonstrated to result in reduced treatment margins. A previous study found that the superior-inferior (SI) margins were reduced from 1.1cm to 0.8cm by implementing respiratory guidance.[28]

2.4. AV BIOFEEDBACK SYSTEM COMBINED WITH MRI AND CT

Recently, Kim et al. (2012) reported the feasibility of respiratory motion management with 15 healthy human subjects using the AV biofeedback system combined with a 3 Tesla MRI.[48-50] These studies demonstrated a reduction of motion artefacts and improvement of organ motion reproducibility in MRI using the AV biofeedback system in conjunction with the real-time position management (RPM) external position management system from Varian Medical Systems. This study demonstrated that using the AV biofeedback system could improve the reproducibility of internal structure's (in this case: the thoracic diaphragm) respiratory motion. By using the AV biofeedback system, diaphragm motion reproducibility was significantly improved (*Figure 4*). Average RMSE in diaphragm displacement of 15 healthy human subjects was reduced from 2.7 mm with free breathing to 1.6 mm with AV biofeedback (p-value < 0.05). Additionally, the average RMSE in the diaphragm motion period was reduced from 1.84 s with free breathing to 0.34 s with AV biofeedback (p-value < 0.05). However, a limitation of this study was that the participants were healthy volunteers, not cancer patients, as such the true clinical viability was difficult to achieve.

While the thoracic diaphragm has been demonstrated to be an accurate tumour surrogate,[39,40] fiducial markers are frequently used clinically due to their increased proximity to the tumour (compared to the diaphragm) and are therefore a highly accurate tumour surrogate.[51,52]

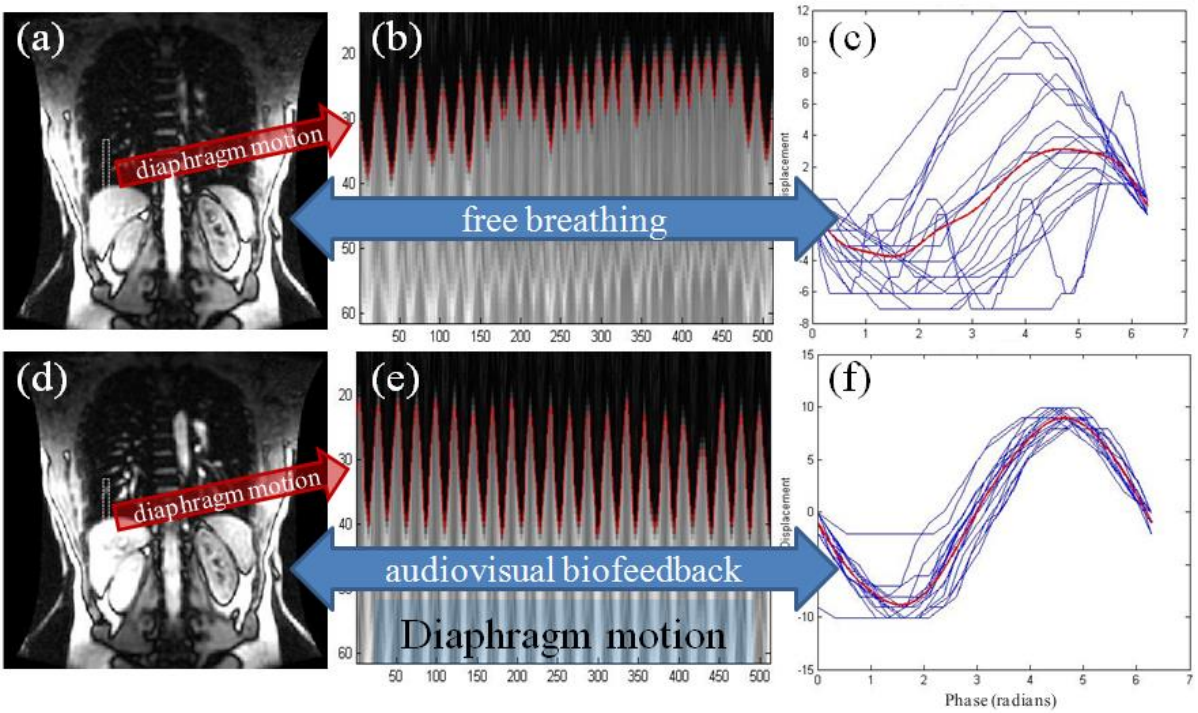


Figure4. *(a, d) ROI (region of interest) boxes on coronal images in Study 6. (b, e) 1D signal profile of the ROI over 512 images. Outline of diaphragm shown (red line). (c, f) Diaphragm motion cycles (blue) and average curve (red) shown in phase domain. By using the AV biofeedback system the diaphragm motion reproducibility has been significantly improved.*

In addition to MRI, AV biofeedback has also been implemented in imaging studies utilising PET[37] and CT.[38,46] AV biofeedback has the advantage of being compatible with a range of imaging modalities, as such, implementation with the CBCT imaging modality will be very straight-forward and the improvements to image quality are expected to be consistent with the previously mentioned AV biofeedback imaging studies. This study is a continuation from the Kim's 2012 MRI study, as the fast MR pulse sequence utilised in that study (fast gradient

echo: fGRE) would have comparable image quality to images obtained using CBCT. The advancement from Kim's study to this one is the recruitment of liver cancer patients in addition to monitoring a more accurate tumour surrogate: fiducial markers implanted within the liver.

2.5. Assessment of the Benefit of reducing tumour margins

Additional margins about the tumour are generally measured as the CTV-to-PTV margins: where CTV is the clinical target volume (approximation of the tumour volume) and PTV is the planning target volume (the CTV with additional margins to account for tumour motion and geometric uncertainties).

A liver cancer study by Molinelli, *et al* (2008) found that the reduction of CTV-to-PTV margins of liver tumours resulted in both dose escalation to the tumour (higher dose to the tumour: more effective in eliminating the tumour) as well as improved sparing of the healthy liver tissue (reducing post-treatment complications and improving long-term survival rate).[53] Molinelli's study found that a reduction of the CTV-to-PTV margin by 50% resulted in a further sparing of health liver tissue by up to 47% (average: 26%).

Therefore, if imaging can be improved to reduce geometric uncertainties in addition to improving motion management techniques to compensate tumour motion more accurately, then the CTV-to-PTV margins can be further reduced resulting in more efficient dose delivery to the tumour itself while improving the sparing of the surrounding healthy tissue. AV biofeedback is proposed to improve both these aspects.

Treatment margins for liver SBRT patients at the Chris O'Brien Lifehouse Department of Radiation Oncology are determined by internal target volume (ITV). ITV is defined as the CTV plus a margin to account for uncertainties in shape, size and position of the CTV, much like the PTV, although the ITV is typically a tighter margin than the PTV.

3.STUDY OBJECTIVES AND AIMS

Liver tumour motion management using AV biofeedback will be investigated using fiducial markers as a surrogate and test the hypothesis that **the more regular respiration as produced by AV biofeedback will result in more reproducible liver tumour motion which will have numerous clinical advantages.** To test this we will conduct a 30 liver cancer patient clinical using CBCT and correlative outcomes study with the following objectives:

3.1. PRIMARY AIM:

Evaluate improvement in the reproducibility of respiratory-related tumour motion for liver cancer patients with the AV biofeedback system: We propose a study involving 30 liver cancer patients. Each patient will undergo a CBCT scan during which two breathing conditions will be tested: (1) with AV biofeedback and (2) without AV biofeedback (free breathing) in order to assess tumour motion reproducibility. Respiratory motion of an external marker and internal fiducial markers (and/or surgical clips) will be assessed via a respiratory displacement and frequency analysis.

3.2. SECONDARY AIM:

Assess the potential clinical benefit of AV biofeedback: Analysis of obtained data will involve:

(1) Based in the respiratory motion analysis, the proportion of patients benefitting from AV biofeedback will be obtained.

(2) Quantification of the improvement in dose distributions and treatment margins with and without AV biofeedback by reconstructing the delivered dose using a method developed for liver SBRT.

(3) Quantification of the reduction in 4D CT errors with/without AV biofeedback by programming the Quasar phantom with the audiovisual and free-breathing traces.

(4) Reconstruction of CBCT images into 4D CBCT using the respiratory signal and compare the image quality with/without AV biofeedback.

(5) Evaluation of the correlation between internal fiducial marker and external marker motion.

(6) An evaluation of the patient and operator experience with the AV biofeedback system though a questionnaire will be performed.

The methods of achieving these aims will be further detailed in section 5.3: Investigation Plan.

To achieve these objectives the following data will be collected:

- External breathing motion data from RPM & AV biofeedback computers:
- CBCT projection & image data:
- Patient and staff surveys
- 4DCT images
- Free breathing CTs
- Patient treatment plan

4.PARTICIPANT SECTION

This study is specifically aimed at liver cancer patients. Patients fitting the eligibility criteria (see below) will be identified and introduced to this study by their treating physician who will participate as a principal investigator in this study.

4.1. INCLUSION CRITERIA

1) Liver cancer patients, either primary hepatocellular carcinoma or liver metastases, eligible for stereotactic radiotherapy
2) > 18 years old
3) No gender or ethnic restrictions
4) Radio-opaque markers implanted (fiducials and/or surgical clips previously implanted in the liver)
5) Ability to give written informed consent and willingness to participate and comply with the study

4.2. EXCLUSION CRITERIA

1) Pregnant/ lactating women
2) <18 years old.
3) Prior radiotherapy treatment to the liver
4) Life expectancy less than 6 months
5) Non-liver cancer patients

4.3. NUMBER OF PARTICIPANTS

30 liver cancer patients. As shown in *Table 1*, 30 participants are considerably greater than the participants involved in the vast majority of previous respiratory guidance studies. Such a number of participants in this study would make it the most comprehensive AV biofeedback study to date. The inclusion of more participants would also produce more accurate and significant results.

4.4. NUMBER OF CENTRES

This study will be conducted solely at Chris O'Brien Lifehouse Department of Radiation Oncology, Sydney.

4.5. DURATION

The expected duration of the study is 2 years. Estimated time of first recruitment is early 2014. The study recruitment phase and data analysis phase will be done concurrently; analysis of data for each patient can commence once CBCT scans have been acquired for that patient. Overall analysis will commence after last patient recruitment.

5.STUDY OUTLINE

The data required for the study: external and internal respiratory signals in addition to the CBCT scans, will be collected before and during treatment. All patients will receive the same CBCT scans.

Each CBCT study (inclusive of setting up and packing away the AV biofeedback system in addition to CBCT scan time) will be completed within a 1 hour timeframe on a single day as per SBRT clinical trial protocol. Once informed consent has been obtained, the principal investigator will schedule a time for the study.

5.1. STUDY EQUIPMENT

The additional hardware needed for this study is comprised of the AV goggles or screen. The CBCT images will be acquired using a Novalis Tx linear-accelerator (linac). In the data analysis stage of the study, further equipment and software will be used, both of which are frequently used in quality assurance tests and treatment planning.

5.1.1. AV BIOFEEDBACK

In this study the audio and visual prompts of the AV biofeedback system will be delivered to the patient via easy to wear and light-weight goggles, shown in *Figure 5*, or a screen, shown in *Figure 6*. The screen to be used is the Google Nexus tablet computer.

Figure 5. *The AV goggles (left) and being worn by a volunteer (right).*

The patients will view a high resolution built-in monitor for the visual component in addition to hearing the audio component via built-in speakers.

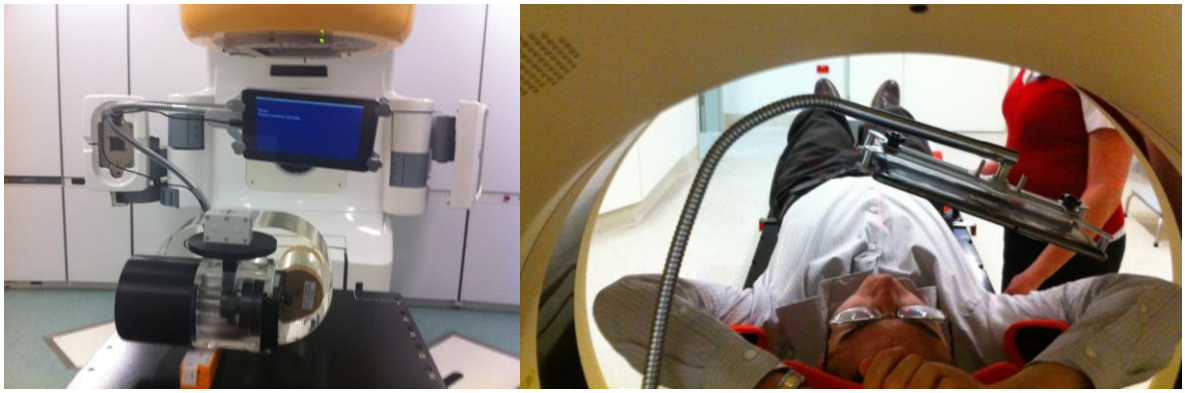


Figure 6. *The screen (Google Nexus tablet computer) in a linac (left) and CT (right) room.*

The Google Nexus tablet has built-in speakers as well as a 3.5mm headphone jack if the patient would rather wear headphones.

The respiratory motion information will be acquired using the RPM system (*Figure 7)*, which is comprised of an infrared (IR) camera tracking the motion of a marker block at a rate of 30 Hz (real-time).

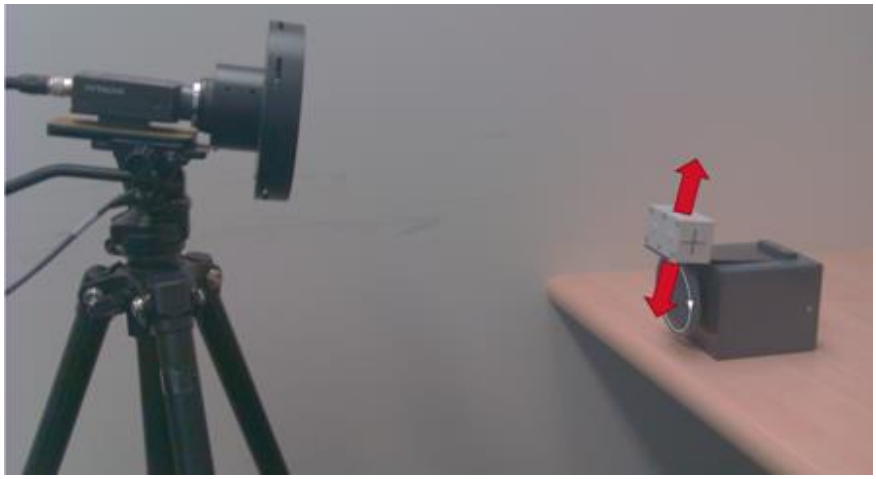


Figure 7. *The RPM system: an IR camera tracking the marker block at a rate of 30 Hz.*

AV biofeedback is a non-invasive, interactive respiratory guide designed to guide the patient towards regular respiration in the most comfortable way possible.

5.1.2. NOVALIS LINEAR ACCELERATOR

For the CBCT scans, a TGA-approved, fully clinical, routine SBRT treatment unit at Chris O'Brien : Novalis Tx Linear Accelerator (*Figure 8*) will be used. As a part of their SBRT treatment plan, each patient will already be receiving 18 CBCT scans. By participating in this study, each patient will receive two additional CBCT scans with an addition piece of equipment: the AV goggles (*Figure 5*) or screen (*Figure 6*), in order to test the AV biofeedback system.

Figure 8.The Novalis Tx Linear Accelerator.

5.1.3. QUASAR PHANTOM

In the data analysis stage of the study, the reduction in 4D CT errors with/without AV biofeedback will be quantified by programming the Quasar phantom (*Figure 9*) with the AV and free-breathing traces.

Figure 9. *The Quasar phantom.*

The Quasar phantom is a breathing simulator and is frequently used in quality assurance tests on radiotherapy systems. By programming the Quasar with an acquired patient respiratory signal we are able to study the effect of AV biofeedback on 4D CT image quality *without* giving additional dose to the patient.

5.1.4. ECLIPSE FOR DOSE RECONSTRUCTION

The impact of AV biofeedback on dose distribution will be assessed using the Varian treatment planning software: Eclipse. In a method developed by Poulsen *et al* (Med Phys, 2012)[1,2] the respiratory motion will be incorporated into treatment plans. Dose distributions and dose volume histograms (DVH) will be acquired through this method to assess the impact of AV biofeedback on the patients' treatment plan. Examples of dose distributions acquired in the Poulsen (Med Phys, 2012)[2] study are shown in *Figure 10*. Also computed by the Eclipse software are the DVHs which are a mathematical tool frequently used in radiotherapy to determine the adequacy of a treatment plan. DVHs graphically describe dose distributions across a target volume in addition to organs at risk. A DVH from Poulsen, *et al*'s (Med Phys, 2012) study is shown in *Figure 11*.

The Eclipse dose reconstruction software is available is both the Radiation Oncology Department at Chris O'Brien Lifehouse as well as the University of Sydney.

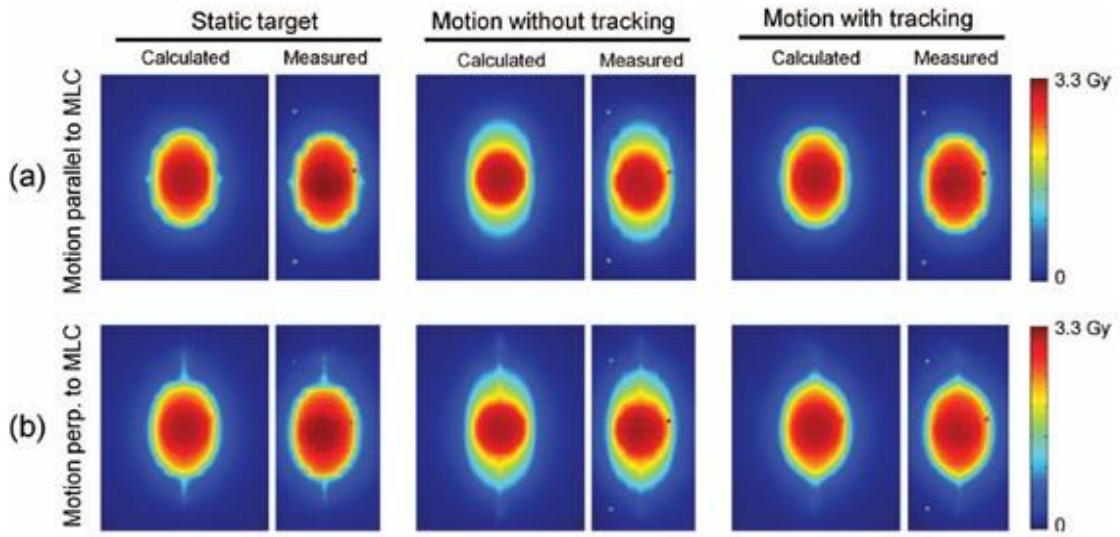


Figure 10. *Calculated (left side of each pair) and measured (right side) 2D dos distributions for a conformal field delivered to a static target and to a moving target with and without dynamic multi-leaf collimator (DMLC) tracking.*

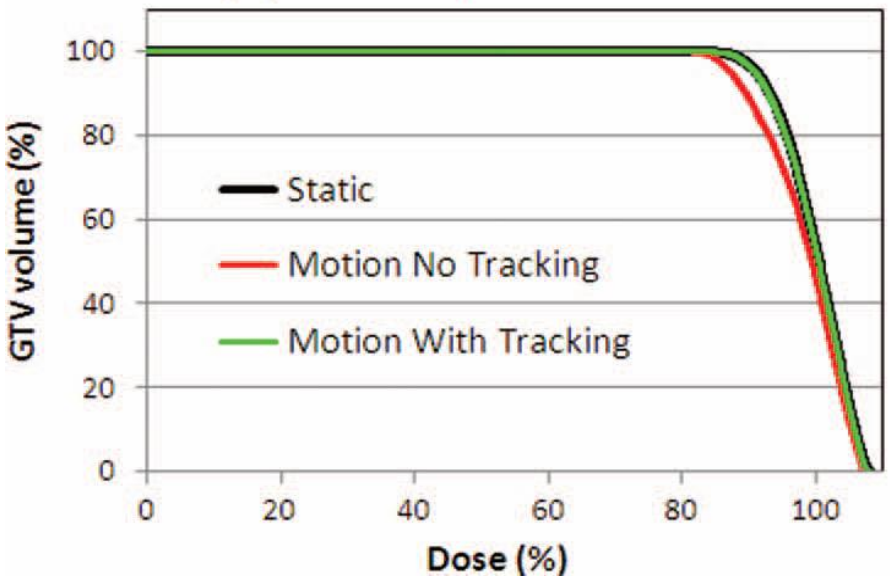


Figure 11. *A DVH from Poulsen's study (Med Phys 2012). It is describing how much of the tumour itself (GTV: Gross Tumour Volume) is receiving what percentage of radiation dose.*

5.2. STUDY FLOW CHART

The study flow chart is shown in *Figure 12*. Details of the investigation plan will be described in section 5.3.

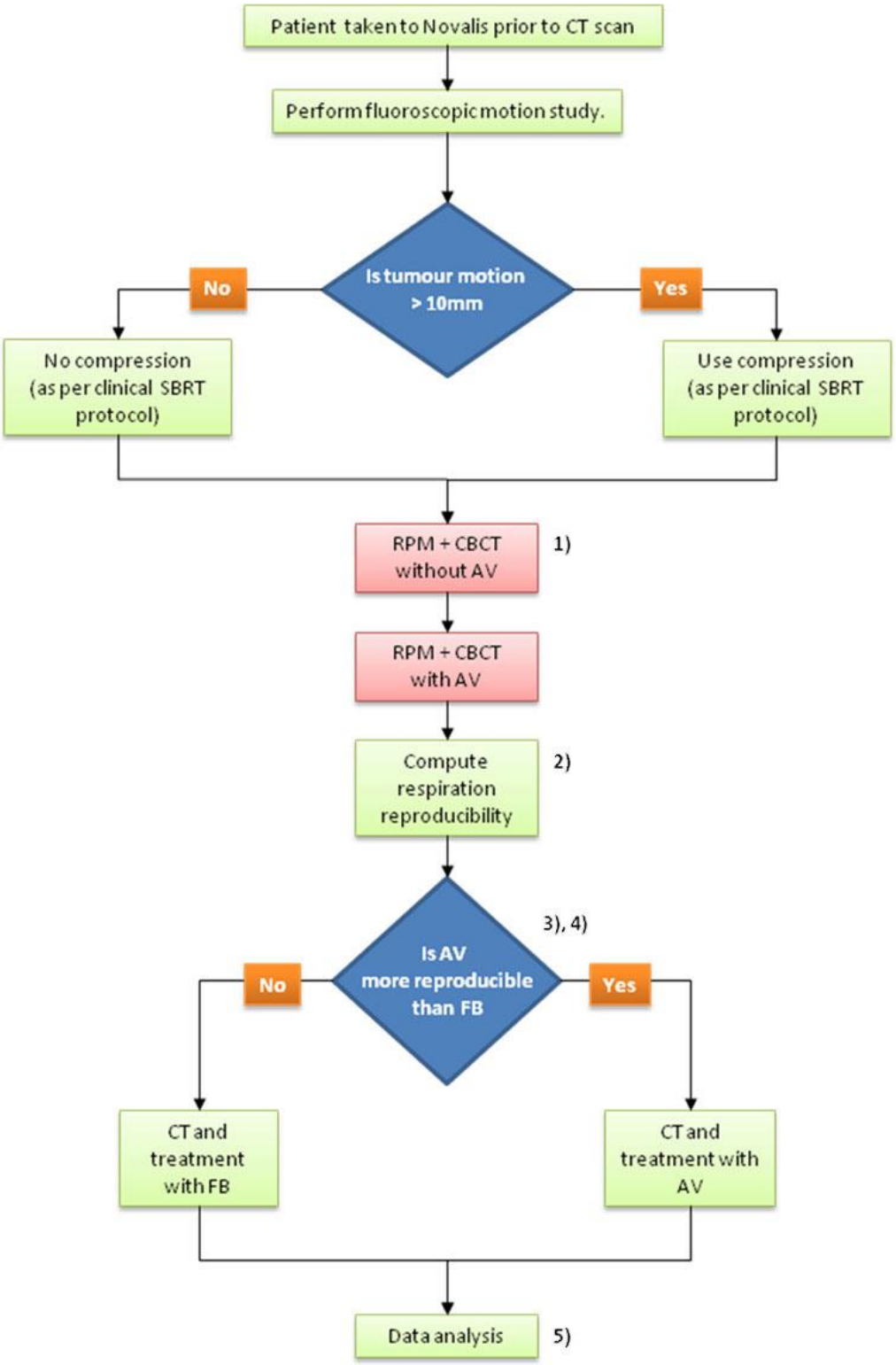


Figure 12. *Data acquisition procedure for the 30 cancer patients in the CBCT AV biofeedback study. Each study will involve the patient breathing both with and without the guidance of AV biofeedback.*

5.3. INVESTIGATION PLAN

The study will progress much the same as per the currently implemented clinical liver SBRT protocol with the addition of an AV biofeedback training session prior to the scans and then the implementation of AV biofeedback during a CBCT scan at the treatment planning stage, a second CBCT scan will also be taken without the implementation of AV biofeedback.
Should fiducial marker motion be more than 10 mm, abdominal compression may be used. Our AV biofeedback system is shown schematically in *Figure 13*. The real-time (30 Hz) respiratory data is input into the respiratory motion management system to determine a patient's respiratory-related motion pattern (waveguide). Two CBCT scans will be taken during the study under two different breathing conditions: (1) with AV biofeedback and (2) without AV biofeedback (free breathing). To improve the image quality and radiation targeting for the patient, all subsequent imaging and treatment sessions will use the most reproducible breathing condition: free breathing or AV biofeedback.

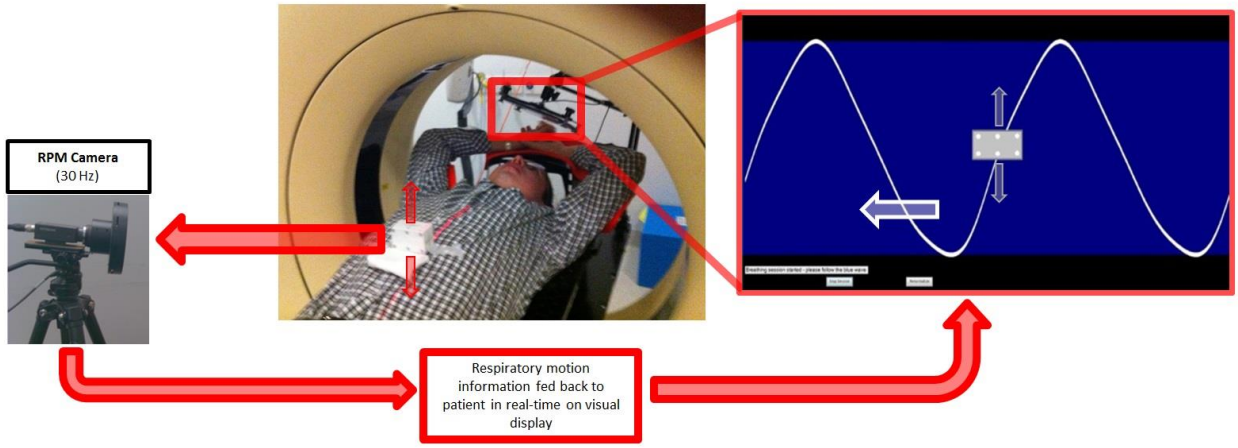


Figure 13. *Schematic AV biofeedback system to be used in this study. Not shown: abdominal compression to be utilised if tumour has range of motion larger than 10mm. Shown here is the use of the screen to show patients the visual display, however, the use of goggles are also available (see Figures 1 & 5).*

During each patient's CBCT scans they will breathe under two conditions: (1) with AV biofeedback and (2) without AV biofeedback (free breathing). To improve the image quality and radiation targeting for the patient, all subsequent imaging and treatment sessions will use the most reproducible breathing condition, free breathing or AV biofeedback.

Numbers 1 – 5 on the study flow chart (*Figure 12*) indicate the progression of the study plan:

1) Patient order selection: Non-randomised. Patients will alternate between what breathing condition is implemented first in their study: AV biofeedback or free breathing.

2) Use external (RPM signal) and internal marker signals for respiratory signals.

Respiratory data analysis; respiratory reproducibility will be quantified by RMSE (in displacement and period).

3) Patient report: proposed report shown in *Figure 14*.

4) Patient/Radiation Therapist (RT) questionnaire: to gauge the level of acceptance of AV biofeedback from both the patient and clinician. (See section 10.2. Questionnaire)

5) Respiratory Data Analysis. For each patient, the acquired internal motion and external respiratory data will be analysed in order to quantify the clinical impact of AV biofeedback through four criteria:

i) Quantify the fraction of patients for whom breathing is more regular (reproducibility calculated in point 2) with AV biofeedback and proceed to simulation and treatment.

ii) Quantify the improvement in dose distributions and DVHs with and without AV biofeedback by reconstructing the delivered dose using the dose reconstruction method of Poulsen *et al* (Med Phys, 2012).[1,2] This dose reconstruction method incorporates the motion information of the target and is compatible with a number of treatment planning systems including Eclipse, Varian Systems.

iii) Quantify the reduction in 4D CT errors with/without AV biofeedback by programming the Quasar phantom with the AV and free-breathing traces.

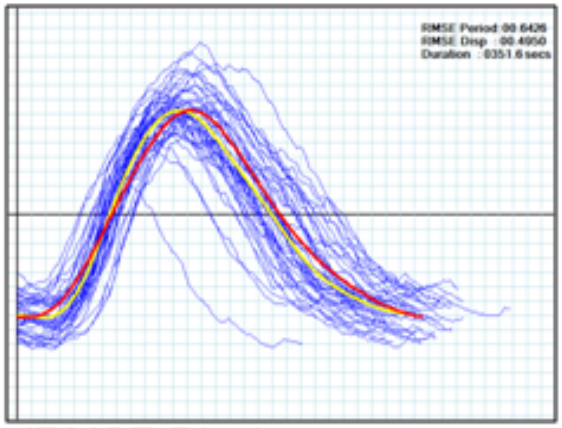
iv) Reconstruct the CBCT into 4D CBCT using the respiratory signal and compare the image quality with and without AV biofeedback.

Patient name:

Medical Record Number:

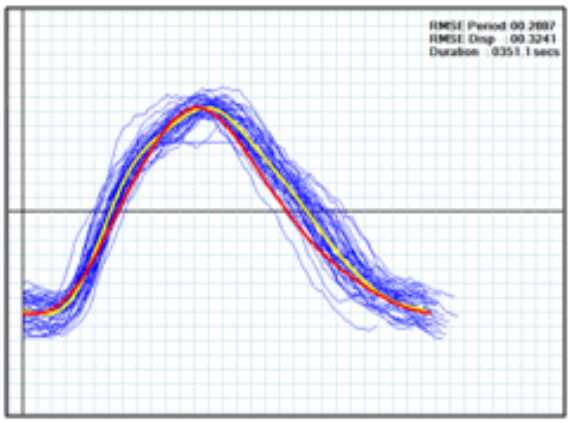
Study Date:

FB



Reproducibility (RMSE Disp):

AV



Reproducibility (RMSE Disp):

Decision: ☐FB ☐ AV

Comments:

Name of Physician: _____

Signature: _____

Figure 14. *Proposed Patient Report, V1.0.*

Procedures	Pre Study Visit Visit with Treating Physician	Pre Study Visit	Study Visit	Post Study Visit/s
Review Inclusion/Exclusion Criteria	✓			
Medical History	✓			
Obtain Informed Consent	✓			
Book Scan Time		✓		
CBCT Scans			✓	
Study Analyses				✓
Review of Study Progression				✓
Treatment and Follow-up Visits (Independent to Study)				✓

5.4. STUDY PROCEDURE RISKS

Considering that patients are receiving standard oncology treatments, which they are subject to regardless of participation in this study, their treating physician will be counselling them on the risk of their appropriate treatments. Studies have found that the risks of major and minor complications as a result of the implantation of fiducial markers are 5% and 17.3%, respectively,[54] and that very few patients have mild side effects lasting more than 2 weeks.[55] However, it should be emphasised that patients will undergo fiducial marker implantation as per clinical SBRT protocol, not as a result of participating in this study.

For the procedures pertaining to this study, the risks to the patient are low: this research study involves exposure to a very small amount of radiation from the CBCT scans (which are done multiple times routinely as a part of SBRT treatment). As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 to 3 millisieverts (mSv) each year. This study will involve the addition of two additional CBCTs: the upper-range estimate of effective dose from this study is about 16.4 mSv (8.2 mSv per CBCT scan).[56] At this dose level, the risk is low. The dose from this study is comparable to that received from routine diagnostic x-ray and nuclear medicine procedures.

The RPM and AV biofeedback systems do not involve any invasive procedures or ionising radiation and are of no risk to the patients.

5.5. Recruitment and Screening

Patients fitting the eligibility criteria will be identified and introduced to this study by the treating physician who will participate as a principal investigator in this study.

5.6. Enrolment Procedure and informed consent process

The patients will be given ample time to completely read the informed consent form as well as ask any questions that they may have.[57,58] The patients will be contacted by the principal investigator with regards to their decision in partaking in the study. Patients that agree to partake in the study will be asked to sign an informed consent form at their next hospital visit.

The participant will receive a study enrolment number and this will be documented in the participant's medical record and on all study documents. Patients who agree to participate will be contacted by principal investigator to organise times for to the study scans to be conducted.

5.7. Informed Consent Process

The principal investigator will be obtaining informed consent from patients after consulting with their physician prior to commencing the study.

5.8. Randomisation Procedure

There is no randomisation procedure in this study.

6.SAFETY

6.1. ADVERSE EVENT REPORTING

6.1.1. CLINICAL TRIALS AND ADVERSE EVENT REPORTING

The principal investigator and sub investigators will report adverse events to the Radiation Safety Officer on site and to the Human Research Ethics Committee and the Research Governance Officer within 72 hours of the event occurring unless immediate notification is required.

6.1.2. ADVERSE EVENT

The AV biofeedback system is not invasive and is not expected to cause any adverse event. The goggles used for AV biofeedback are easy to put on and are comfortable to wear. The Google Nexus tablet computer also to be used as the screen for is held above the patient by a tablet-holder clamped on to the treatment couch; the screen is held at a comfortable distance from to patient and is anticipated to be a more comfortable option over the goggles. For the audio component, there is volume control on the goggles and tablet themselves for built-in speakers. The other procedures performed (fiducial marker/surgical clips, CBCT scans) are standard/routinely performed for SBRT treatment therefore no adverse effect is anticipated by the participation in this study

The risks associated with the acquisition of radiological scans are outlined in the risk Section 5.4. (No known side effects).

6.1.3. SERIOUS ADVERSE EVENT (SAE)

We do not anticipate any serious adverse events as a result of the procedures pertaining to this study.

6.1.4. DEVICES EVENTS

Standard imaging protocols and full clinical, treatment and imaging software will be used in the acquisition of imaging scans in this study. We do not anticipate that any adverse event will occur as a result of AV biofeedback as the addition equipment needed to implement AV biofeedback: the goggles, are lightweight and easy to wear (and take off), in addition to the screen and tablet-holder are is easy to clamp to and remove from the treatment couch. Accidental protocol breaches will be reported to the hospital's Radiation Safety Committee.

6.2. SERIOUS ADVERSE EVENT REPORTING

The principal investigator and sub investigators will report adverse events to the Radiation Safety Officer on site and to the Human Research Ethics Committee and the Research Governance Officer within 72 hours of the event occurring unless immediate notification is required.

6.3. DATA SAFETY AND MONITORING BOARD

The imaging modalities that are used in this study are approved for clinical practice, therefore this study we will not nominate a separate Data and Safety Monitoring Board.

Our steering committee (investigators and sub investigators including consumer representatives) will meet monthly to monitor the conduct of the study and assess progress. In addition, the principal and majority of sub investigators will maintain weekly contact via

email and face-face or teleconference meetings in order to facilitate implementation of the study and provide quality assurance to all aspects of the study. The principal investigator will be on-site to personally conduct, oversee, and supervise all of the activities.

6.4. EARLY TERMINATION

We do not anticipate any reason for early termination of the study.

7.BLINDING AND UNBLINDING

There is no blinding in this study.

8.STATISTICAL CONSIDERATIONS

8.1. SAMPLE SIZE, POWER CALCULATION AND ANALYSIS PLAN

According to preliminary results from 15 healthy human subjects, assuming a type I error rate of 5%, 80% power and a moderate effect size of 0.34σ for the paired differences between free breathing and AV biofeedback, a sample size of 30 patients will be required. If we assume that the standard deviations of these differences in the patient population will be approximately double that of the healthy volunteers then the minimal detectable difference will be 0.068, ($\sigma = 0.2$).

For the primary objective, tumour motion reproducibility with and without AV biofeedback will be quantified. Results will be evaluated using the RMSE method and compared using statistical analysis methods such as the Student t-test. The possible changes in treatment planning will be evaluated qualitatively by visual inspection of dose distribution and quantitatively by analysing dose-volume metrics derived from dose-volume histograms (DVHs) as described by Poulsen *et al*.[1,2]

9.CONFIDENTIALITY AND STORAGE AND ARCHIVING OF STUDY DOCUMENTS

Collected data, as itemised on page 16, will be collected from the subjects. After acquisition the CBCT data will be de-identified, however, patient data could be made re-identifiable to obtain additional clinical information for the data analysis stage of the project, but only by the principal investigator. De-identified data will be stored on a secure, password protected backed up database that will be created, much the same to what we have designed for our previous studies. A separate key of the subject study number and their medical record number will be securely stored by the principal investigator to allow re-identification if necessary. Only the principal investigator will have the ability to re-identify subjects. All other investigators will only have access to the de-identified data. The data will be stored for 15 years as per clinical trial guidelines.

The location of data storage will be in the University of Sydney's Medical Foundation Building. Access to the building requires swipe card access; therefore, the general public has no access to it. In addition to this, the lab rooms within the Medical Foundation Building require a key to enter it.

10.DISCLOSURE OF CONFLICT OF INTEREST

Audiovisual biofeedback is being developed towards commercialisation. This has led to the incorporation of a company, Respiratory Innovations Pty Ltd, by University of Sydney investigators Prof. Paul Keall, Mr. Kuldeep Makhija, and Mr. Sean Pollock. No financial support is provided by Respiratory Innovations to any of the investigators or to the investigation itself; however, Paul Keall, Kuldeep Makhija, and Sean Pollock are shareholders in Respiratory Innovations.

No patient data will be used for promotion for Respiratory Innovations outside of what is publically available, e.g. presentations or publications.

11.APPENDIX

11.1. LIST OF ABBREVIATIONS

- AV Biofeedback: Audiovisual biofeedback

  The respiratory guidance system to be testing in this study composing of screen or goggles and motion tracking

- FB: Free Breathing

  The respiratory condition during which AV biofeedback will not be used

- RMSE: Root mean square error.

  Metric to quantify the reproducibility of a respiratory signal. A lower value is indicative of a more reproducible signal.

- CBCT: Cone beam computed tomography

  Medical imaging modality to be used to monitor fiducial marker motion

- RPM: Real-time position management

  Infra-red tracking camera and marker block used to obtain the external respiratory signal for the real-time input for AV biofeedback

- SBRT: Stereotactic body radiotherapy

  Cancer radiation treatment which involves the high-precision delivery of high-dose radiation to a localised area in a small number of treatment fractions.

- DVH: Dose volume histogram

  Mathematical representation of three-dimensional dose distributions in a two-dimensional graph.

- mSv: milli Sieverts

  Sieverts are the SI unit of equivalent absorbed radiation dose

- TGA: Therapeutic Goods Administration
- GTV: Gross Tumour Volume

  GTV is the physical volume of the tumour

- CTV: Clinical Target Volume

  CTV is the approximation of tumour volume (given imaging uncertainties)

- PTV: Planning Target Volume

  PTV is the CTV with additional margins to account for variations in size, shape and position of the tumour.

11.2. QUESTIONNAIRE

Audiovisual (AV) Biofeedback Survey

Goal: To evaluate your experience with the audiovisual (AV) biofeedback guidance system and identify any areas where development is needed to improve the AV biofeedback experience.

Patient status

Disease and stage:	Body-mass index:
Lung function:	or Height/Weight:
Immobilisation:	Cognitive ability:
Treatment schedule:	Heart rate/ blood pressure:
Performance status:	

Date:

Audiovisual (AV) Biofeedback Patient Survey

Goal: To evaluate your experience with the audiovisual (AV) biofeedback guidance system and identify any areas where you feel development is needed to improve the AV biofeedback experience.

Introduction: In medical imaging and radiotherapy, irregular breathing negatively impacts image quality, in addition to inaccurate tumour targeting. AV biofeedback provides respiratory guidance to produce consistent respiratory motion. AV biofeedback will help to improve the quality of imaging scans in addition to the accuracy of radiotherapy treatment.

Timing: After initial simulation session and within last week of treatment

Demographics

Age range:	Impeded eyesight: y / n
Sex:	Impeded hearing: y / n
Height:	Highest level of education:
Weight:	Frequency of computer use:
	Anxiety level:

1 (not at all anxious) – 10 (very anxious)

(1) Do you feel your breathing was more consistent using the AV biofeedback?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(2) Was the training session that you had prior to this session helpful?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(3) Did you feel physically comfortable with the AV biofeedback system?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(4) Did you feel the AV biofeedback visual	Too slow		Just right		Too fast

guide (blue curve) was too slow or fast?	1	2	3	4	5
	Comment:				

(5) Did you feel the AV biofeedback visual guide (blue curve) was too shallow or deep?	Too shallow		Just right		Too deep
	1	2	3	4	5
	Comment:				

(6) Did you like having the music?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(7) Did the music help you breathe more consistently?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(8) Did you feel anxious during the session?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(9) Do you have any comments or suggestions either on your experience or how we can improve the AV Biofeedback system?

Audiovisual (AV) Biofeedback Radiotherapist Survey

Goal: To quantify the user acceptance of audiovisual (AV) biofeedback and identify areas to improve the user AV biofeedback experience.

Introduction: In medical imaging and radiotherapy, variations in cycle-to-cycle breathing results in imaging artefacts, leading to inaccurate radiation beam coverage and tumour targeting. AV biofeedback guides patients to produce regular respiratory motion using an AV device combined with a respiratory monitoring system. The AV biofeedback system will help to improve the quality of scans and the accuracy of radiotherapy treatment for patients.

Timing: After initial simulation session and within last week of treatment for each patient

Demographics

Position:

Years of experience:

(1) Do you think that the training session was useful for the patient?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(2) Do you think the AV biofeedback system helped your patient to breathe more regularly?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(3) Was the AV biofeedback system easy to setup?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(4) Was the AV biofeedback system easy to operate?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(5) Would you recommend the AV	No		Moderately		Yes

biofeedback guidance to your colleagues at other centres to implement in similar treatment?	1	2	3	4	5
	Comment:				

(6) Do you have any comments or suggestions on your experience or how we can improve the AV Biofeedback system?

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Investigation of liver tumour respiratory motion for SBRT cancer patients using audiovisual biofeedback

INFORMATION FOR PARTICIPANTS

Introduction

You are invited to participate in this study because you have liver cancer and will be receiving a course of standard radiotherapy.

The aim of your cancer treatment is to deliver the radiation as precisely as possible to the liver and to spare the surrounding organs such as the parts of the liver unaffected by the cancer and kidneys. However, even when are lying still, the liver and surrounding organs will move when you breathe. In order to compensate for the liver movement, we need to treat a "margin" around the liver to be certain that all of the cancer is being treated every day. If we can help you to visualise and regulate your breathing using an audio-visual device, we may be able to reduce the movement and make this margin smaller, allowing more accurate targeting of the radiation beam to the tumour and, reducing the side effects and, importantly, the radiation dose to the surrounding normal organs.

This Information Sheet gives detailed information about the research study, which your Doctor will discuss with you. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part. Participating in the study is voluntary. Please take the time to read the information sheet carefully, and discuss it with family, friends and/or your GP if you wish. Please ask if there is anything you do not understand or if you would like more information. Once you understand the study, you will be asked to sign the Consent Form if you wish to participate. You will have a copy to keep as a record.

The study is being conducted by:

Dr Regina Tse (Department of Radiation Oncology, Chris O'Brien Lifehouse)

Dr Robin Hill (Department of Radiation Oncology, Chris O'Brien Lifehouse)

Gwi Cho (Department of Radiation Oncology, Chris O'Brien Lifehouse)

Darren Martin (Department of Radiation Oncology, Chris O'Brien Lifehouse)

Professor Paul Keall (Radiation Physics Laboratory, Sydney Medical School, University of Sydney)

Sean Pollock (PhD student, Radiation Physics Laboratory, Sydney Medical School, University of Sydney)

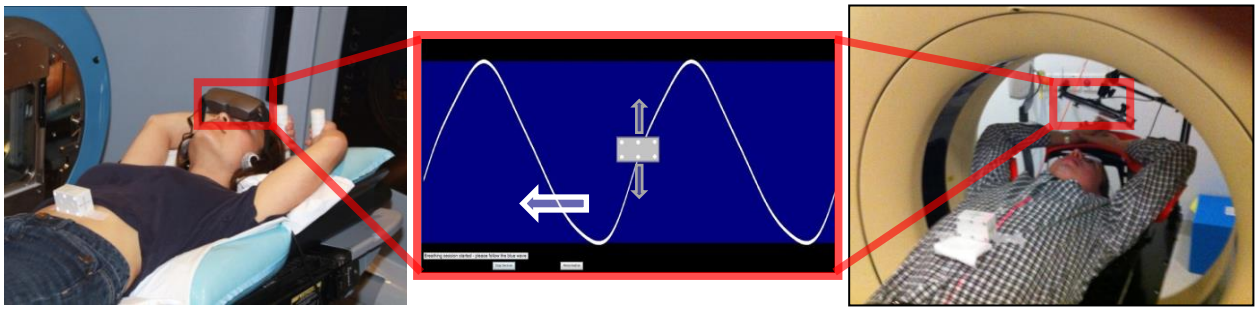
Danny Lee (PhD student, Radiation Physics Laboratory, Sydney Medical School, University of Sydney)

Sean Pollock is conducting this study as a part of the requirements for the degree of Doctor of Philosophy in Medicine under the supervision of Professor Paul Keall.

It is planned that thirty (30) patients will be recruited from the Chris O'Brien Lifehouse into this study.

What is the purpose of this study?
The aim of the study is to evaluate whether the Audio Visual (AV) Biofeedback system will improve the reproducibility of respiratory motion.

This AV biofeedback system comprises a screen or goggles that you view in addition to speakers and controlling software. The goggles or screen allow you to visualize your respiration pattern on a graph (see illustrations below) and with this feedback, allow you to control and regulate your breathing.



The goggles (left) and screen (right) displaying the AV biofeedback guiding software (centre).

What will happen to me if I decide to take part?
As part of your standard SBRT planning and treatment you will have 18 Cone Beam CT (CBCT) scans which are used to position you during radiotherapy. If you are participating in this study, you will have 2 extra CBCT scans done at your planning visit. During the CBCT scans, two breathing conditions will be tested:

(1) with you using AV biofeedback and
(2) without using AV biofeedback (free breathing).

The pattern of your breathing will be measured,- whichever method (with AV biofeedback or without) that produces more regular and consistent breathing patterns will be selected for use throughout your treatment.

When you are breathing with the AV biofeedback system, you will either be wearing a pair of goggles or viewing a screen. The AV biofeedback system will guide you to produce regular breathing.

You will also be asked to complete a questionnaire which will take about 2 minutes to do. You may also be asked to do a follow-up questionnaire later in your treatment, depending on the results of the initial study.

Finally, the researchers would like to have access to your medical record to obtain information relevant to this study.

What are the risks?
All medical procedures - whether for diagnosis or treatment, routine or experimental – involve some risk. In addition, there may be risks associated with this study that are presently unknown and unforeseeable. In spite of all precautions, you might develop medical complications from participating in this study.

The goggles that you will wear as part of the AV biofeedback are similar to a pair of glasses and are not expected to cause any discomfort. However, if you feel uncomfortable at any stage, they can be immediately taken off.
The screen that you may view is a tablet computer that will be held a comfortable distance from you by a table-mounted tablet stand.

The CBCT scans are similar to regular CT scans. The dose from the two (2) extra CBCT in this study is comparable to that received from routine diagnostic x-ray and nuclear medicine procedures. At this dose level, no harmful effects of radiation have been demonstrated and the risk is low.

Please inform us if you have participated in any other research studies using radiation in the last five years.

Please keep this form in a safe place for the next five years in case you volunteer for any more studies using radiation, when you should show it to the Investigator.

It is important that women participating in this study are not pregnant and do not become pregnant during the course of the study. If you suspect that you are pregnant while you are receiving treatment on this study, you should advise your study doctor immediately.

What are the benefits?
While we intend that this research study furthers medical knowledge and may improve radiotherapy for liver cancer and lessen its side effects (and for treatment of other cancers which move as the patient breathes), we cannot guarantee that it will be of benefit to you. However, if the AV biofeedback system proves successful it will continue to be used in your treatment plan. In addition, the images obtained in this study will be used for your treatment plan.

What are the alternatives?
This study is purely voluntary and if you choose not to participate in this study, you will be offered the standard SBRT for your liver cancer in this hospital. Your decision will not affect your treatment, follow-up or relationship with any of the medical staff involved in your care.

Costs
Participation in this study will not cost you anything, nor will you be paid.

Compensation for injuries or complications
If you suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

In addition, you may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). You do not give up any legal rights to compensation by participating in this study.

Voluntary Participation
Participation in this study is entirely voluntary. You do not have to take part in it. If you do take part, you can withdraw at any time without having to give a reason.

Whatever your decision, please be assured that it will not affect your medical treatment or your relationship with the staff who are caring for you.

Confidentiality
All the information collected from you for the study will be treated confidentially, and only the researchers named above will have access to it. The study results may be presented at a conference or in a scientific publication, but individual participants will not be identifiable in such a presentation.

Further Information
When you have read this information, Dr. Regina Tse will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact her on (02) 9515 8057.

Results of Project
It may be a number of years before the results of this research are available. The results will be published in medical journals. Please ask your doctor if you want to know more about this.

Ethics Approval and Complaints
This study has been approved by the Ethics Review Committee (RPAH Zone) of the Sydney Local Health District. Any person with concerns or complaints about the conduct of this study should contact the Executive Officer on 02 9515 6766 and quote protocol number X13-0089.

Disclosure of conflict of interest
AV biofeedback is also being developed towards commercialisation. This has led to the incorporation of a company, Respiratory Innovations Pty Ltd, by University of Sydney investigators Prof. Paul Keall, and Mr. Sean Pollock. No financial support is provided by Respiratory Innovations to any of the investigators or to the investigation itself; however, Paul Keall and Sean Pollock are shareholders in Respiratory Innovations. No patient data will be used for promotion for Respiratory Innovations outside of what is publically available, e.g. presentations or publications.

This information sheet is for you to keep.

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CLINICAL TRIAL PROTOCOL

AVIATOR: Audio-Visual Investigation Advancing ThOracic Radiotherapy

Version Number: V5.0

Date of Protocol: 04/05/2015

Version History		
Version 1	Accepted by HNE HREC	Approved: October 9, 2013
Version 2	- Additional secondary patient-specific objective added: 12 month toxicity follow-up - Figures amended to show AV biofeedback software update. - Gosford Hospital added at 7th study site	Approved: January 22, 2014
Version 3	- Serious Adverse Event (SAE) details amended to only necessitate the reporting of SAEs directly related to AVIATOR study - Royal Prince Alfred Hospital changed to Chris O'Brien Lifehouse - Removal of Dr Apsara Windsor from Gosford team (specialises in breast, not lung)	Approved: June 6, 2014
Version 4	- "Section 8: Confidentiality and storage and archiving of study documents" updated to contain more detailed description of data management methods	Approved: February 25, 2015
Version 5	- Additional investigators added - Current investigators updated - Investigator section formatted to better arrange investigator list - Table in section 4.1. *Study Work Flow* updated	

SYNOPSIS

Protocol title: **AVIATOR**: Audio-Visual Investigation Advancing ThOracic Radiotherapy

Protocol version: V5.0

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Summary

Study Title:	**AVIATOR**: Audio-Visual Investigation Advancing ThOracic Radiotherapy
Protocol version:	V5.0
Objectives	There is a clear link between irregular breathing and errors in medical imaging and radiation treatment. We assume that irregular respiration is a surrogate for clinical outcomes in lung cancer radiotherapy. In a prospective multi-institutional randomised clinical trial we will test the impact of AV biofeedback on clinical outcomes. *Primary objective*: Test the hypothesis that AV biofeedback will significantly improve breathing regularity and reduce medical imaging errors for lung cancer patients undergoing radiotherapy. *Secondary objectives*: *Patient-specific* objectives will evaluate the impact of AV biofeedback by: (1) Quantifying the proportion of patients for whom breathing is more regular with AV biofeedback, (2) Quantifying the variability in breathing motion throughout a course of treatment, (3) Quantifying the improvement in image quality with AV biofeedback, (4) Evaluating the patient experience through a perception of care survey, (5) Developing indications and contra-indications for the use of AV biofeedback, (6) Quantifying the differences in image-guided radiotherapy (IGRT) shifts during treatment, and (7) recording toxicity outcomes for up to 12 months after treatment has been completed. *Department-specific* objectives will evaluate the impact of AV biofeedback on clinical testing by: (1) Quantifying any practice changes (e.g. margin reduction), (2) Quantifying the impact on workflow using the AV biofeedback device through time-motion studies, (3) Evaluating the operator and clinician confidence in the AV biofeedback device's reliability and clinical efficacy through a technology-impact survey, (4) Quantifying the system robustness through hardware and software fault reporting, and (5) Performing system quality assurance, sharing the results through a web-based upload and provide feedback for QA improvement.
Study design	We will perform a comprehensive clinical evaluation of the AV biofeedback system, a multi-institutional study will be performed in the following radiation oncology departments in the NSW/ACT region: Canberra Hospital, Calvary Mater

	Hospital, Nepean Cancer Centre, Northern Sydney Cancer Centre, Chris O'Brien Lifehouse, Westmead Hospital, and Gosford Hospital. Our methodological framework will be based on the widely used Technology Acceptance Model (TAM).[1,2] The TAM gives qualitative scales for two specific variables, perceived usefulness and perceived ease of use, which are fundamental determinants for user acceptance. Planned sample size Across the seven departments there will be a **minimum of 75 patients** (+10% dropout: 83 patients). Selection criteria 1) Lung cancer patients 2) >18 years old 3) No gender or ethnic restrictions 4) An ECOG score in the range of 0 to 2 5) Able to give written informed consent and willingness to participate and comply with the study 6) No pregnant / lactating woman
Study procedure	Prior to each patient's planning and treatment they will undergo a breathing session during which they will breathe both with and without the guidance of AV biofeedback. Preceding each of these breathing sessions will be an AV biofeedback training session to familiarise the patient with the system. After the breathing session has been completed, the most reproducible breathing condition (AV biofeedback or free breathing) will be determined via respiratory analysis. It will be the most reproducible breathing condition that will continue to be used throughout the rest of that particular patient's planning and treatment. Each patient will then be monitored throughout their treatment, noting any differences in image quality and dose distributions as a result of their breathing. The AV biofeedback system is simple and easy to implement; the system consists of a respiratory sensor, a computer with customised software and a display screen. The simplicity of the AV biofeedback system makes it compatible with a number of imaging and treatment modalities. Eligible patients that have agreed to participate in the study and have given informed consent will breathe both with and without the guidance of AV biofeedback. The most reproducible breathing condition will then be implemented in their planning and treatment. Further details on study procedure can be found in Section 4: Study Outline.

	Patient Time Commitment Each session will take a total of 1 hour, inclusive of setting and packing up the AV biofeedback system in addition to AV biofeedback training, but it may be completed in less time than this. After each session the patient will be asked to complete a questionnaire regarding the AV biofeedback system; each questionnaire is designed to only take 2 minutes to complete. Data Analysis For each patient the acquired respiratory sensor data will be analysed in order to quantify the clinical impact of AV biofeedback through the following measurements: 1) Quantify the proportion of patients for whom respiration is more regular with the guidance of AV biofeedback. 2) Quantify the variability in breathing motion throughout a course of treatment. Respiratory results will be evaluated using the root mean squared error (RMSE) method and compared using statistical analysis methods such as the Student t-test. 3) Quantify the differences in IGRT shifts during treatment 4) Quantify any practice changes, such as margin reduction
Estimate the clinical benefit	Successful completion of this trial and positive testing of the primary hypothesis will give clinicians a simple tool to improve breathing regularity and reduce imaging and treatment errors for cancer radiotherapy patients. AV biofeedback will enable (1) identification and delineation of primary tumours and positive nodes, (2) identification and avoiding critical structures, (3) reduction of false positives and false negatives during image interpretation, (4) improvement of rigid and deformable registration algorithm performance to facilitate online corrections and adaptive radiotherapy strategies and (5) reduction of margins, leading to lower toxicity. From a patient perspective, the successful implementation of AV biofeedback will allow patients to be empowered by active participation in their treatment. From a department perspective, it will allow them to perform system QA in addition to developing indications for the use of AV biofeedback. The clinical benefit will also be assessed by recording toxicities for up to 12 months after the patient's treatment is complete. This will offer insight into the benefits of AV biofeedback to patient outcomes. Successful completion of this study will ensure Australia is at the forefront of technological developments and clinical improvements and pave the way for broader clinical use.

Statistical Considerations	Without the AV biofeedback system, it is anticipated that approximately 40% of patients experience regular breathing. Increasing this proportion to 60% using the AV biofeedback system would be considered clinically worthwhile and promising for further investigation in a larger study. Based on the Simon's design, a sample size of 50 patients receiving the AV biofeedback system will have at least 80% power with 95% confidence to rule out a regular rate of 40% in favour of a 60% rate. The proposed design will be a randomized phase II with a 50 patients receiving the intervention and 25 standard care; adding 10% (8 patients) to account for contamination/drop out gives a total of 83 patients. Patients will be stratified by treating institution and for treatment intent (palliative vs. radical) to ensure similar balance in the arms across the sites.
Duration of Study	2 years

Contents

1.INTRODUCTION

Lung cancer has the highest incidence of cancer-related death in Australia,[3] and more than 50% of lung cancer patients are treated with radiotherapy. However, the precision of radiotherapy can be reduced due to respiratory-related tumour motion, leading to increased irradiation of healthy surrounding tissues, resulting in a significant increase in radiation-related toxicity,[4-6] this is further exacerbated when respiration is irregular in nature (deep/shallow breaths, baseline shifts, suspended breathing, etc.).[7,8] A 1Gy increase in tumour dose results in a 4% improvement in survival,[4] however, a 0.5cm range of tumour motion can cause a 4~5% variation in radiation dose[6] which leads to an increase in mean dose to healthy surrounding tissues resulting in an increase in risk of pneumonitis and radiation toxicity.[5,9]

Techniques such as respiratory gating, breath-holds and tumour tracking are clinically useful for tumour motion management.[7,10,11] However, irregular respiration can reduce the efficiency of such motion techniques[12,13] in addition to causing motion artefacts and anatomic errors in medical imaging.[14-19]

Respiratory guidance is one such technique which specifically aims to produce regular patient breathing. At the forefront of respiratory guidance is the **audiovisual (AV) biofeedback** system (*Figure 1*), developed by Venkat, *et al.*[13] AV biofeedback is a real-time, interactive and personalised respiratory guide designed to help the patient breathe regularly. AV biofeedback has demonstrated a reduction in average cycle-to-cycle variations in respiratory amplitude and period by up to 50% and 70% respectively,[13] which is beneficial in improving motion reproducibility for respiratory-gated radiotherapy[20] in addition to reducing blurring artefacts in 4D PET[21] and CT.[22]

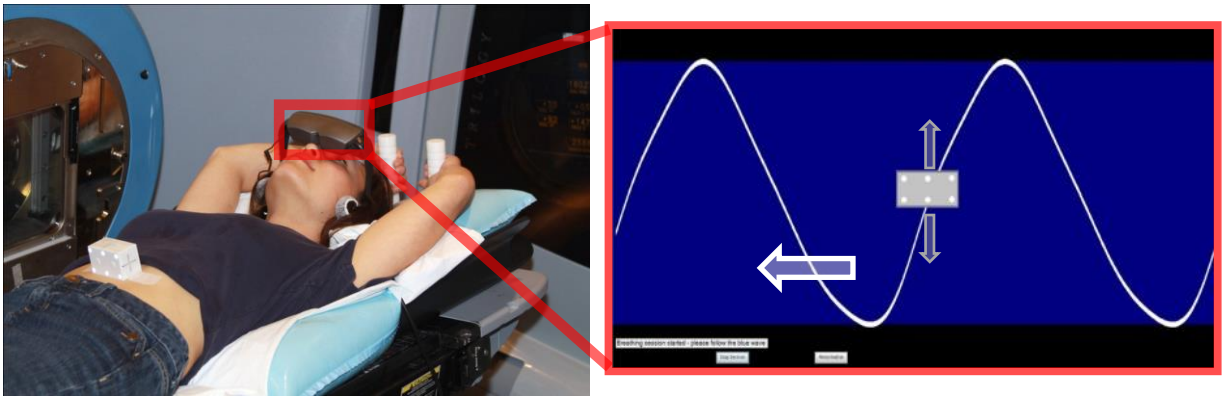


Figure 1. *AV biofeedback system (left). AV goggles and real-time position management (RPM) marker block on the abdomen shown (IR camera not shown, see section 5.1: Study Equipment). The visual display (right) as seen by the subject (sans arrows) of the AV biofeedback system shows the guiding wave (white curve) and a marker position (grey marker) in real time.*

This system is ideally to be utilized for image-guided radiotherapy (IGRT) , during which the tumour motion can be managed by regularising respiratory motion based on the correlation between the external abdominal position (location of RPM marker) and the tumour itself.[23,24]

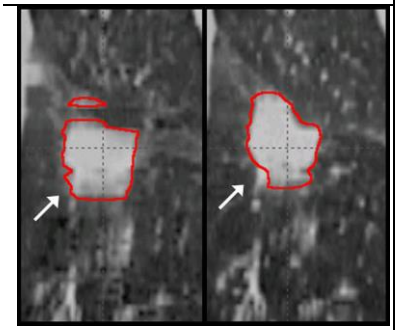
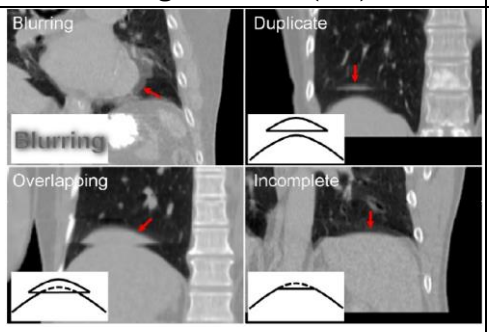
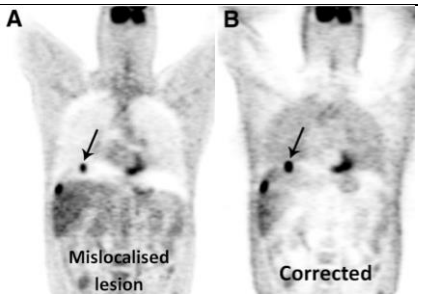
Despite the positive results of AV biofeedback studies to date, the participants have thus far largely been healthy volunteers, which are sufficient when investigating tumour surrogates. There has also not been any analysis of the patient perception of AV biofeedback to understand and stratify responders and non-responders to the training. Here, we will perform clinical testing of AV biofeedback in seven radiation oncology departments. Our study differentiates itself from previous investigations by being multi-institutional, randomised, with a much larger number of patients, the use of an improved AV biofeedback device, the inclusion of patient-reporting and a comprehensive technology assessment.

2.BACKGROUND

2.1. IRREGULAR BREATHING LEADS TO MEDICAL IMAGE AND TREATMENT ERRORS

There is a clear link between respiratory irregularity and errors in medical imaging and treatment, as shown in *Table 1* and *Table 2*. Irregular breathing patterns are shown in *Figure 2* and *Figure 3*, demonstrating baseline drifts and inconsistent amplitude and period. The impact of this irregularity on medical images and targeting are shown *Table 1*, and are elaborated on in *Table 2*.

Table 1. Clinical errors in medical images due to irregular respiration. Further studies in which these errors have been investigated are listed in the bottom row.

Tumour delineation errors	**Image artefacts (CT)**	**Image artefacts (PET)**
		
From Persson *et al.* (2010)[25]	From Yamamoto *et al.* (2008)[15]	From Sureshbabu *et al.* (2005)[26]
Persson[25] and Ge[27]	Pan,[18] Fitzpatrick,[28] Abdelnour,[14] Yamamoto[15] and Low[29]	Sureshbabu[26] and Yang[21]

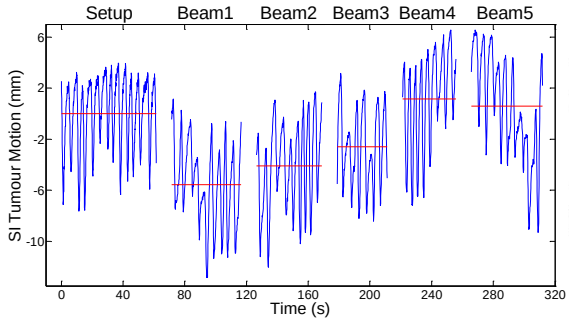


Figure 2. *Example of tumour motion (superior-inferior) during radiation treatment showing the variation in period, baseline, magnitude and mean position. Adapted from Worm.*[30]

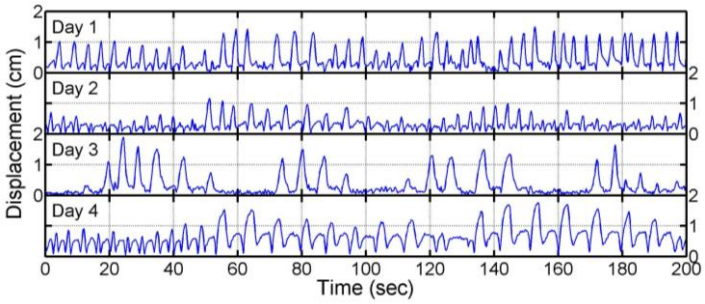


Figure 3. *Example of irregular patient breathing both during treatment (intrafraction) and from day-to-day (interfraction). 46 of 50 patients had errors with an 11mm average error. From Yamamoto.*[15]

Table 2 details previous studies investigating the impact of irregular respiration on radiotherapy planning and treatment:

Table 2. *Clinical Problems of Irregular Respiration*

Clinical Problem	Author	# of participants	Imaging Modality	Comments on clinical problem
Tumour edge detection errors	Persson[25]	19 patients	4DCT	• Variations in delineated gross tumour volume (GTV) sizes of up to 15.6 cm^3 • Delineation error occurred in 16 out of 20 tumours across 19 patients.
Tumour edge detection errors	Ge[27]	10 patients	4DCT	• Disagreement in treatment margins between planning and treatment. (Under- and over-estimation) • Overestimation: 39% of the fractions in 7 of 10 patients. Median overestimation: 11.4 mm (SI), 2.5 mm (AP), and 2.5 mm (LR) • Underestimation: 53% of the fractions in 8 of 10 patients. Median underestimation: 3.9 mm (SI), 3.0 mm (AP) and 1.7 mm (LR)
Image artefacts	Yamamoto[15]	50 patients	4DCT	• 90% of patients had at least one artefact (other than blurring) in the diaphragm / heart. Mean magnitude of artefact: 11.6 mm • 30% of patients had at least one artefact (other than blurring) in the lung / mediastinum
Image artefacts	Pan[18]	10 patients	4DCT	• Image artefacts: incomplete, overlapping, duplicate and blurring artefacts.
Image artefacts	Abdelnour[14]	Phantom 2 patients	4DCT	• Incorrect/incomplete binning for both phase and amplitude 4D-CT binning. • Phase binning: average consistency error ($\mu_e \pm \sigma_e$) ranged from 18%±20% to 30%±35%. • Amplitude binning: average consistency error ($\mu_e \pm \sigma_e$) ranged from 11%±14% to 20%±24%.
Image artefacts	Yang[21]	Motion phantom programmed with patient breathing	PET	• Average increase in structure due to image blurring was 1.3±2.2 mm. • Dice coefficient (metric of overlap between two volumes): 0.88±0.10
Inaccurate motion prediction	Murphy[31]	9 patients	CyberKnife infra-red tracking	• Observed trend that with more irregular respiratory signals came a larger prediction error.
Inaccurate motion prediction	Pollock[32]	15 healthy volunteers	MRI	• Inaccurate respiratory motion prediction for both internal and external surrogates • Prediction accuracy became increasingly unreliable at higher system latencies

2.2. DEVELOPMENT OF BREATHING TRAINING IN RADIATION ONCOLOGY

To address the problem of respiratory irregularity, various methods of patient respiratory guidance have been applied by other groups, as summarised in *Table* 3.

Table 3. *Development of breathing-guidance*

Author, year	Breathing Sensor	Subjects	Developments in Breathing-Guidance
Wang, 1995[33]	Bellows belt	6	• Verbal prompts for breath-hold MRI
Wang, 1995[34]	MR navigator	6	• Visual prompts for multiple breath-hold MRIs
Wong, 1999[10]	Flow monitor	12	• Immobilizing breathing motion
Vedam, 2003[12]	RPM	5	• Visual motion wave with two motion limits (inhale and exhale limits) • Early respiratory-guidance biofeedback (no audio, visual biofeedback limited to inhale/exhale limits)
George, 2005,[35] 2006[20,36]	RPM	24	• Visual motion bar with two motion limits and verbal instruction ("breathe in", "breathe out") • Similar to Vedam (2003) with the addition of audio prompts (however, audio and visual prompts were tested separately)
Lim, 2007[37]	Thermocouple	10	• Visual guidance with audio prompt. • Baseline drift not detected using the thermocouple
Locklin, 2007[38]	Bellows belt	16	• Visual biofeedback only for breath-hold CT scans • Bellows belt signal is self-correcting, and any variations in respiratory baseline or amplitude are lost
Venkat, 2008[13]	RPM	10	• First generation AV biofeedback system. • Audio and visual prompts performed simultaneously • Customizable to volunteer breathing • Visual prompt: wave- and bar guide were tested. • Wave-guide found to be the more effective of the two. • Audio prompts: ascending and descending tones for inhale and exhale, respectively. • Healthy volunteer study
Kim, 2012[39] Pollock, 2013[40]	RPM	15	• More developed version of AV biofeedback, continuing on from Venkat's study. • Visual prompt: wave-guide • Audio prompt: music (polyphonic midi-files) that changes in speed if subject deviated from wave-guide. • Set-up compatible with MRI. • Healthy volunteer study
AVIATOR 2013-2015	RPM	83	• Most recent version of AV biofeedback. • Visual prompt: wave-guide • Audio prompt: music (classical music, mp3-compatible) that fades out should the subject deviate from the breathing limits. • Survey of clinicians and patients to be taken for technological assessment of AV biofeedback • Randomised and stratified • Multi-department nature of study will give strong indication of clinical applicability • Will be the first study to comprehensively assess the impact of respiratory-guidance on clinical oncology planning & treatment for both patients and clinicians

As shown in *Table3*, respiratory-guidance has developed from simple verbal instructions for breath-holds to the interactive, customizable and real-time AV biofeedback to be tested in this study. This study will involve the recruitment of at least 75 participants (+10% to counter dropout: 83 participants), which is considerably greater than the participants involved in previous respiratory guidance studies. Such a number of participants in this study would make it the most comprehensive AV biofeedback study to date. The inclusion of more participants in a randomised clinical trial would also produce more accurate and significant results.

2.3. AUDIOVISUAL BIOFEEDBACK SYSTEM

As shown in *Table 3*, the AV biofeedback system is the culmination of years of respiratory-guidance research with a real-time, interactive and personalised respiratory-guidance system. AV biofeedback has demonstrated to reduce average cycle-to-cycle variations in respiratory amplitude and period by up to 50% and 70% respectively,[13] which has also shown to be beneficial in improving motion reproducibility for respiratory-gated radiotherapy[20] in addition to reducing blurring artefacts in 4D PET[21] and CT.[22] A schematic of the AV biofeedback system is shown below in *Figure 4*.

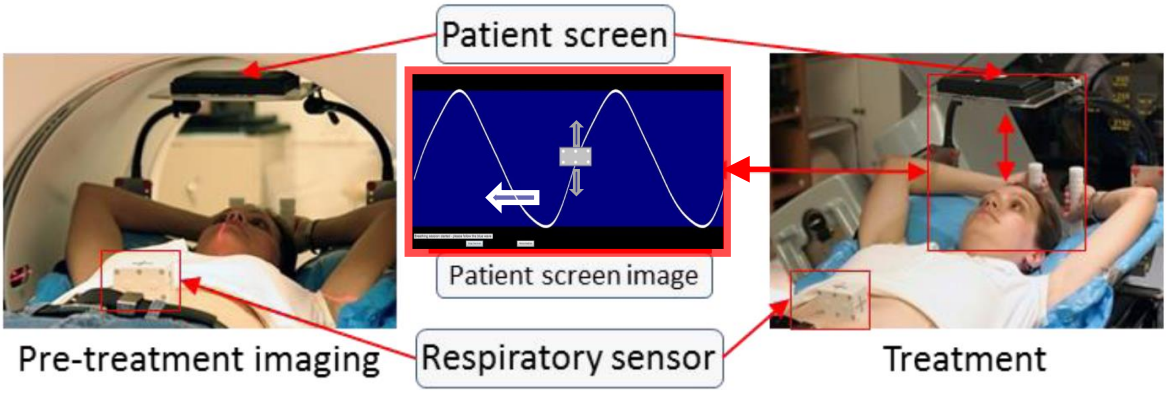


Figure 4. *The University of Sydney AV biofeedback device as used for pre-treatment imaging and treatment. The system consists of a respiratory sensor, a computer with customised software and a patient screen. The patient sees a visual representation of their current breathing and tries to match this to a personalised pattern of more regular breathing.*

A RPM system tracks the motion of an external marker positioned on the patient's abdomen, this respiratory-motion is used to calculate an average cycle of respiration (using a Fourier series fit from 10 obtained respiratory cycles). This average cycle is used as the wave-guide (white curve in *Figure 4*); it continually moves from right-to-left across the visual display and acts as part of the visual prompt for AV biofeedback. Also on the visual display is a grey marker moving vertically up-and-down, it is the goal of the patient to match this grey marker over the white wave-guide. The grey marker is made to look like the RPM marker block to be used in monitoring the patient's breathing.
The audio component of AV biofeedback is classical music playing to the patient; the music fades out should they deviate from the breathing limits (blue region shown in *Figures 1 & 4*). AV biofeedback has been shown to be compatible in a number of imaging and treatment modalities,[21,39,41] as well as utilising different types of visual displays;[39,41,42] the screen-setup as shown in *Figure 4* will be utilized here, however, if one or more departments are not equipped with these or faults occur, there are other options available.
Previous AV biofeedback studies have involved the recruitment of healthy volunteers, not cancer patients. This study will be the first to assess the impact of AV biofeedback on clinical oncology planning and treatment for both patients and clinicians.

3.STUDY OBJECTIVES AND AIMS

3.1. OBJECTIVES

This study aims to assess the AV biofeedback system efficacy in a clinical setting. To test this we will conduct an 83 lung cancer patient clinical study across 7 departments with the following objectives:

Primary objective: In a prospective multi-institutional randomised clinical trial we will test the hypothesis that AV biofeedback will significantly improve breathing regularity and reduce medical imaging errors for lung cancer patients undergoing imaging and treatment procedures during radiotherapy. The patients will be randomised in a 2:1 ratio, with 2/3 of the patients being recruited into the AV biofeedback (intervention) arm and 1/3 in the free breathing (control) arm.

Secondary objectives will involve patient-specific and department-specific objectives:

Patient-specific objectives are to evaluate the impact of AV biofeedback by:

1) Quantifying the proportion of patients for whom breathing is more regular with AV biofeedback,
2) Quantifying the variability in breathing motion throughout a course of treatment,
3) Quantifying the improvement in image quality with AV biofeedback,
4) Evaluating the patient experience through a perception of care survey,
5) Developing indications and contra-indications for the use of AV biofeedback,
6) Quantifying the differences in image-guided radiotherapy (IGRT) shifts during treatment, and
7) Recording toxicity outcomes for up to 12 months after treatment has been completed.

Department-specific objectives are to evaluate the impact of AV biofeedback on clinical testing by:

1) Quantifying any practice changes (e.g. margin reduction),
2) Quantifying the impact on workflow using the AV biofeedback device through time-motion studies,
3) Evaluating the operator and clinician confidence in the AV biofeedback device's reliability and clinical efficacy through a technology-impact survey,
4) Quantifying the system robustness through hardware and software fault reporting, and
5) Performing system quality assurance, sharing the results through web-based uploads and provide feedback for QA improvement.

Our methodological framework will be based on the widely used Technology Acceptance Model (TAM).[1,2] The TAM gives qualitative scales for two specific variables, perceived usefulness and perceived ease of use, which are fundamental determinants for user acceptance.

3.2. PARTICIPANT SECTION

This study is aimed at patients receiving radiation therapy for their treatment of lung cancer. Patients fitting the eligibility criteria (see below) will be identified and introduced to this study by their treating physicians, who will participate as investigators in this study.

3.3. INCLUSION CRITERIA

1) Lung cancer patients (no restrictions to type of radiotherapy being received)
2) >18 years old
3) No gender or ethnic restrictions
4) An ECOG score in the range of 0 to 2
5) Able to give written informed consent and willingness to participate and comply with the study

6) No pregnant / lactating woman

3.4. NUMBER OF PARTICIPANTS

A minimum of 75 lung cancer patients. Adding a 10% drop-out rate yields 83 patients; the explanation for this is given in Section 7: Statistical Considerations. As shown in *Table 3*, 83 participants are considerably greater than the participants involved in previous respiratory guidance studies. Such a number of participants in this study would make it the most comprehensive respiratory guidance study to date. The inclusion of more participants would also produce more accurate and significant results. Statistical justification for 83 patients is elaborated on in Section 7: Statistical Consideration.

3.5. NUMBER OF CENTRES

This study will be conducted across 7 radiation oncology departments in the NSW/ACT region: Canberra Hospital, Calvary Mater Hospital, Nepean Cancer Centre, Northern Sydney Cancer Centre, Chris O'Brien Lifehouse, Westmead Hospital, and Gosford Hospital.

3.6. DURATION

The expected duration of the study is 2 years. Estimated time of first recruitment is early 2014. The study recruitment phase and data analysis phase will be done concurrently; analysis of data for each patient can commence once images have been acquired for that patient. Overall analysis will commence after last patient recruitment.

4.STUDY OUTLINE

Prior to each patient's planning and treatment they will undergo a breathing session during which they will breathe both with and without the guidance of AV biofeedback. Preceding each breathing session will be an AV biofeedback training session to familiarise the patient with the system. After the breathing session has been completed, the most reproducible breathing condition (AV biofeedback or free breathing) will be determined via respiratory analysis. It will be the most reproducible breathing condition that will continue to be used throughout the rest of that particular patient's planning and treatment. Each patient will then be monitored throughout their treatment, noting any differences in image quality and dose distributions as a result of their breathing.

Once informed consent has been obtained, the principal investigator will schedule a time for the study.

4.1. STUDY FLOW CHART

The study flow for each department will vary slightly depending on department preferences. The general study flow chart is shown in *Figure 5*. For more details on randomisation and stratification, see Section 7: Statistical Considerations.

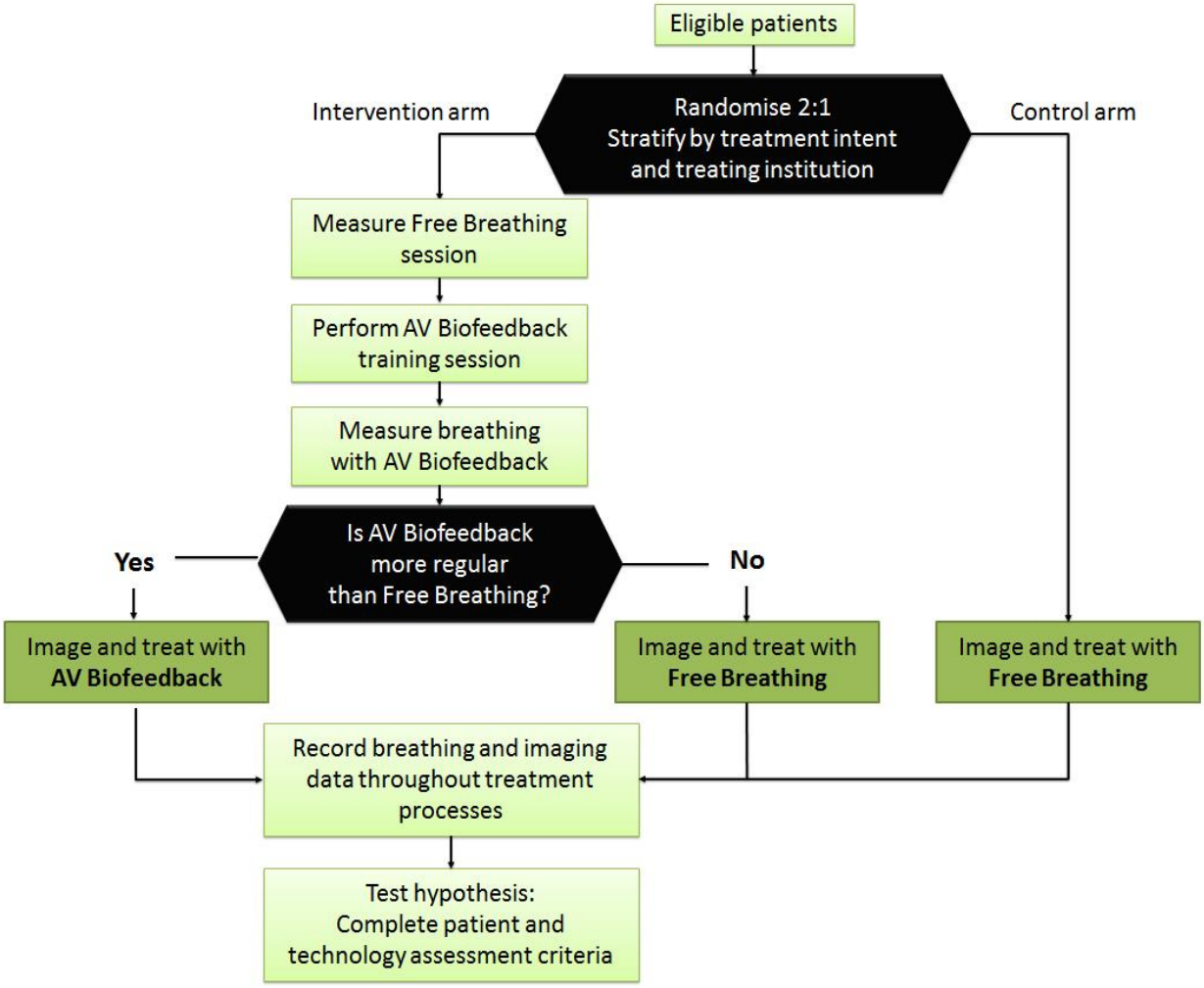


Figure 5. *AVIATOR study flowchart.*

Procedures	Pre Study Visit Visit with Treating Physician	Pre Study Visit	Study Visit	Post Study Visit/s
Review Inclusion/Exclusion Criteria	✓			
Medical History	✓			
Obtain Informed Consent	✓			
Book Scan Time		✓		
CT sim Scans			✓	
Study Analyses				✓
Review of Study Progression				✓
Treatment and Follow-up Visits				✓

4.2. STUDY PROCEDURE RISKS

By participating in this study, the risks to the patient are extremely low: this research study involves the inclusion of respiratory sessions of AV biofeedback and free breathing. These study sessions involve the use of the RPM system and the additional equipment of a visual display (e.g. monitor, tablet computer), none of which are of any risk to the patient. The RPM and AV biofeedback systems do not involve any invasive procedures or ionising radiation and are of no risk to the patients. Any imaging and radiation treatment that follows are a part of the patient's standard oncology treatments, which they are subject to regardless of participation in this study. The patient's treating physician will be counselling them on the risk of their appropriate treatments.

4.3. RECRUITMENT AND SCREENING

Patients fitting the eligibility criteria will be identified and introduced to this study by the treating physicians who will participate as investigators in this study.

4.4. ENROLMENT PROCEDURE AND INFORMED CONSENT PROCESS

The patients will be given ample time to completely read the informed consent form as well as ask any questions that they may have. The patients will be contacted by the principal investigator with regards to their decision in partaking in the study. Patients that agree to partake in the study will be asked to sign an informed consent form at their next hospital visit.

The participant will receive a study enrolment number and this will be documented in the participant's medical record and on all study documents. Patients who agree to participate will be contacted by principal investigator to organise times for to the study scans to be conducted.

4.5. INFORMED CONSENT PROCESS

The principal investigator will be obtaining informed consent from patients after consulting with their physician prior to commencing the study.

4.6. RANDOMISATION PROCEDURE

A randomised procedure will be used in this study.

5.SAFETY

5.1. ADVERSE EVENT REPORTING

5.1.1. CLINICAL TRIALS AND ADVERSE EVENT REPORTING

The principal investigator and sub investigators will report adverse events to the Radiation Safety Officer on site and to the Human Research Ethics Committee and the Research Governance Officer within 72 hours of the event occurring unless immediate notification is required.

5.1.2. ADVERSE EVENT

The AV biofeedback system is not invasive and is not expected to cause any adverse event. The visual component involves viewing a display (e.g. monitor, tablet computer); for the audio component, the computer tablet will have built-in speakers, alternatively, the in-house speaker system could be utilised.

5.1.3. SERIOUS ADVERSE EVENT (SAE):

Adverse events are considered 'serious' if they threaten life or function. SAEs are defined as any adverse event which: results in death (i.e. fatal/grade 5 CTC AE); is life-threatening (i.e. grade 4 CTC AE); requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect.

Given the simple and non-invasive nature of this study's setup, we do not anticipate any serious adverse events as a result of the procedures pertaining to this study.

5.1.4. DEVICES EVENTS

Standard imaging protocols and full clinical, treatment and imaging softwares will be used in the acquisition of imaging scans in this study. Accidental protocol breaches will be reported to the hospital's Radiation Safety Committee.

5.2. SERIOUS ADVERSE EVENT REPORTING

SAE reporting in this study will pertain only to procedures directly related to this study's workflow; i.e. additional procedures undergone by patients not related to the AVIATOR trial (e.g. chemotherapy, surgery) that result in an SAE will not be reported for this study. This will limit the SAEs to be reported in this study to imaging and external-beam radiation therapy procedures.

The principal investigator and sub investigators will report adverse events to the Radiation Safety Officer on site and to the Human Research Ethics Committee and the Research Governance Officer within 72 hours of the event occurring unless immediate notification is required.

5.3. DATA SAFETY AND MONITORING BOARD

The imaging modalities that are used in this study are approved for clinical practice, therefore this study we will not nominate a separate Data and Safety Monitoring Board.

Our steering committee (investigators and sub investigators including consumer representatives) will meet monthly to monitor the conduct of the study and assess progress. In addition, the chief and majority of sub investigators will maintain weekly contact via email and face-face or teleconference meetings in order to facilitate implementation of the study and provide quality assurance to all aspects of the study. The chief investigator will be on-site to personally conduct, oversee, and supervise all of the activities.

5.4. EARLY TERMINATION

We do not anticipate any reason for early termination of the study.

6.BLINDING AND UNBLINDING

There is no blinding in this study.

7.STATISTICAL CONSIDERATIONS

7.1. SAMPLE SIZE, POWER CALCULATION AND ANALYSIS PLAN

The statistical considerations for this study are largely based on a previous study conducted at Virginia Commonwealth University (VCU) by the chief investigator, Prof Paul Keall, on 24 lung cancer patients.[36,42] 26 patients were recruited for the VCU study, however, 2 patients dropped out due to not being treated with radiotherapy or rapid worsening of disease, and so their data was not collected. A clinically significant different in clinical improvement due to AV biofeedback has been determined to be a margin calculation of less than 5 mm. Irregular breathing causes larger systematic errors (Σ) from motion artefacts and variations between the planned and treated anatomy as well as random day to day variations (σ) in the treated anatomy (see *Table 1* and *Figures 2 & 3*). To combine systematic and random errors and estimate the margin contribution due to breathing irregularity we will use the van Herk method[43]: margin = $2.5\Sigma + 0.7\sigma$. From this calculation, there were 14/24 patients with margins <5 mm with AV biofeedback, while only 5/24 for free breathing.

In this proposed study, we'd like to increase the proportion of patients with reduced margins calculated using the van Herk method. Therefore we have designed an exploratory phase II randomised study examining the potential impact of an AV biofeedback system in regulating breathing in patients receiving radiation therapy for the treatment of lung cancer. Without this system, it is conservatively estimated that approximately 40% of patients experience regular breathing (margin component below 5mm). Increasing this proportion to 60% using the AV biofeedback system would be clinically worthwhile. Based on Simon's design,[44] a sample size of 50 patients receiving the AV biofeedback system will have at least 80% power with 95% confidence to rule out a regular rate of 40% in favour of a 60% rate. To minimise patient selection bias and provide an estimate of regular breathing from a contemporary control, the proposed design will be a randomized phase II with a 50 patients receiving the intervention and 25 standard care. Patients will be randomised in a 2:1 ratio, with 2/3 of the patients being recruited into the AV biofeedback (intervention) arm and 1/3 in the free breathing (control) arm as shown in Figure 5. 2:1 randomisation is appropriate as within the interventional arm there is a screening procedure where only patients whose breathing is more regular with AV biofeedback use this system for their imaging and treatment procedures (*Figure 5*). Patients will be stratified by treating institution and for treatment intent (palliative vs. radical) to ensure similar balance in the arms across the sites. As the study is not powered for formal comparisons between the groups, estimates of the proportion of patients which do not experience irregular breathing will provide information as to whether further investigation is warranted.

Assuming a contamination and dropout rate of no more than 10%, this study will require that 75+8=83 patients be recruited (the 10% value was based on the 2/26 patient drop-out rate in the VCU study). The estimated patient numbers are conservative because they are derived from the 24-lung cancer patient VCU study which used a cruder breathing training system that what will be used in this study.

Patients at each institution will be treated per department protocol with no additional constraints on dose, fractionation, immobilisation or image guided procedures. Results will be adjusted for institution (using a fixed effect) to account for differences between institutions.

8.CONFIDENTIALITY AND STORAGE AND ARCHIVING OF STUDY DOCUMENTS

Collected respiratory data, CT images, demographic information, and treatment data will be collected from the subjects at each site. At the randomisation stage of the study, patient's will receive a trial ID, this is to ensure that the data saved for the trial is done so under this de-identified trial ID. However, patient data could be made re-identifiable to obtain additional clinical information for the data analysis stage of the project, but only by the chief investigator, Professor Paul Keall. De-identified data will be transferred from each study site (hospital) to the study sponsor (University of Sydney) for analysis. De-identified data will then be stored on a secure, password protected backed up database that will be created, much the same to what we have designed for previous University of Sydney studies. A separate key of the subject study number and their medical record number will be securely stored by the chief investigator to allow re-identification if necessary. Only the chief investigator will have the ability to re-identify subjects. All other investigators will only have access to the de-identified data. De-identified data transfer from study site to study sponsor will be performed in accordance with each study site's ethics and security allowances and protocols. The data will be stored for 15 years as per clinical trial guidelines. Data across the multiple study sites will be shared via an online file sharing component (e.g. Redmine).

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Department Name, Site Name

Investigating breathing training for lung cancer radiotherapy

INFORMATION FOR PARTICIPANTS

INTRODUCTION

You are invited to participate in this study because you have lung cancer and will be receiving a course of standard radiotherapy.

The aim of your cancer treatment is to deliver the radiation as precisely as possible to the lung and to spare the nearby organs such as the parts of the lung unaffected by the cancer, as well as the heart and liver. However, even when you are lying still, the lung and surrounding organs will move when you breathe. If we can help you to monitor and regulate your breathing using an audio-visual guidance device, we may be able to more accurate target the radiation beam to the cancer.

This information sheet provides detailed information about the study including its purpose and all the procedures involved. Your doctor will also discuss this with you. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part. Participating in the study is voluntary. Please take the time to read the information sheet carefully, and discuss it with family, friends and/or your GP if you wish. Please ask if there is anything you do not understand or if you would like more information. Once you understand the study, you will be asked to sign the Consent Form if you wish to participate. You will have a copy to keep as a record.

The study is being conducted within this institution by:

Dr _____ (site physician)

Professor Paul Keall (Radiation Physics Laboratory, Sydney Medical School, University of Sydney)

Dr Ricky O'Brien (Radiation Physics Laboratory, Sydney Medical School, University of Sydney)

Sean Pollock (PhD student, Radiation Physics Laboratory, Sydney Medical School, University of Sydney)

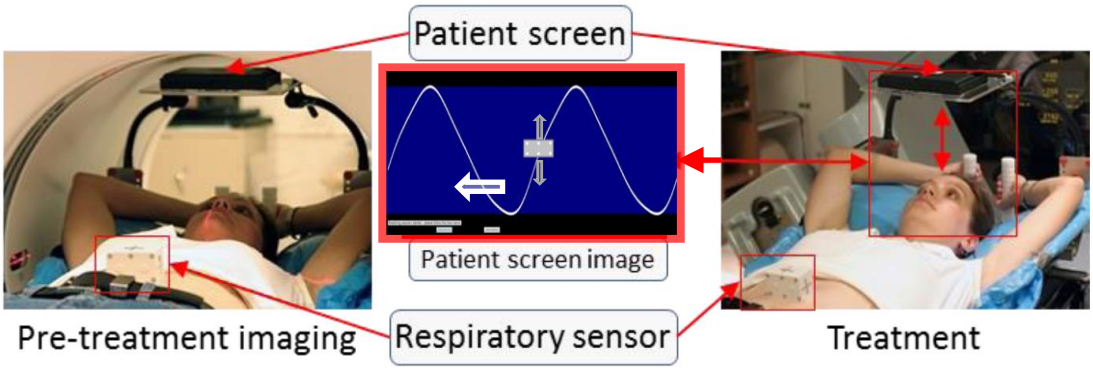
Sean Pollock is conducting this study as a part of the requirements for the degree of Doctor of Philosophy in Medicine under the supervision of Prof. Paul Keall.

It is planned that eighty-three (83) patients will be recruited across the NSW and ACT region into this study.

What is the purpose of this study?

The aim of the study is to evaluate whether breathing training will improve the regularity of your breathing, and therefore, lung motion.

The breathing training system is comprised of a screen, speakers and controlling software. The screen allows you to visualise your pattern of breathing on a graph (see illustrations below) and with this feedback, allow you to control and regulate your breathing.



What will happen to me if I decide to take part?

This study will begin with testing which breathing condition will be best for you to use throughout the rest of the study. This will be either: (1) with breathing training, or (2) free breathing. We will compare the results from these two breathing conditions, and whichever one is deemed to yield the best results for you will be the one that will be selected for usage throughout your treatment. The initial test will only take approximately 15 minutes; the extra time needed during your treatment due to using breathing training will only be approximately 10 minutes.

When you are breathing with the training system, you will be watching a screen and listening to music. The training system will guide you to produce regular breathing.

You will also be asked to complete a questionnaire which will take about 2 minutes to do. You may also be asked to do a follow-up questionnaire later in your treatment, depending on the results of the initial study. In this questionnaire we want to gauge your opinion of the training system and suggest ways we could improve upon it.

However, by participating in this study you may not even need to use breathing training; this could be due to one of two reasons:

1) In the initial test, you performed better breathing freely, so breathing training is not best for you.

2) This study is *randomised*. A randomised study means that the patients are split into two groups: a tested group and an untested group. The tested group will be tested with breathing training, and the untested group will have their treatment as per normal, with no breathing training. This is done so the researchers can compare their new technology the current clinical standard and determine how much it might improve upon it.

Finally, the researchers would like to have access to your medical record to obtain information relevant to this study.

What are the risks?

All medical procedures - whether for diagnosis or treatment, routine or experimental – involve some risk. In addition, there may be risks associated with this study that are presently unknown and unforeseeable. In spite of all precautions, you might develop medical complications from participating in this study.

The visual display for breathing training will be either wearing display-goggles with a built-in screen or watching a computer screen held in place by a clamp to the bed. Such setups are not expected to cause any discomfort. However, if you feel uncomfortable at any stage, do not hesitate to notify staff.

Please inform us if you have participated in any other research studies using radiation (or exposed by other means, e.g. occupational) in the last five years. By participating in this study, you will not be exposed to any additional radiation that would otherwise be a part of your treatment; this study will be performed *alongside* your treatment. However, it should be noted that the prescribed imaging procedures do involve a small level of radiation exposure; at radiation dose level of the imaging procedures, no harmful effects of radiation have been demonstrated and the risk is low.

Please keep this form in a safe place for the next five years in case you volunteer for any more studies using radiation, when you should show it to the Investigator.

It is important that women participating in this study are not pregnant and do not become pregnant during the course of the study

What are the benefits?

You may not benefit from participating in this study; while we intend that this research study furthers medical knowledge and may improve radiotherapy for lung cancer and lessen its post-treatment side effects (and for treatment of other cancers which move as the patient breathes), we cannot guarantee that it will be of benefit to you. However, if breathing training proves successful it will continue to be used in your treatment plan. In addition, the images obtained in this study will be used for your treatment plan.

What are the alternatives?

This study is purely voluntary and if you choose not to participate in this study, you will be offered the standard radiation treatment for your lung cancer in this hospital. Your decision will not affect your treatment, follow-up, or relationship with any of the medical staff involved in your care.

Costs

Participation in this study will not cost you anything, nor will you be paid.

Compensation for injuries or complications

If you suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

In addition, you may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). You do not give up any legal rights to compensation by participating in this study.

Voluntary Participation

Participation in this study is entirely voluntary. You do not have to take part in it. If you do take part, you can withdraw at any time without having to give a reason. If you decide to withdraw from the study all the information relation to you will be destroyed. Whatever your decision, please be assured that it will not affect your medical treatment or your relationship with the staff who are caring for you.

Confidentiality

All the information collected from you for the study will be treated confidentially, and only the researchers named above will have access to it. The study results may be presented at a conference or in a scientific publication, but individual participants will not be identifiable in such scientific distributions. Researchers from the University of Sydney will be analysing the data for this study, therefore the data we obtain from your participation in this study will be transferred securely and confidentially from the hospital to the University of Sydney for analysis.

Further Information

When you have read this information, Dr _____ (site physician) will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact him/her on (02) _____.

Results of Project

It may be a number of years before the results of this research are available. The results will be published in medical journals. Please ask your doctor if you want to know more about this.

Ethics Approval and Complaints

This research has been approved by the Hunter New England Human Research Ethics Committee of Hunter New England Local Health District, Reference 12/08/21/3.01
Should you have concerns about your rights as a participant in this research, or you have a complaint about the manner in which the research is conducted, it may be given to the researcher, or, if an independent person is preferred, to Dr Nicole Gerrand, Manager Research Ethics and Governance, Hunter New England Local Health District, Locked Bag 1, New Lambton NSW 2305, telephone (02) 49214950, email HNEHREC@hnehealth.nsw.gov.au

This information sheet is for you to keep.

Audio-Visual Investigation Advancing Thoracic Radiotherapy (AVIATOR)

PARTICIPANT CONSENT FORM

I,

.....

[name]

of

.....

[address]

have read and understood the Information for Participants on the above named research study

and have discussed the study with

.....

I have been made aware of the procedures involved in the study, including any known or expected inconvenience, risk, discomfort or potential side effect and of their implications as far as they are currently known by the researchers.

I understand that my participation in this study will allow the researchers and others, as described in the Information for Participants, to have access to my medical record, and I agree to this.

I freely choose to participate in this study and understand that I can withdraw at any time.

I also understand that the research study is strictly confidential.

I hereby agree to participate in this research study.

NAME:

.....

SIGNATURE:

.....

DATE:

.....

NAME OF WITNESS:

.....

SIGNATURE OF WITNESS:

.....

NAME OF INVESTIGATOR:

.....

SIGNATURE OF INVESTIGATOR:

.....

PROJECT TITLE: Audio-Visual Investigation Advancing Thoracic Radiotherapy (AVIATOR)

SPONSOR: The University of Sydney

SITE:

PRODUCT: Audiovisual (AV) biofeedback

HREC ID: 13/08/21/4.01

INVESTIGATOR'S BROCHURE

Version: 1.0

Version Date: 30 April, 2014

Confidential

Table of contents

1. Introduction

AV biofeedback is a simple, personalised and customisable respiratory guidance system which aims to produce regular patient breathing. The problem that AV biofeedback is addressing is that should a lung cancer patient's breathing be irregular, it can result in incorrect information presented in medical imaging in addition to incorrect tumour targeting in radiotherapy. This can result in an increase in radiation dose delivered to healthy tissue and less precise dose delivered to the tumour itself. The following details the software required for the implementation of this novel technique. By facilitating regular breathing we can improve the quality of planning images as well as the accuracy of radiation treatment delivery.

The AVIATOR trial aims to assess the AV biofeedback system efficacy in a clinical setting. To test this we will conduct a 75 lung cancer patient clinical study across 7 departments with the following objectives:

Primary objective: In a prospective multi-institutional randomised clinical trial we will test the hypothesis that AV biofeedback will significantly improve breathing regularity and reduce medical imaging errors for lung cancer patients undergoing imaging and treatment procedures during radiotherapy. The patients will be randomised in a 2:1 ratio, with 2/3 of the patients being recruited into the AV biofeedback (intervention) arm and 1/3 in the free breathing (control) arm.

Secondary objectives will involve patient-specific and department-specific objectives:
Patient-specific objectives are to evaluate the impact of AV biofeedback by:

1) Quantifying the proportion of patients for whom breathing is more regular with AV biofeedback,
2) Quantifying the variability in breathing motion throughout a course of treatment,
3) Quantifying the improvement in image quality with AV biofeedback,
4) Evaluating the patient experience through a perception of care survey,

5) Developing indications and contra-indications for the use of AV biofeedback,
6) Quantifying the differences in image-guided radiotherapy (IGRT) shifts during treatment, and
7) Recording toxicity outcomes for up to 12 months after treatment has been completed.

Department-specific objectives are to evaluate the impact of AV biofeedback on clinical testing by:

1) Quantifying any practice changes (e.g. margin reduction),
2) Quantifying the impact on workflow using the AV biofeedback device through time-motion studies,
3) Evaluating the operator and clinician confidence in the AV biofeedback device's reliability and clinical efficacy through a technology-impact survey,
4) Quantifying the system robustness through hardware and software fault reporting, and
5) Performing system quality assurance, sharing the results through web-based uploads and provide feedback for QA improvement.

2. Physical Properties

A software package has been written by The University of Sydney that will be used in the Clinical Trial to guide the patients to breathe regularly. The system is called AV biofeedback. The system, for approval through TGA CTN process, is illustrated in Figure 1 and detailed below.

2.1 Alterations to Standard Treatment

The AV biofeedback system is simple and easy to use; there will be no alterations to standard treatment as part from the use of AV biofeedback: the same images will be acquired and the same treatment will be delivered as per department protocol.

There will be an addition of audio and visual prompts displaying the AV biofeedback interface to the patient as well as the controlling software in the control room. An example of the AV biofeedback interface as well as in-room displays is shown in Figure 1.

After imaging and treatment it is imperative that the following data be saved: RPM files, AV biofeedback files, image files, questionnaires.

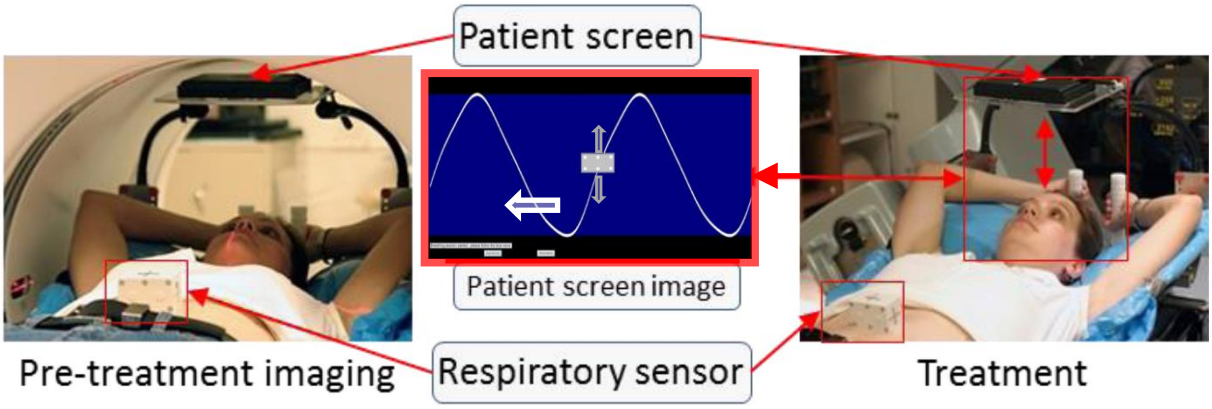


FIGURE 1. The AV biofeedback system. The visual display (centre) as seen by the subject (sans arrows) of the AV biofeedback system shows the guiding wave (white curve) and a marker position (marker block) as an indicator of their real time breathing.

2.2 AV biofeedback software

This software for AV biofeedback is known as the Sydney University Audio-Visual biofeedback Experience (SUAVE). SUAVE will read the breathing signal from the RPM system and display this breathing signal to the patient. The primary functionality of AV biofeedback for this clinical trial is:

1) Compile a patient-specific guiding wave
2) Commence breathing-guidance session
3) Analyse breathing session

These points are illustrated in Figure 2:

The AV biofeedback software is operated by treatment staff. The menu items detail the necessary operations to complete during patient imaging/treatment. Point 1 above only needs to be performed once per patient to ensure consistent breathing across imaging and treatment sessions.

3. Effects in Humans

3.1 Safety and Efficacy

The AV biofeedback system does not result in any additional radiation dose.

A tablet-computer screen for the breathing guidance will be held in place by a clamp to the bed. Such a setup is not expected to cause any discomfort or risk of injury to the patient.

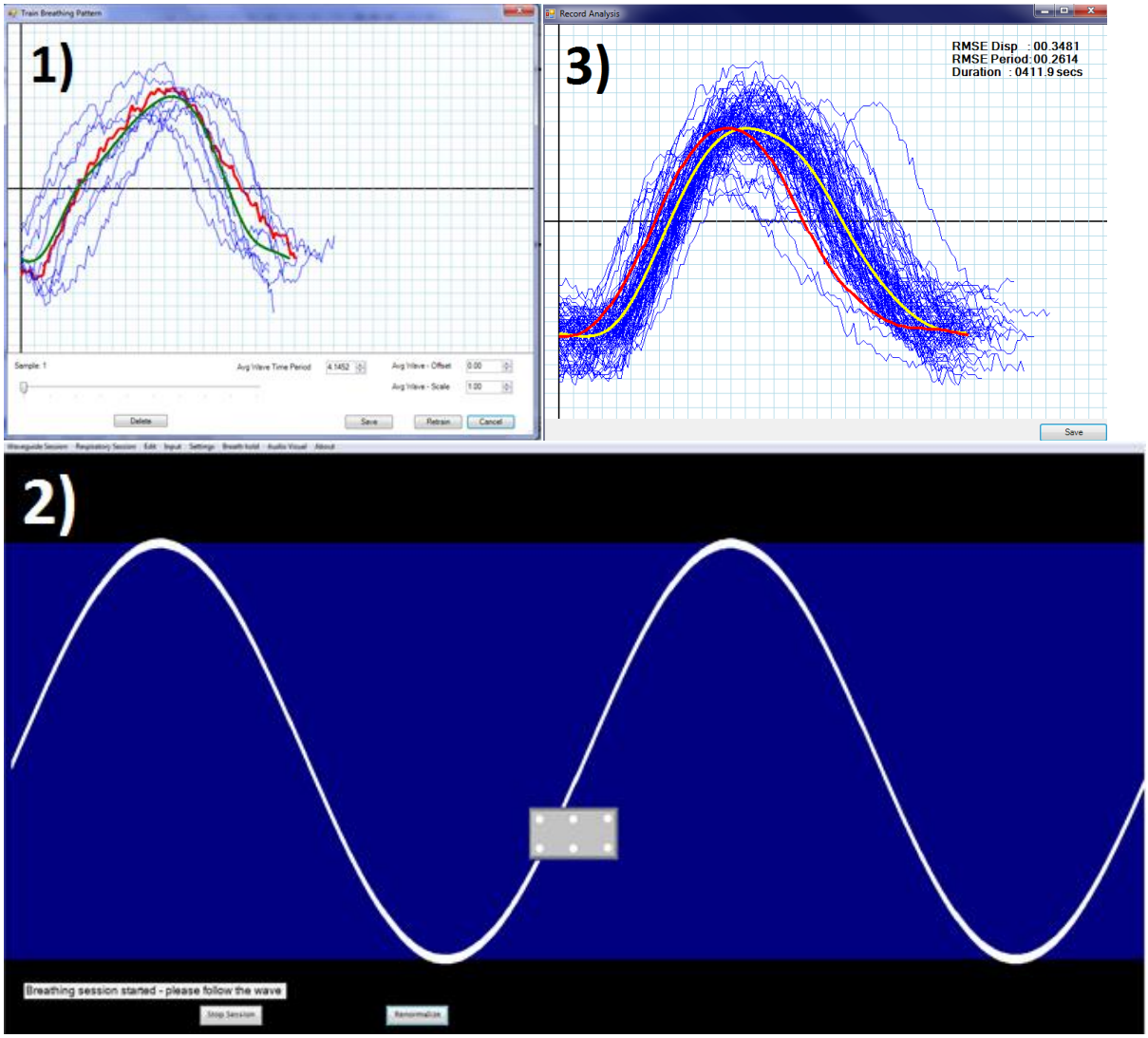


FIGURE 2. Primary functionalities of SUAVE software. Numbers 1-3 correspond to points 1-3 in section *2.2. AV biofeedback software*. 1) the calculation of a guiding wave using patient breathing data. 2) Patient display of their guiding wave and real-time breathing motion. 3) Analysis of breathing with regularity metrics in the top-right corner of the display.

Audiovisual (AV) Biofeedback Toxicity Report

Goal: To determine any impact on patient outcomes by identifying radiation-related toxicities and their severity 12 months after treatment has concluded.

Introduction: To correlate the impact of such study objectives as breathing regularity, margin-calculation, and image quality with patient outcomes. Should the primary object of the study achieve a positive result, then we would expect the patients in the AV biofeedback arm to have less numerous and less severe radiation-related toxicities.
Toxicities listed here were taken from *Common Terminology Criteria for Adverse Events (CTCAE), Version 4.* The grading of severity here will largely remain consistent with the CTCAE document:

- **Grade 1**: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2**: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL (Activities of Daily Living).
- **Grade 3**: Severe or medcally significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL
- **Grade 4**: Life-threatening consequences; urgent intervention indicated.
- **Grade 5**: Death related to AE.

Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, not bedridden.

Timing: To be completed up to 12 months after patient treatment has concluded with each patient follow up.

Date:

Patient ID:

Toxicity/Outcome	Severity/Grade				
Pneumonitis (inflammation of lung tissue)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Comments:				
Radiation fibrosis (scarring of lung tissue)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Comments:				
Dyspnoea (shortness of breath)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Comments:				
Dysphagia (difficulty swallowing)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Comments:				
Odynophagia (painful swallowing)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Comments:				
Pleuritic pain (inflammation of the pleura)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Comments:				

Toxicity/Item(?)	Severity/Grade				
Oesophagitis (inflammation of the oesophagus)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Comments:				
Fistula (abnormal communication between anatomic sites/organs)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Nature of fistula / comments:				
Respiratory failure	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Comments:				
Sleep Apnea (cessation of breathing for short periods during sleep)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Comments:				
Fatigue	Not present		Moderate		Severe
	1	2	3	4	5
	Comments:				
Stenosis (abnormal narrowing of vessel/tubular organ)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Nature of stenosis / comments:				

Toxicity/Item(?)	Severity/Grade				
Lung Function (lung function test)	Improved		No difference		Worsened
	1	2	3	4	5
	Score/Comments:				
Nausea	Not present		Moderate		Severe
	1	2	3	4	5
	Comments:				
Sexual Function	Improved		No difference		Worsened
	1	2	3	4	5
	Comments:				
Number of unscheduled visits since treatment's end	*Number of unscheduled visits:*				
	Comments:				
Cancer Reoccurrence	Yes			No	
	Comments:				

ADDITIONAL COMMENTSS (and/or additional issue(s) not already covered)	*Comments*:

_____	_____	_____
Oncologist name	Signature	Date

Audiovisual (AV) Biofeedback Patient Survey

Goal: To evaluate your experience with the audiovisual (AV) biofeedback guidance system and identify any areas where you feel development is needed to improve the AV biofeedback experience.

Introduction: In medical imaging and radiotherapy, irregular breathing negatively impacts image quality, in addition to inaccurate tumour targeting. AV biofeedback provides respiratory guidance to produce consistent respiratory motion. AV biofeedback will help to improve the quality of imaging scans in addition to the accuracy of radiotherapy treatment.

Timing: After initial simulation session and within last week of treatment

Demographics

Age range:	Impeded eyesight: y / n
Sex:	Impeded hearing: y / n
Height:	Highest level of education:
Weight:	Frequency of computer use:
	Anxiety level:

1 (not at all anxious) – 10 (very anxious)

(1) Do you feel your breathing was more consistent using the AV biofeedback?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(2) Was the training session that you had prior to this session helpful?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(3) Did you feel physically comfortable with the AV biofeedback system?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(4) Did you feel the AV biofeedback visual guide (blue curve) was too slow or fast?	Too slow		Just right		Too fast
	1	2	3	4	5
	Comment:				

(5) Did you feel the AV biofeedback visual guide (blue curve) was too shallow or deep?	Too shallow		Just right		Too deep
	1	2	3	4	5
	Comment:				

(6) Did you like having the music?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(7) Did the music help you breathe more consistently?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(8) Did you feel anxious during the session?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(9) Do you have any comments or suggestions either on your experience or how we can improve the AV Biofeedback system?

Audiovisual (AV) Biofeedback Radiotherapist Survey

Goal: To quantify the user acceptance of audiovisual (AV) biofeedback and identify areas to improve the user AV biofeedback experience.

Introduction: In medical imaging and radiotherapy, variations in cycle-to-cycle breathing results in imaging artefacts, leading to inaccurate radiation beam coverage and tumour targeting. AV biofeedback guides patients to produce regular respiratory motion using an AV device combined with a respiratory monitoring system. The AV biofeedback system will help to improve the quality of scans and the accuracy of radiotherapy treatment for patients.

Timing: After initial simulation session and within last week of treatment for each patient

Demographics

Position:

Years of experience:

(1) Do you think that the training session was useful for the patient?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(2) Do you think the AV biofeedback system helped your patient to breathe more regularly?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(3) Was the AV biofeedback system easy to setup?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(4) Was the AV biofeedback system easy to operate?	No		Moderately		Yes
	1	2	3	4	5
	Comment:				

(5) Would you recommend the AV	No		Moderately		Yes

biofeedback guidance to your colleagues at other centres to implement in similar treatment?	1	2	3	4	5
	Comment:				

(6) Do you have any comments or suggestions on your experience or how we can improve the AV Biofeedback system?

Appendix III

Published Case Report of patient 1 recruited into the study detailed in Chapter 4. Published in *The Journal of Medical Imaging and Radiation Oncology* (2015; **59**(5) 654-656)

RADIATION ONCOLOGY—CASE OF THE MONTH

First clinical implementation of audiovisual biofeedback in liver cancer stereotactic body radiation therapy

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Conflict of interest: Paul Keall is one of the inventors of US patent # 7955270 and Paul Keall, Sean Pollock, Ricky O'Brien and Kuldeep Makhija are shareholders of Respiratory Innovations, an Australian company that is developing a device to improve breathing stability. No funding or support was provided by Respiratory Innovations.

Submitted 19 March 2015; accepted 21 June 2015.

doi:10.1111/1754-9485.12343

Summary

This case report details a clinical trial's first recruited liver cancer patient who underwent a course of stereotactic body radiation therapy treatment utilising audiovisual biofeedback breathing guidance. Breathing motion results for both abdominal wall motion and tumour motion are included. Patient 1 demonstrated improved breathing motion regularity with audiovisual biofeedback. A training effect was also observed.

Key words: abdomen; intervention; physics; radiation oncology imaging; radiation oncology; respiratory.

Introduction

Liver tumours are highly mobile due to their proximity to the thoracic diaphragm. When a patient's breathing motion is irregular, it exacerbates both systematic and random errors which compromise the accuracy of radiation therapy.[1,2] To reduce these errors, breathing guidance strategies have been investigated to facilitate stable and regular breathing.[3,4] This study represents a milestone in breathing guidance investigations as it addresses a gap in the literature by assessing the impact of the breathing guidance system, audiovisual biofeedback (AVB), on intra- and inter-fraction liver tumour motion, via fiducial marker surrogacy, in liver cancer patients undergoing stereotactic body radiation therapy (SBRT). The AVB system, shown in Figure 1, utilises audio and visual prompts to guide the patient to breathe regularly. External breathing motion from the Real-time Position Management (RPM) system (Varian Medical Systems, Palo Alto, CA, USA) of the patient's abdominal wall is shown on the patient display. The marker block moves up as they inhale and down as they exhale. The patient adjusts their breathing such that the marker block stays within the blue region and traces the motion of the waveguide (white wave in Fig. 1).

Case report

Patient 1 was a 65-year-old male with metastatic (recurrent) cholangiocarcinoma and received 36 Gy across 6 fractions using volumetric-modulated arc therapy-based SBRT to a 30 mm solitary lesion in segment 8 of the liver. Due to previous liver resection, this patient had pre-existing surgical clips implanted into his liver, which were utilised for image guidance. He had a number of other

Journal of Medical Imaging and Radiation Oncology

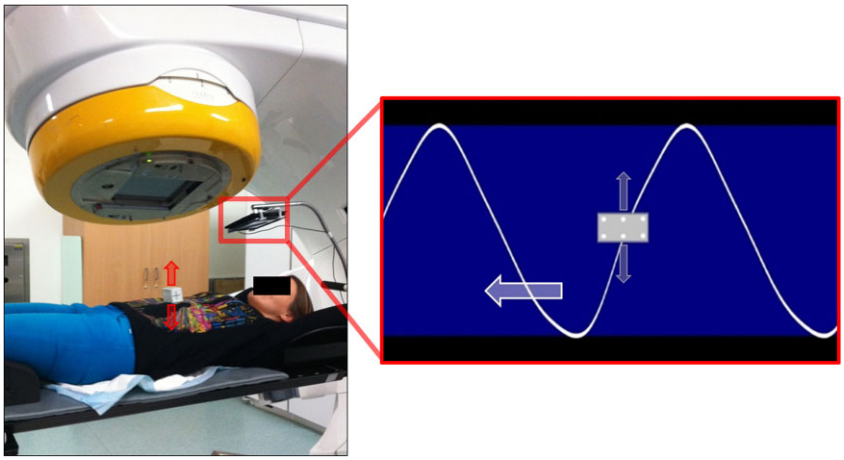

Fig. 1. Study setup in the linac bunker with the Real-time Position Management (RPM) marker block and patient display (left). AVB (audiovisual biofeedback) interface (right).

comorbidities including bronchiectasis with impaired pulmonary function and was of Karnofsky performance status 1. Prior to treatment planning, a screening procedure was performed to ensure that the most regular breathing condition (free breathing (FB) or AVB) was utilised throughout the patient's subsequent course of SBRT. Breathing motion was monitored for 4 minutes for each of the breathing conditions FB and AVB; at the 2-minute mark, cone beam CT (CBCT) images were acquired. Determining which breathing condition would be selected was based on the regularity of the 4 minutes of external breathing motion (quantified by the root mean square error (RMSE) in displacement and period); the lower the RMSE, the more regular the breathing motion. Decisions were made *in situ* using a function within the AVB software. Patient 1's screening procedure yielded the decision to utilise AVB for the remainder of their course of SBRT.

Patient 1's treatment planning and treatment delivery proceeded as per the currently implemented clinical liver SBRT protocol with the addition of the AVB setup (see Fig. 1). CBCT images were acquired prior to treatment delivery on each day of treatment, motion of the surgical clips was extracted from the CBCT projection images utilising a method developed by Fledelius *et al.*,[5] as a surrogate for tumour motion. Figure 2 and Figure 3 demonstrate the breathing motion results across patient 1's course of radiotherapy. It was also observed that AVB increased the average range of tumour motion from 1.5 cm for FB, to 1.8 cm for AVB.

Discussion

This study reported on the first patient recruited into a clinical trial investigating the use of breathing guidance during a course of liver SBRT planning and treatment

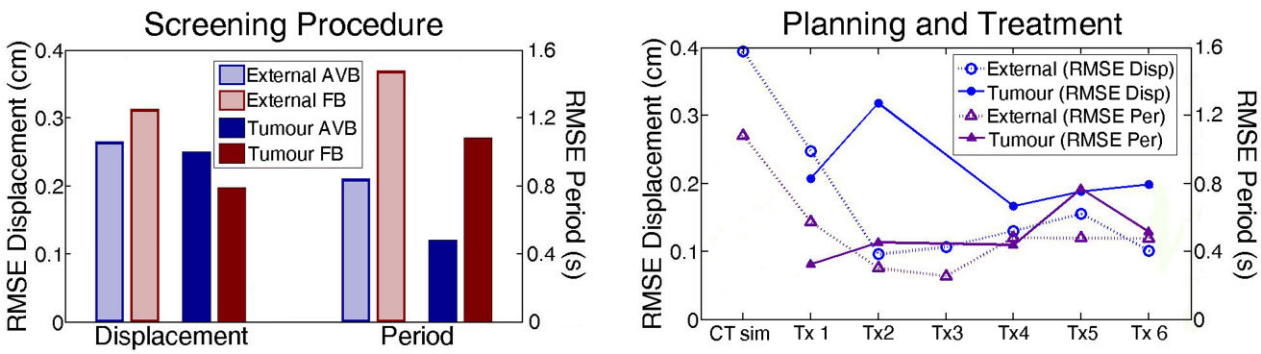

Fig. 2. AVB (audiovisual biofeedback) and FB (free breathing) RMSE (root mean square error) results for Screening Procedure (left); and results for AVB across patient 1's course of treatment (right), for RMSE of displacement (RMSE Disp, blue circle markers) and RMSE of period (RMSE Per, purple triangle markers). External motion shown as hollow markers/bars and dotted lines, tumour motion shown as solid markers/bars and unbroken lines.

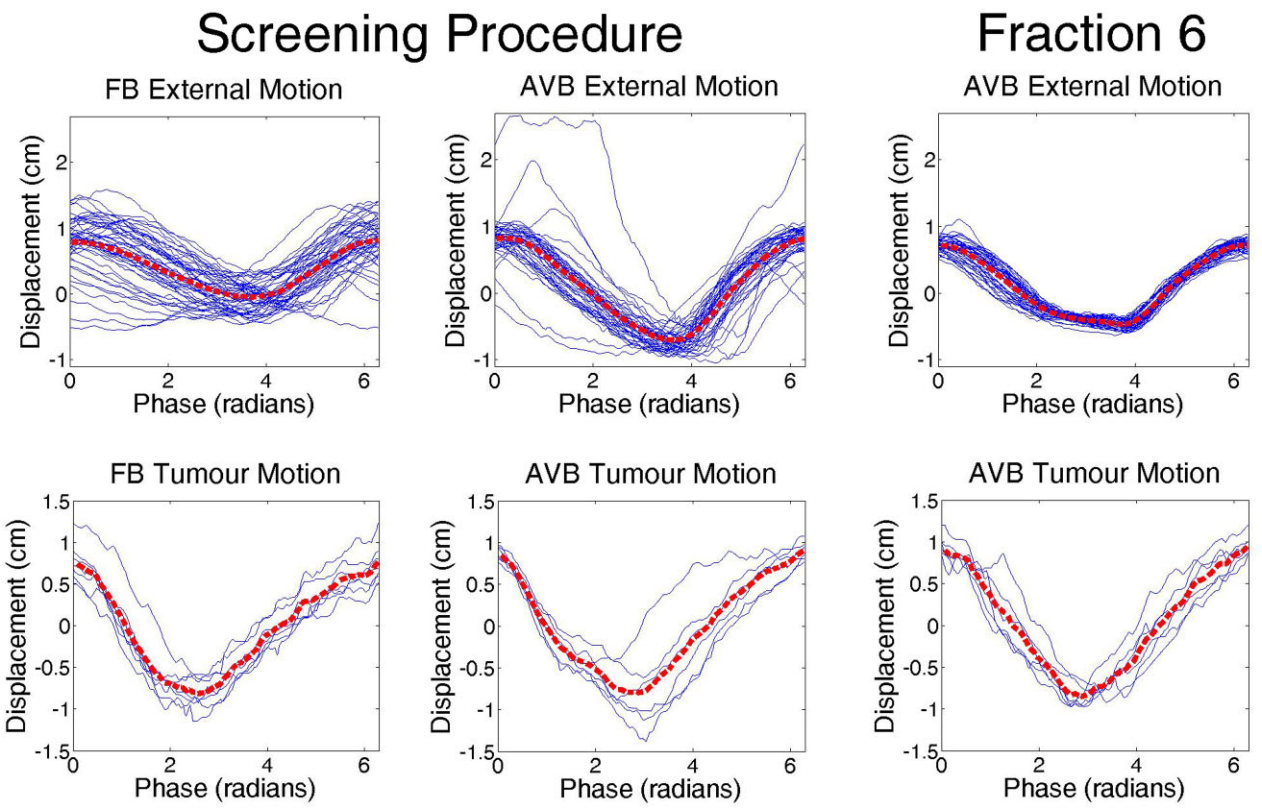

Fig. 3. The external motion (top) and tumour (bottom) individual breathing cycles for FB and AVB Decision Sessions (left) and Fraction 6 (right). Unbroken blue lines represent each individual breathing cycle, and the dotted red line is the average cycle.

utilising an initial screening procedure. A training effect was observed, with the patient's breathing motion becoming more regular inter-fractionally, plateauing at peak regularity around Fraction 3. It was also observed that AVB increased breathing amplitude compared with FB. Given that the AVB waveguide peak-to-peak amplitude was set at 1.5 cm and the observed external peak-to-peak amplitude was 1.7 cm indicates that Patient 1 'over-shot' the AVB breathing limits. For future patients in this study further attention will be given to managing breathing motion amplitude and patient training.

In conclusion, the first patient recruited into this study yielded the decision to utilise AVB through their course of SBRT. Patient 1 demonstrated good acceptance of the breathing guide in addition to increasingly regular breathing throughout their course of SBRT.

Acknowledgements

This project was supported by an NHMRC Australia Fellowship and the Bob and Nancy Edwards Scholarship. The authors thank Julie Baz for reviewing this paper for clarity.

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2. Persson GF, Nygaard DE, Brink C, Jahn JW, Munck af Rosenschöld P, Specht L *et al*. Deviations in delineated GTV caused by artefacts in 4DCT. *Radiother Oncol* 2010; **96**: 61–6.
3. Kim T, Pollock S, Lee D, O'Brien R, Keall P. Audiovisual biofeedback improves diaphragm motion reproducibility in MRI. *Med Phys* 2012; **39**: 6921.
4. George R, Chung TD, Vedam SS, Ramakrishnan V, Mohan R, Weiss E *et al*. Audio-visual biofeedback for respiratory-gated radiotherapy: impact of audio instruction and audio-visual biofeedback on respiratory-gated radiotherapy. *Int J Radiat Oncol Biol Phys* 2006; **65**: 924–33.
5. Fledelius W, Worm E, Elstrøm UV, Petersen JB, Grau C, Høyer M *et al*. Robust automatic segmentation of multiple implanted cylindrical gold fiducial markers in cone-beam CT projections. *Med Phys* 2011; **38**: 6351–61.

Appendix IV

Documentation provided for study site credentialing for the clinical trial presented in Chapter 5

AVIATOR Site Credentialing

Prior to commencing patient recruitment patient, each site needs to complete the following credentialing, please tick off as completed:

CREDENTIALING ITEM	COMPLETE
1) Perform patient Randomisation call	
2) Pass AV biofeedback Daily & Monthly QA using motion phantom in the: a) CT imaging room	
b) Treatment room	
3) Simulate CT imaging and treatment sessions with a volunteer in the: a) CT imaging room (complete Analysis and Decision Form as well)	
b) Treatment room	
4) Anonymised data transferred to University of Sydney secure storage	

Once the above Credentialing points have been completed and signed off by a member of the Radiation Physics Laboratory, that site is open to patient recruitment.

Required Documentation to complete this Credentialing:

- AV biofeedback QA (version 3 – 'Breathe Well')
- Patient questionnaire
- Staff questionnaire
- Session information form
- AVIATOR Randomisation document

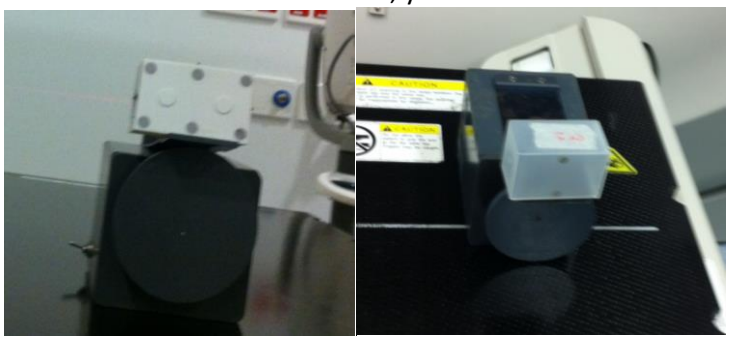
For further details and assistance on the AV biofeedback system setup, user guide, and study workflow, please see the following:

- AV biofeedback User Guide (version 4.1)
- Clinical Workflow
- AV biofeedback system components (version 7.1)

Contents

Performing QA with motion phantom

These motion phantom tests will test the completion of quality assurance (QA), setup compatibility with department equipment, and incorporation of AV biofeedback procedures into department protocol. In addition to the AV biofeedback software and hardware, you will also need a motion phantom:



The motion phantom dry run is performed in both the CT sim room and linac room, the workflow and checklist needs to be completed individually for each room.
At the start of the study, each patient will have been given a study ID number, use this number as the patient name in AV biofeedback software to create a New Patient, and for reference for when you load an Existing Patient.

CT sim room - Phantom		
Action	**Steps**	**Success (y/n)** ***If 'no', detail why***
AV biofeedback system setup	1. Setup AV biofeedback system and motion phantom.	
	2. Move couch to patient imaging position with motion phantom in place at the typical position of a patient's abdomen.	
AV biofeedback Quality Assurance	3. Complete AV biofeedback Daily QA	
	4. Complete AV biofeedback Monthly QA	
Imaging with AV biofeedback	5. Perform 4D-CT scan as per department protocol with the AV biofeedback system running.	
	6. Stop Session and save data	
Data retrieval	7. Save the following data to the database allocated by [site data manager]: a. RPM breathing files	
	b. Image files	
	c. AV biofeedback software breathing files	
	8. University of Sydney researchers received saved data?	

_____	_____	_____
Site credentialing name	Signature	Date

_____	_____	_____
RPL name	Signature	Date

Linac room - Phantom		
Action	**Steps**	**Success (y/n)** ***If 'no', detail why***
AV biofeedback system setup	1. Setup AV biofeedback system and motion phantom.	
	2. Move couch to patient treatment position with motion phantom in place at the typical position of a patient's abdomen.	
AV biofeedback Quality Assurance	3. Complete AV biofeedback Daily QA	
	4. Complete AV biofeedback Monthly QA	
Imaging/ treatment with AV biofeedback	5. Perform CBCT scan (if linac has OBI) as per department protocol with the AV biofeedback system running. a. Record start and finish times of imaging from AV biofeedback software.	
	6. Stop Session and save data	
Data retrieval	7. Save the following data to the database allocated by [site data manager]: a. RPM breathing files	
	b. Image files	
	c. AV biofeedback software breathing files	
	8. University of Sydney researchers received saved data?	

_____	_____	_____
Site credentialing name	Signature	Date

_____	_____	_____
RPL name	Signature	Date

Dry-run with a volunteer

These volunteer tests will test the setup compatibility with department equipment, and incorporation of AV biofeedback procedures into department protocol as well as performing breathing session analysis and decision form (CT room only).

The volunteer dry run is performed in both the CT sim room and linac room, the workflow and checklist needs to be completed individually for each room.

CT sim room - Volunteer		
Action	**Steps**	**Success (y/n)** ***If 'no', detail why***
AV biofeedback system setup	1. Setup AV biofeedback system and couch for lung cancer patient imaging, with volunteer.	
	2. Move couch to patient imaging position with volunteer positioned in accordance with department lung cancer patient protocol.	
Free breathing session	3. Create a New Patient under the name "AV TEST" and start Free Breathing session	
	4. After four minutes stop respiratory session and save session	
AV biofeedback session	5. Acquire a new waveguide, and commence a new respiratory session.	
	6. After 1 minute, ask volunteer if breathing-guide is OK. If not modify waveguide based on volunteer comments (increase/decrease waveguide amplitude/period) and start respiratory session with modified waveguide.	
	7. After loading new waveguide (or not, depending on volunteer comments), have volunteer follow AV biofeedback for four minutes. Stop session and save data.	
AV biofeedback Analysis and Decision Form	8. Analyse and save the Free Breathing and AV biofeedback breathing sessions using 'Analyse'.	
	9. Fill in and save Breathing Decision Form	
Data retrieval	10. Save the following data to the database allocated by [site data manager]: a. RPM breathing files	
	b. AV biofeedback software breathing files	
	c. Respiratory Analysis images	
	d. Decision Form	
	11. University of Sydney researchers received saved data?	

_____	_____	_____
Site credentialing name	Signature	Date
_____	_____	_____
RPL name	Signature	Date

Linac room - Volunteer		
Action	**Steps**	**Success (y/n)** ***If 'no', detail why***
AV biofeedback system setup	1. Setup AV biofeedback system and motion phantom	
	2. Move couch to patient treatment position with volunteer positioned in accordance with department lung cancer patient protocol.	
AV biofeedback session	3. Load existing "AV TEST" patient and load their waveguide. a. Record start and finish times of imaging from AV biofeedback software.	
	4. After four minutes, end respiratory session and save session	
Data retrieval	5. Save the following data to the database allocated by [site data manager]: a. RPM breathing files	
	b. AV biofeedback software breathing files	
	6. University of Sydney researchers received saved data?	

_____	_____	_____
Site credentialing name	Signature	Date

_____	_____	_____
RPL name	Signature	Date

Last Updated: 26th February 2015

AVIATOR Site Credentialing

Prior to commencing patient recruitment patient, each site needs to complete the following credentialing, please tick off as completed:

CREDENTIALING ITEM	COMPLETE
1) Pass AV biofeedback Daily & Monthly QA using motion phantom in the: a) CT imaging room	
b) Treatment room	
1) Simulate CT imaging and treatment sessions with a volunteer in the: c) CT imaging room (complete Analysis and Decision Form as well)	
d) Treatment room	
2) Anonymised data transferred to University of Sydney secure storage	

Once the above Credentialing points have been completed and signed off by a member of the Radiation Physics Laboratory, that site is open to patient recruitment.

Required Documentation to complete this Credentialing:

- AV biofeedback QA (version 3 – 'Breathe Well')
- Patient questionnaire
- Staff questionnaire
- Session information form

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AV biofeedback system components (version 7.1)

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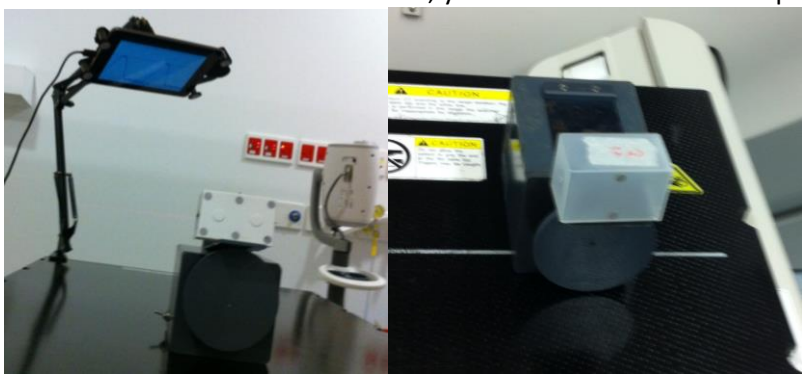


The motion phantom dry run is performed in both the CT sim room and linac room, the workflow and checklist needs to be completed individually for each room.
At the start of the study, each patient will have been given a study ID number, use this number as the patient name in AV biofeedback software to create a New Patient, and for reference for when you load an Existing Patient.

CT sim room - Phantom		
Action	**Steps**	**Success (y/n)** ***If 'no', detail why***
AV biofeedback system setup	1. Setup AV biofeedback system and motion phantom.	
	2. Move couch to patient imaging position with motion phantom in place at the typical position of a patient's abdomen.	
	3. Setup has adequate clearance of imaging bore?	
AV biofeedback Quality Assurance	4. Complete AV biofeedback Daily QA	
	5. Complete AV biofeedback Monthly QA	
Imaging with AV biofeedback	6. Perform 4D-CT scan as per department protocol with the AV biofeedback system running.	
	7. Stop Session and save data	
Data retrieval	8. Save the following data to the database allocated by [site data manager]: a. RPM breathing files	
	b. Image files	
	c. AV biofeedback software breathing files	
	9. University of Sydney researchers received saved data?	

_____	_____	_____
Site credentialing name	Signature	Date

_____	_____	_____
RPL name	Signature	Date

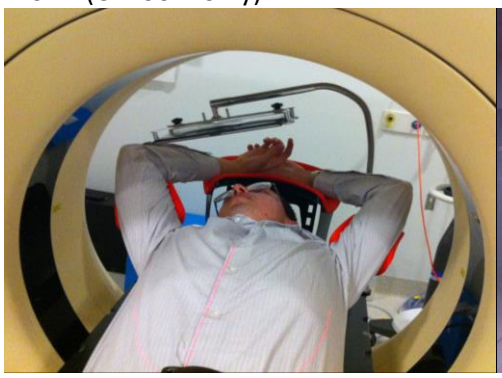
Linac room - Phantom		
Action	**Steps**	**Success (y/n)** ***If 'no', detail why***
AV biofeedback system setup	1. Setup AV biofeedback system and motion phantom.	
	2. Move couch to patient treatment position with motion phantom in place at the typical position of a patient's abdomen.	
	3. Rotate the gantry 360° about the couch. Setup has adequate clearance of gantry?	
AV biofeedback Quality Assurance	4. Complete AV biofeedback Daily QA	
	5. Complete AV biofeedback Monthly QA	
Imaging/ treatment with AV biofeedback	6. Perform CBCT scan (if linac has OBI) as per department protocol with the AV biofeedback system running. a. Record start and finish times of imaging from AV biofeedback software.	
	7. Stop Session and save data	
Data retrieval	8. Save the following data to the database allocated by [site data manager]: a. RPM breathing files	
	b. Image files	
	c. AV biofeedback software breathing files	
	9. University of Sydney researchers received saved data?	

_____	_____	_____
Site credentialing name	Signature	Date

_____	_____	_____
RPL name	Signature	Date

Dry-run with a volunteer

These volunteer tests will test the setup compatibility with department equipment, and incorporation of AV biofeedback procedures into department protocol as well as performing breathing session analysis and decision form (CT room only).




The volunteer dry run is performed in both the CT sim room and linac room, the workflow and checklist needs to be completed individually for each room.

CT sim room - Volunteer		
Action	**Steps**	**Success (y/n)** ***If 'no', detail why***
AV biofeedback system setup	1. Setup AV biofeedback system and couch for lung cancer patient imaging, with volunteer.	
	2. Move couch to patient imaging position with volunteer positioned in accordance with department lung cancer patient protocol.	
	3. Setup has adequate clearance of imaging bore?	
Free breathing session	4. Create a New Patient under the name "AV TEST" and start Free Breathing session.	
	5. After four minutes stop respiratory session and save session	
AV biofeedback session	6. Acquire a new waveguide, and commence a new respiratory session.	
	7. After 1 minute, ask volunteer if breathing-guide is OK. a. If not, edit waveguide accordingly.	
	8. After loading new waveguide (or not, depending on volunteer comments), have volunteer follow AV biofeedback for four minutes. Stop session and save data	
AV biofeedback Analysis and Decision Form	9. Analyse and save the Free Breathing and AV biofeedback breathing sessions using 'Analyse'	
	10. Fill in and save Breathing Decision Form.	
Data retrieval	11. Save the following data to the database allocated by [site data manager]: a. RPM breathing files	
	b. AV biofeedback software breathing files	
	c. Respiratory Analysis images	
	d. Decision Form	

	12. University of Sydney researchers received saved data?	

_____	_____	_____
Site credentialing name	Signature	Date
_____	_____	_____
RPL name	Signature	Date

Linac room - Volunteer		
Action	**Steps**	**Success (y/n)** ***If 'no', detail why***
AV biofeedback system setup	1. Setup AV biofeedback system and motion phantom	
	2. Move couch to patient treatment position with volunteer positioned in accordance with department lung cancer patient protocol.	
	3. Rotate the gantry 360° about the couch. Setup has adequate clearance of gantry?	
AV biofeedback session	4. Load existing "AV TEST" patient and load their waveguide a. Record start and finish times of imaging from AV biofeedback software.	
	5. After four minutes, end respiratory session and save session	
Data retrieval	6. Save the following data to the database allocated by [site data manager]: a. RPM breathing files	
	b. AV biofeedback software breathing files	
	7. University of Sydney researchers received saved data?	

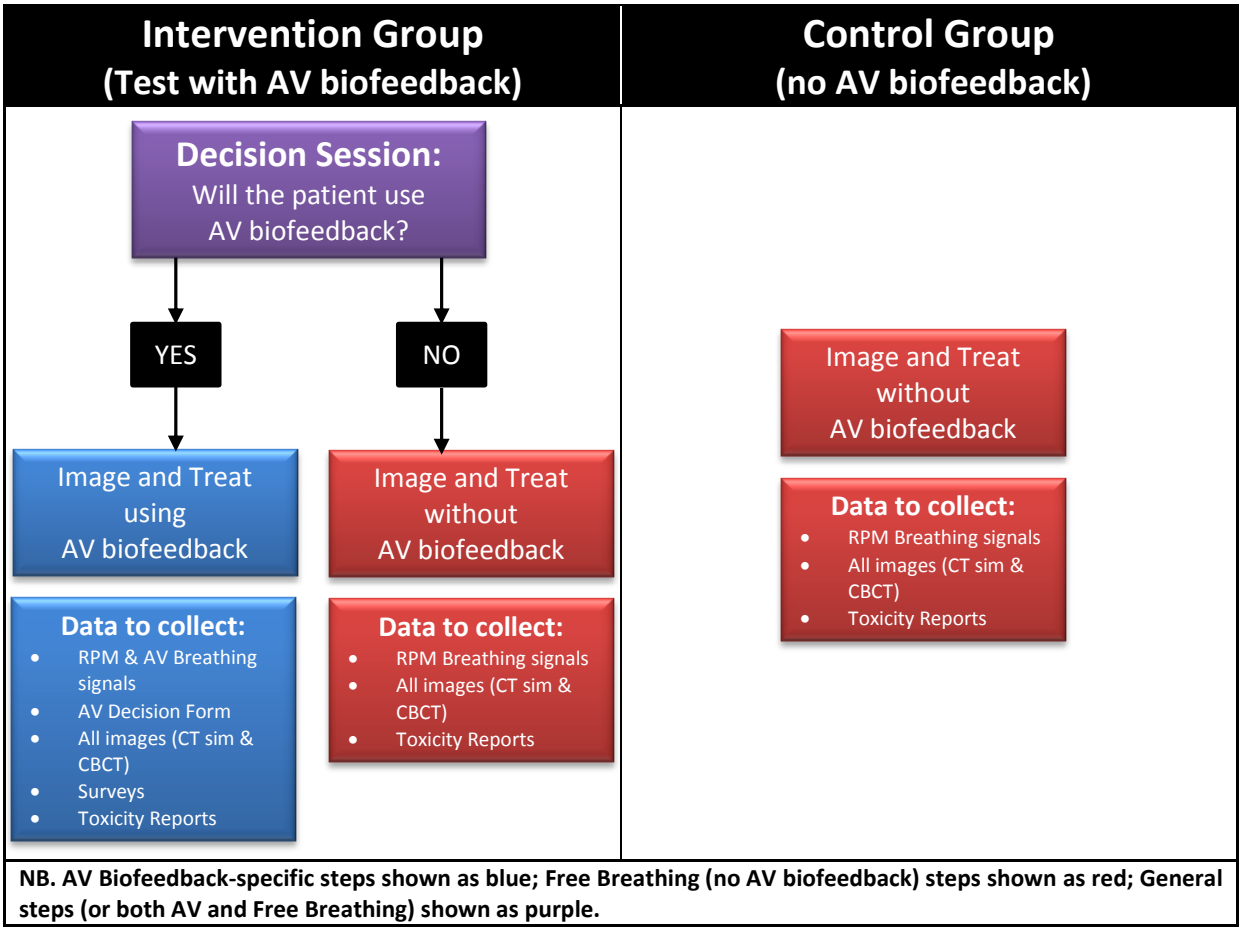
_____	_____	_____
Site credentialing name	Signature	Date
_____	_____	_____
RPL name	Signature	Date

Last Updated: 27th February 2015

AVIATOR Clinical Workflow

1. General Workflow

The AVIATOR study is a randomised clinical trial, as such, not all patients will be using the breathing-guidance system: audiovisual (AV) biofeedback. Once an eligible patient has been identified, the Canberra Hospital data manager will contact the University of Sydney Randomisation group to know which study group each patient will be allocated to as well as receiving that patient's Trial ID number. Below are the general workflows for two AVIATOR study groups:



NB. AV Biofeedback-specific steps shown as blue; Free Breathing (no AV biofeedback) steps shown as red; General steps (or both AV and Free Breathing) shown as purple.

What follows is an outline for each of these steps.
For more details on AV Biofeedback see documents:

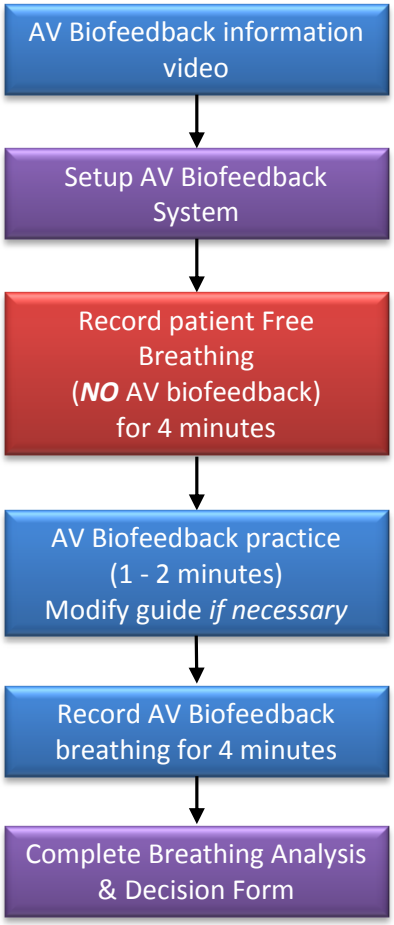
- User Guide (Version 4-2)
- AVIATOR Protocol (Version 5)
- BreatheWell QA (Version 3-1)

2. Intervention Group

The AVIATOR trial is randomised in a 2:1 ratio meaning that for every 3 patients that are recruited into the study, 2 of them will be allocated to the intervention group to be tested with AV biofeedback while 1 in 3 are allocated to the control group. The advantage of using AV biofeedback is that their breathing becomes more regular; however, to ensure that this is the case, each patient will undergo a Decision Session prior to their CT sim and treatment to determine whether AV biofeedback is the best option for them. Once Randomisation has been performed the patient will receive a 'Trial ID', use this number to label and save the relevant AVIATOR trial data.

2.1. Decision Session

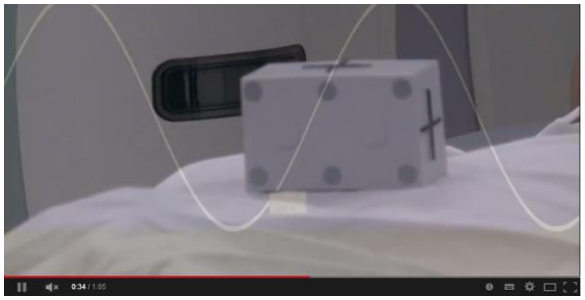
There are cases where patients naturally have regular breathing, or have difficulty following the AV biofeedback guide, so a Decision Session will be performed to determine whether it is best to use AV biofeedback for each patient. The general workflow of the Decision Session is below:



What follows are the details and user guide for each of the above processes.

2.1.1 AV Biofeedback information video

A brief (~1 minute) information video has been made to inform the patients about what AV Biofeedback is and what they will be required to do to follow it. Have the patient watch the video on the research computer before they go into the CT sim room and answer any question that they may have (video file should be on the research computer's desktop).



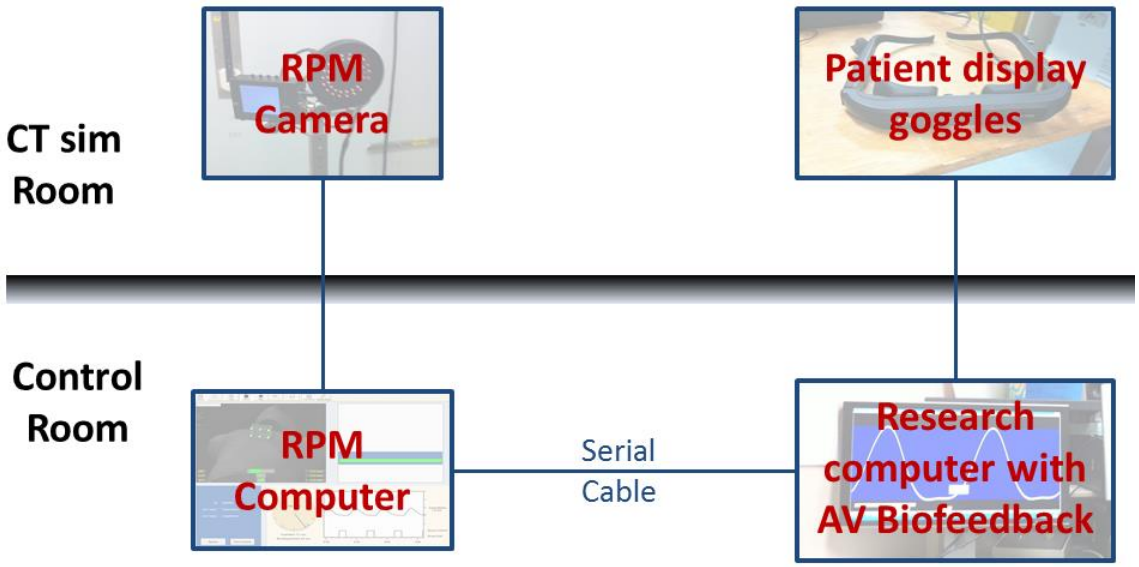
Screen shot from information video

2.1.2 Setup AV Biofeedback System

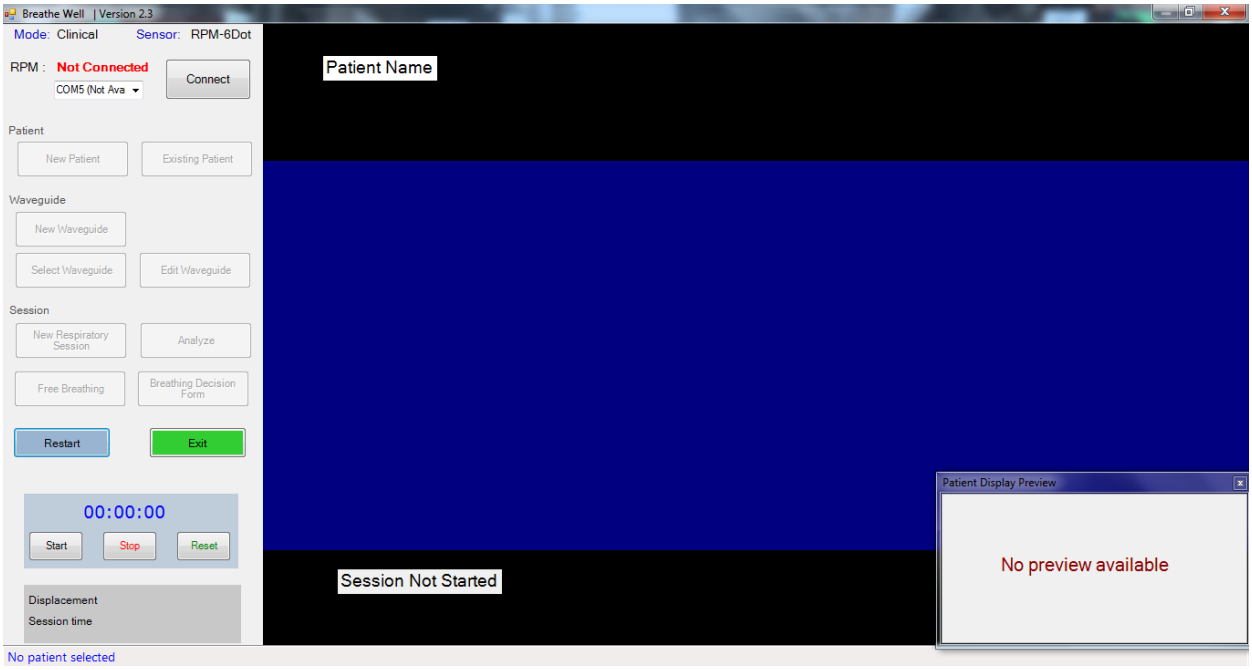
Equipment needed:

- Research computer with AV Biofeedback software (called 'BreatheWell) installed
- Audio-visual (AV) display goggles
- RPM System
- Cabling

Schematic of the setup is shown below:



Open up AV Biofeedback using the 'Breathe Well' desktop icon on the Research computer:
You will see the initial AV Biofeedback screen:

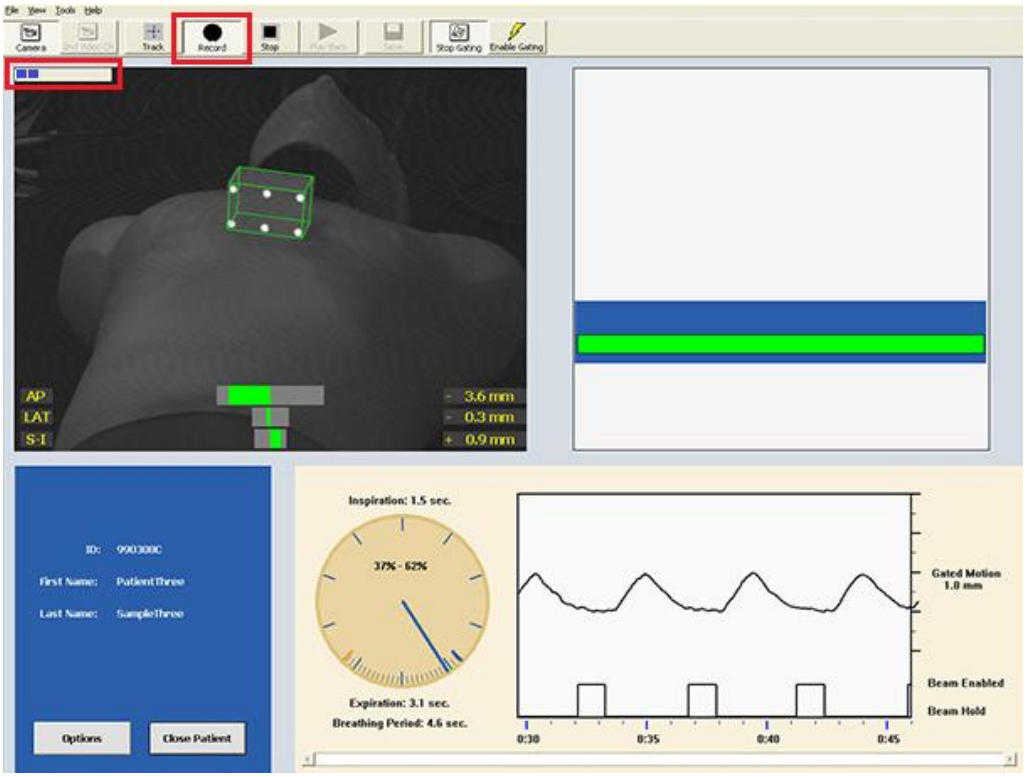


If the *Patient Display Preview* reads “No preview available” (like it does above) it means that the display goggles are not properly connected to the AV biofeedback computer.
The functions to perform on the Breathe Well software (in order) are:

1) Connect to RPM
2) Create New Patient / Load Existing Patient
3) Create New Waveguide / Load Existing Waveguide
4) New Respiratory Session
5) Analyze
6) Breathing Decision Form

Once the patient is on the couch ensure that the RPM is both tracking AND recording the RPM marker block motion. In the RPM screenshot on the following page, the Record button is highlighted and a bar containing blue blocks is highlighted. Once the number of blue blocks on the bar is 3 or fewer, click ‘Record’.

If there are more than 3 blue blocks it means that the phase calculation is not performing optimally, and errors can occur in the Breathe Well software if the number of blue blocks exceeds 3 for an extended period of time.

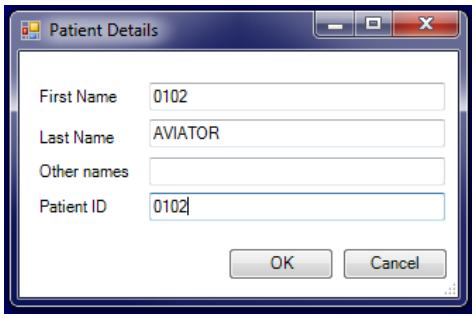


Screen shot of RPM. There are fewer than 3 blue blocks present on the highlighted bar, so it's good to Record.

Once the RPM is recording the breathing signal, in the Breathe Well software click 'Connect' to start receiving the RPM breathing signal (if unsuccessful, try a different COM# from the dropdown menu in the Breathe Well software and click 'Connect' again).

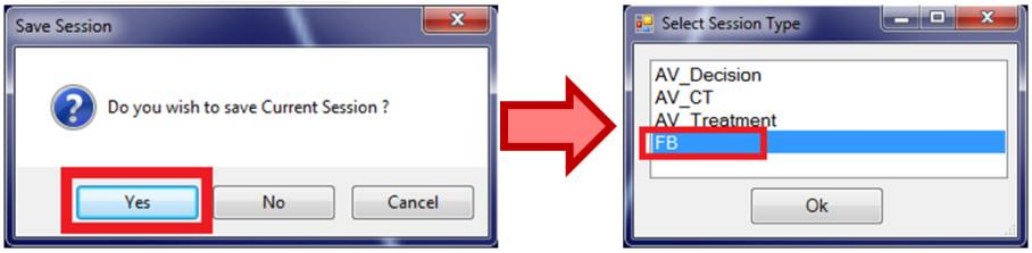
2.1.3. Record Patient Free Breathing

Once connected to the RPM, click 'New Patient' and enter Trial ID (received with the Randomisation call) as their first name, 'AVIATOR' as their last name, and their Trial ID again as the Patient ID:

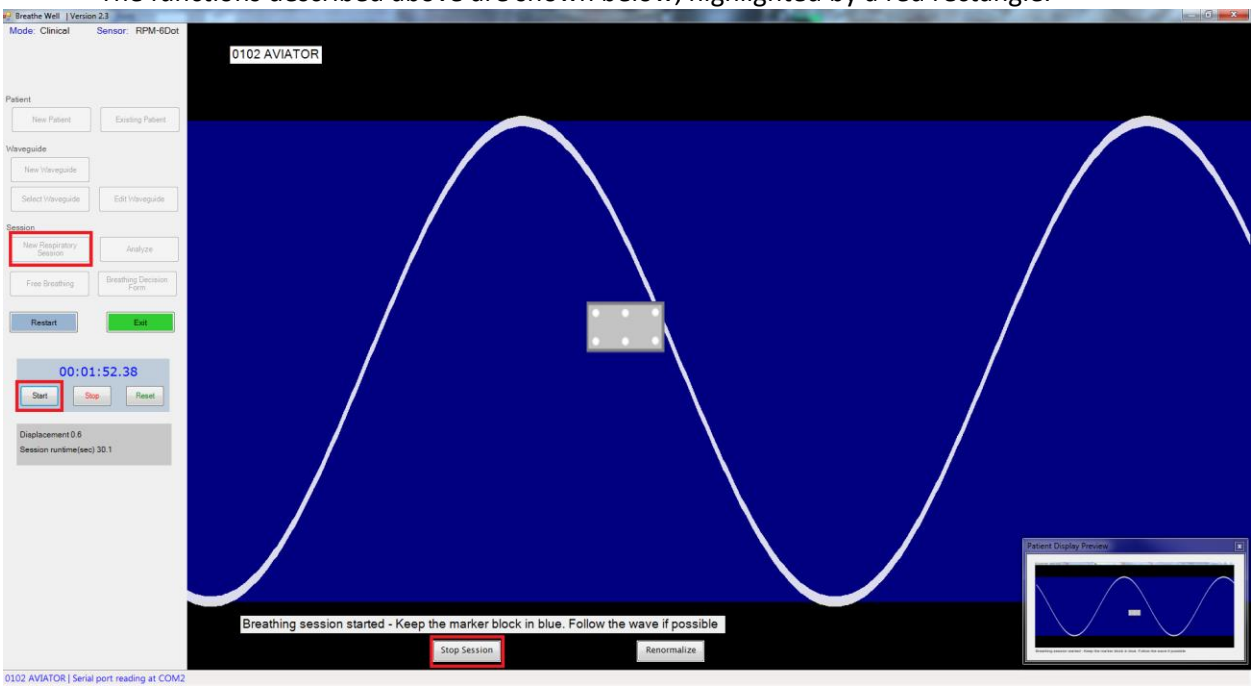


Do ***not*** have the patient wear the display goggles at this point and ensure that the music is **muted**. It is important that they breathe as naturally as possible without instruction.

- After you have created a New Patient file, click 'New Waveguide', this will acquire 10 breaths to and calculate the average of these to create the waveguide, and save it without any modifications.
- Click 'New Respiratory Session' and once the wave appears on the screen click 'Start' on the stopwatch panel:
- At 4 minutes click 'Stop Session' and save the data as 'FB':



- The functions described above are shown below, highlighted by a red rectangle.



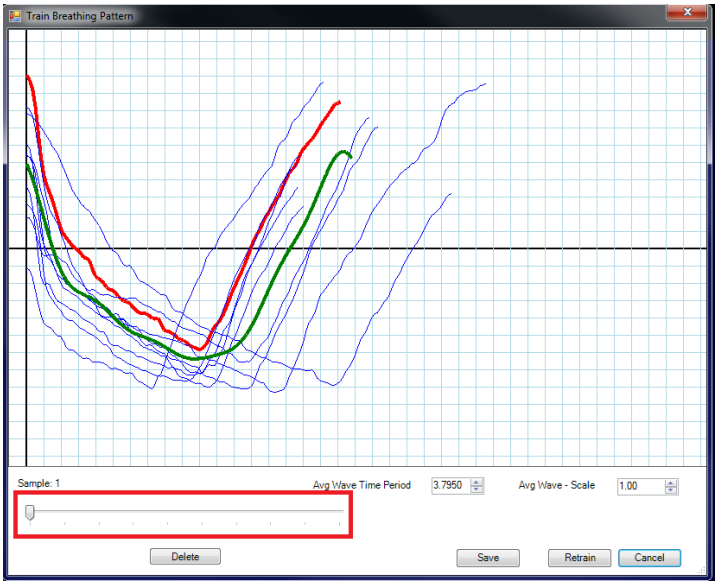
- After the session has been saved, click ‘Analyse’, this will analyse the session you just saved
- In the analysis screen, click ‘Save’ and then close the analysis screen.
- Click ‘Reset’ in the Breathe Well software
- Stop and save in the RPM software, then re-track and record in preparation for the AV biofeedback session.

<u>This concludes the Free Breathing Session.</u>

2.1.4. AV Biofeedback Practice

With the RPM tracking and recording the signal, now the patient wears the display goggles and unmute the audio. In the Breathe Well software:

- Connect to RPM
- Click 'Existing Patient' and select the correct 'Trial ID AVIATOR' patient
- Click 'New Waveguide', AV Biofeedback will acquire 10 breaths before displaying them to you:

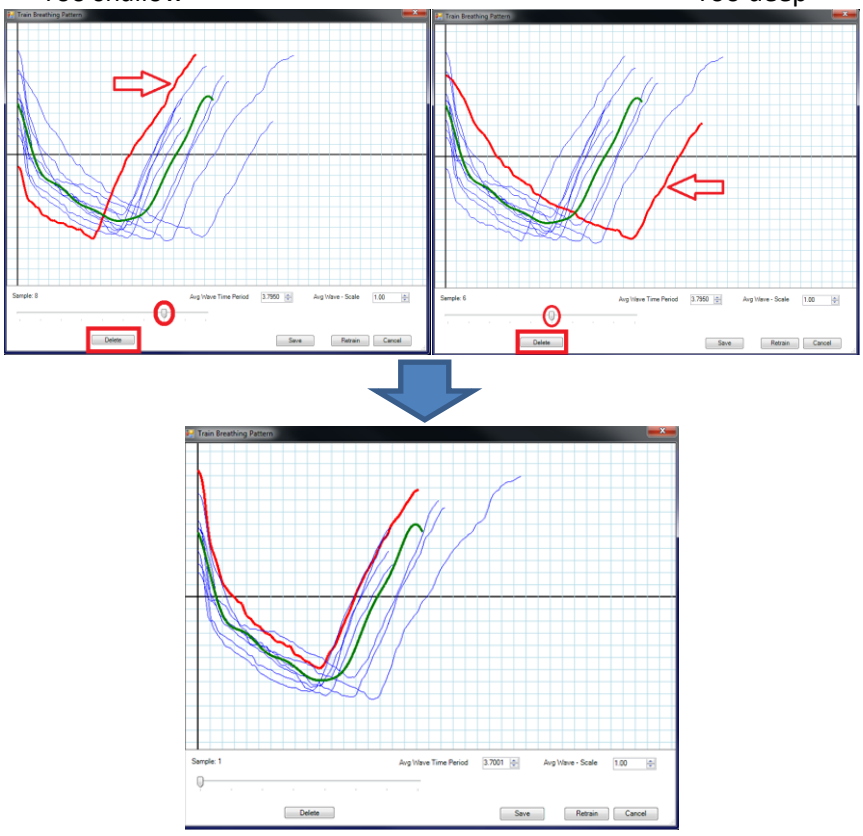


Blue curves: each of the 10 acquired breathing cycles
Red curve: a selected blue curve
Green curve: the average of the blue curves, which will be displayed as the waveguide
The slider-bar (highlighted by the red rectangle) underneath the curves scrolls through each of the 10 cycles.

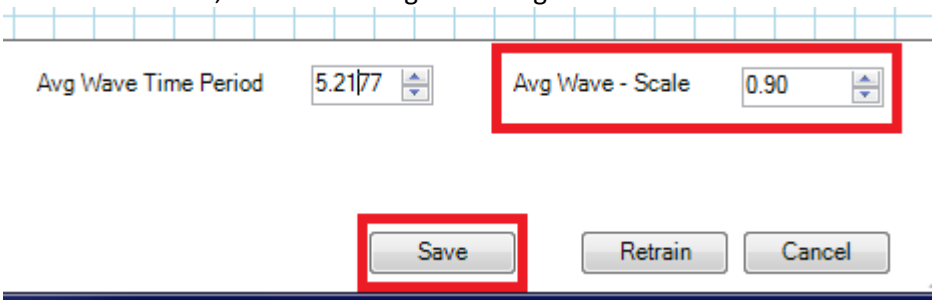
If there are any outlier breathing cycles not representative of their "normal" breathing (e.g. overly-deep breaths, coughs, yawns, etc.) select them using the slider-bar and delete them:

Too shallow

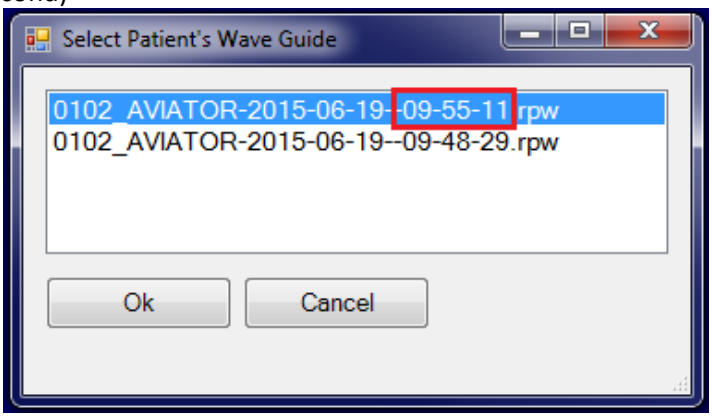
Too deep



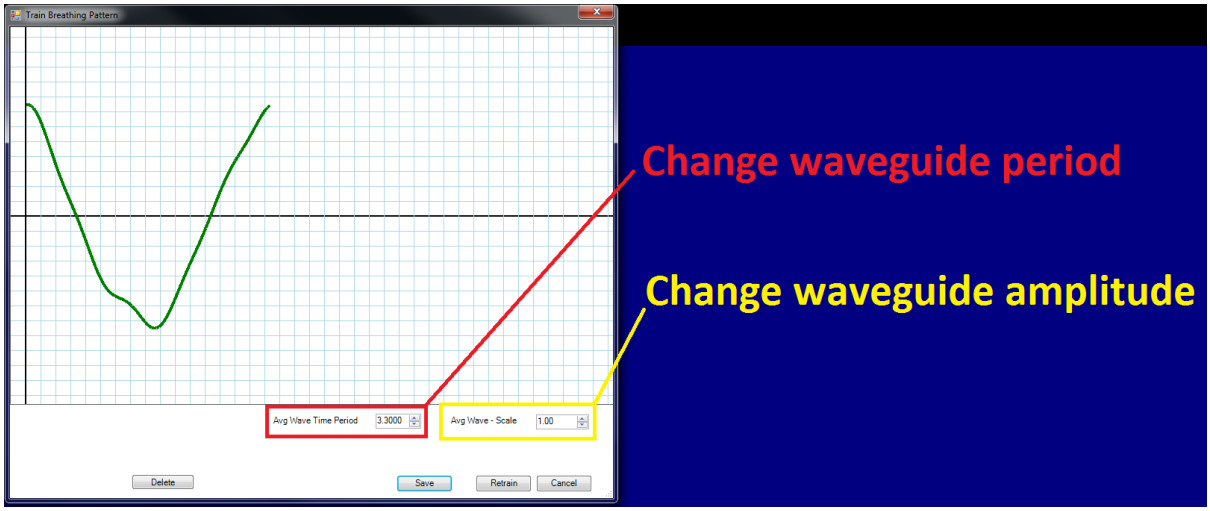
- An issue with making patients conscious of their breathing is that they tend to put more effort in to their breathing, inadvertently breathing slightly more deeply than they usually would.
    - To counter this, scale the waveguide's 'Avg Wave – Scale' from 1.0 down to 0.9



- The 'Avg Wave Time Period' (given in seconds) can also be modified if it exceeds the limits of 4D-CT reconstruction (e.g. 10 breaths per minute: 6 seconds).
- Save this waveguide
- Next click 'Select Waveguide' and select the one you just saved (most recently saved files appear at the top of the list – time the file was created highlighted with red rectangle: hour:minute:second)

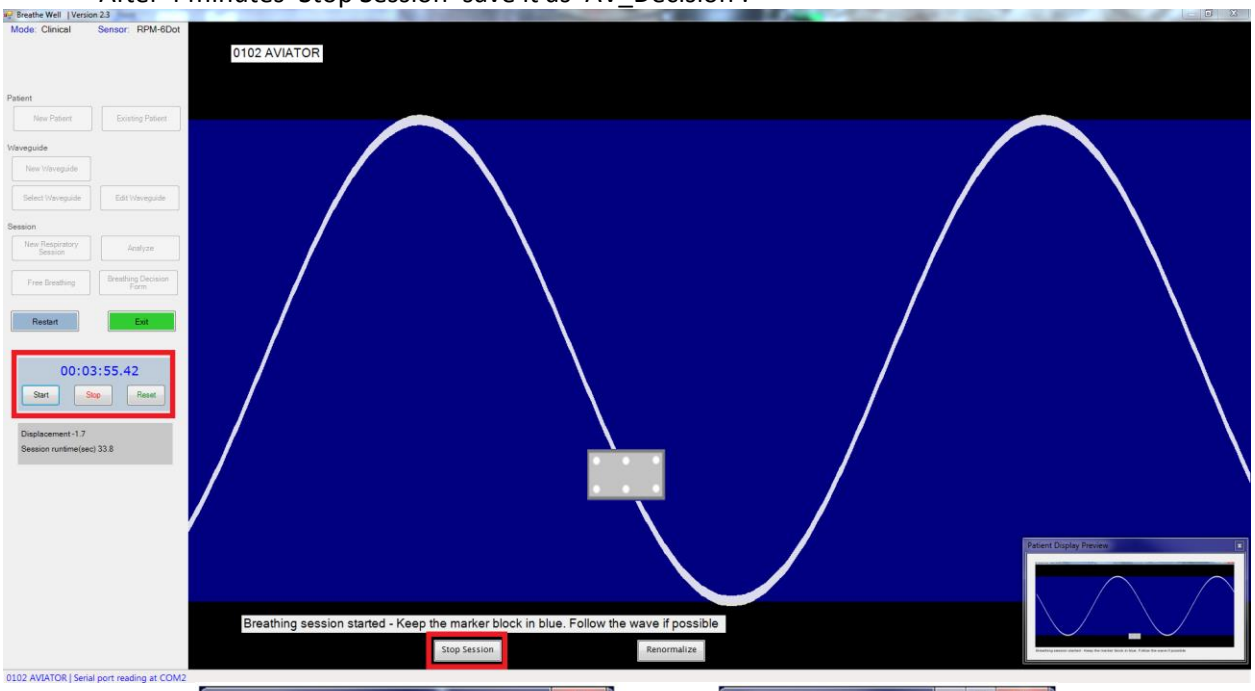


- Click 'New Respiratory Session', this will commence AV biofeedback guided breathing. After a brief calculation of mean position the waveguide will appear and the music will begin to play.
- Give the patient 1 minute to attempt the AV biofeedback guidance (use the sidebar stopwatch if necessary). Are there any issues?
    - Is the patient having difficulty staying within the blue region?
    - Is the patient having difficulty following the waveguide? (Is it too fast? Too slow?)
- If points a) and/or b) are issues, then a modification of the waveguide may be necessary: click Reset → Existing Patient → Edit Waveguide and select the recently acquired Waveguide you wish to modify
- This will bring up the selected waveguide and options to modify it:

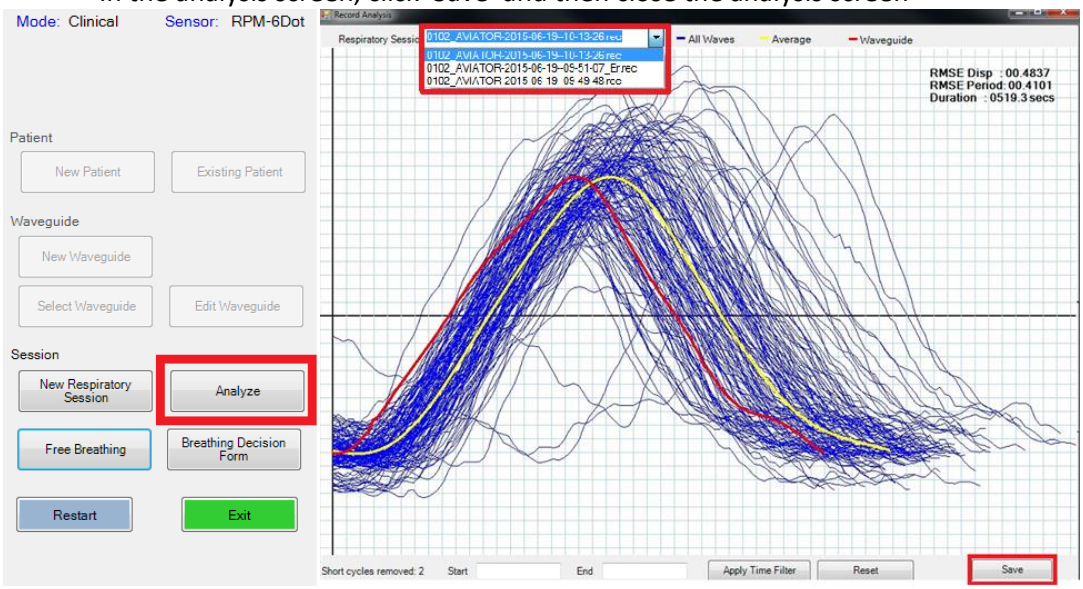


- If patient consistently moved outside of the blue region, increase Waveguide Amplitude (it's a scaling factor, so changing it from 1.0 to 1.2 will yield a waveguide with 1.2×Amplitude).
  - OR if the patient remained well within the blue region, perhaps decreasing the amplitude from 1.0 to 0.8 may be more appropriate
- If patient found the waveguide to move too fast, increase Waveguide Period
- If patient found the waveguide to move too slow, decrease Waveguide Period
- Only minor modifications to these numbers should achieve the desired result.
- Save modified waveguide

- Click 'New Respiratory Session'; after a brief moment to position the marker in the correct position, the breathing session will commence.
- Once the white waveguide appears on the screen (and the music commences) click 'Start' on the sidebar stopwatch.
- After 4 minutes 'Stop Session' save it as 'AV_Decision':



- After the session has been saved, click ‘Analyse’, this will analyse the session you just saved
- In the analysis screen, click ‘Save’ and then close the analysis screen

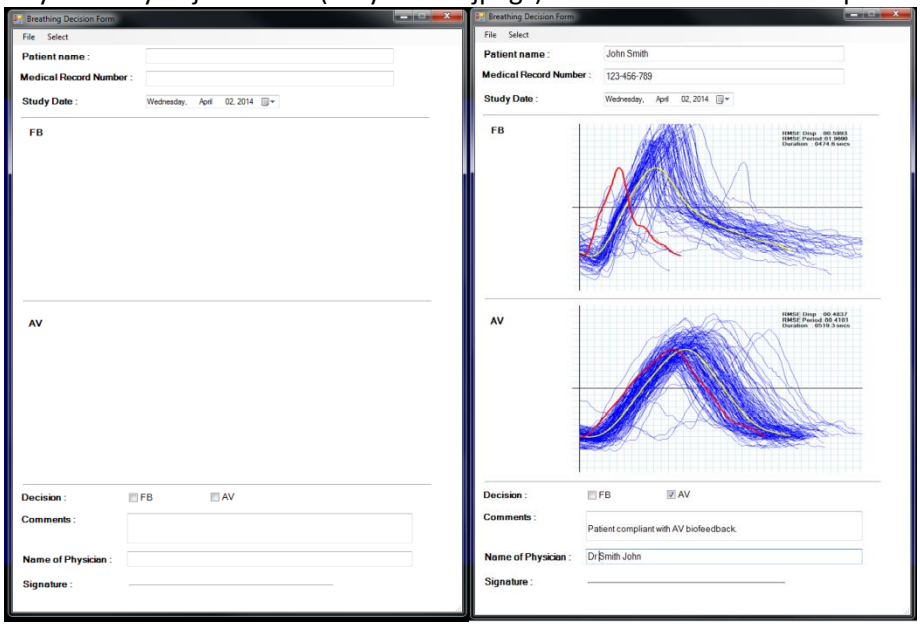


- Stop and save in the RPM software.
- *Aside: in the analysis form, the blue curves are each individual breath, the red curve is the waveguide, and the yellow curve is the average curve based on all the blue breaths*
    - *RMSE Disp is a measure of how much all the breaths vary from this average curve*

<u>This concludes the AV Biofeedback Session</u>

2.1.5. Breathing Decision Form

- Now that both breathing sessions have been performed and both sessions have been analysed and saved click 'Breathing Decision Form'
- This will bring up the Decision Form window, select the AV biofeedback (AV) and Free Breathing (FB) analysis files you just saved (they will be jpegs) and fill in the rest of the patient details:



Breathing Decision Form.
Left: Unfilled. Right: Complete.

Note: Enter the same patient name and ID information here as you did in creating a new patient file (Trial ID and AVIATOR).

Decisions are made by which breathing session has the lower '**RMSE Disp**' value. In this instance, the AV biofeedback session was more regular (RMSE Disp (AV) = 0.48, less than RMSE Disp (FB) = 0.59).

There is no threshold for how much less the RMSE value needs to be to make the decision (e.g. if RMSE Disp (AV) = 0.48, and RMSE Disp (FB) = 0.49, then AV would still be the decision).

Save the Decision Form as a PDF.

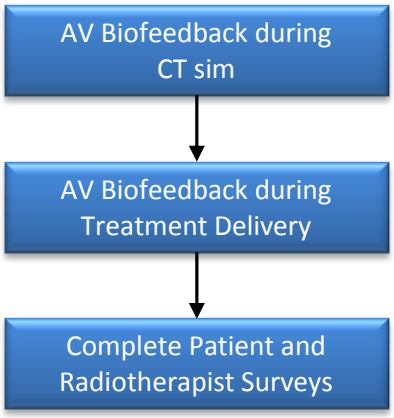
The entire Decision Session takes approximately 20-30 minutes to complete.

- If Decision Session is being performed on a different day to the CT sim, have the patient and the staff member who operated the Breathe Well software complete the patient and staff surveys
    - If Decision Session and CT sim session are being performed on the same day, wait until the CT sim is completed to perform the surveys.

This concludes the Decision Session.

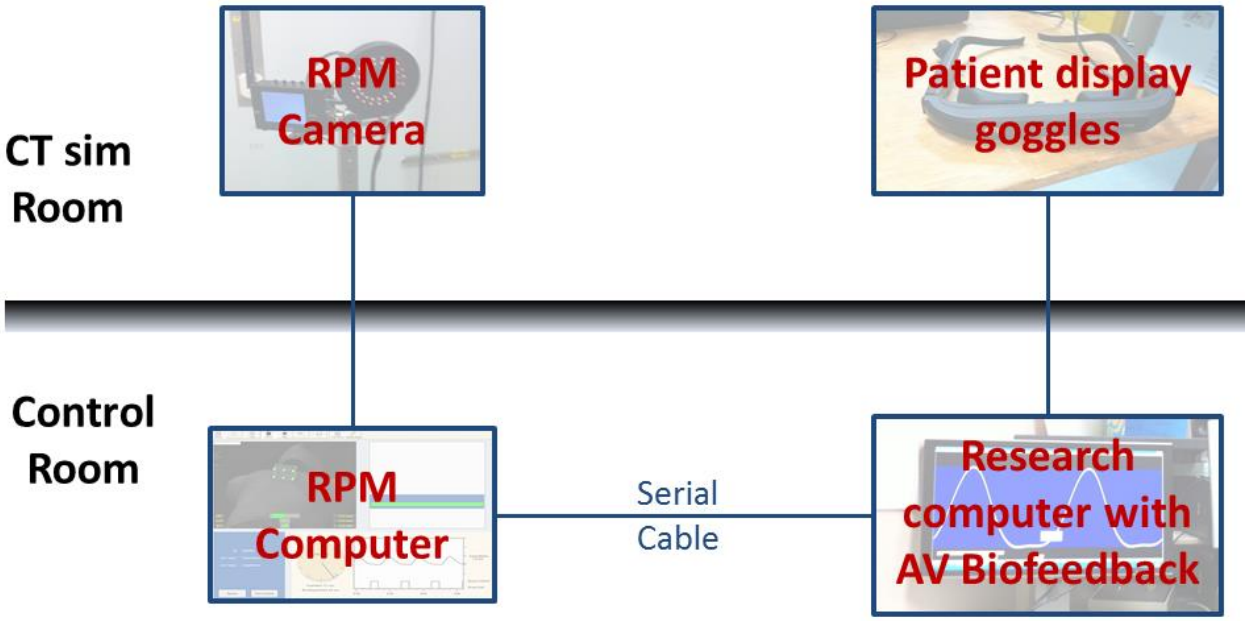
2.2. Image and Treat Using AV Biofeedback

Continuing on from the previous section, we will first address those patients for whom, based on the Decision Session, AV Biofeedback was selected to remain in their imaging and treatment.

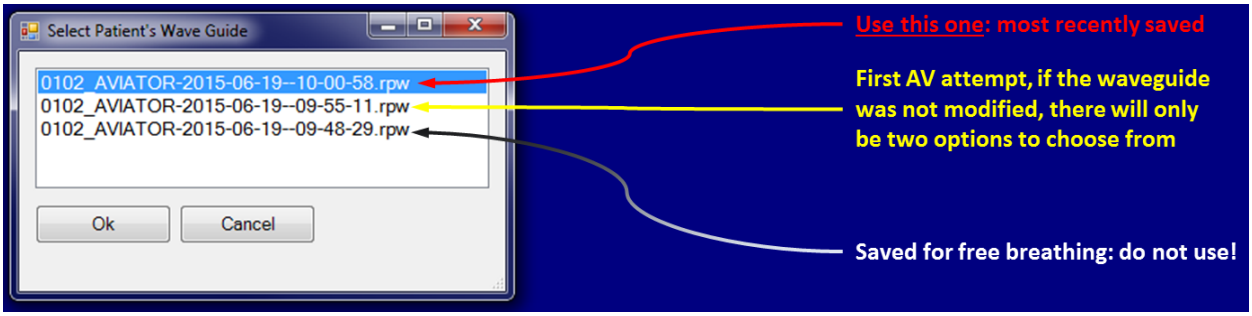


2.2.1. CT sim with AV Biofeedback

The setup here is the same as used for the Decision Session:

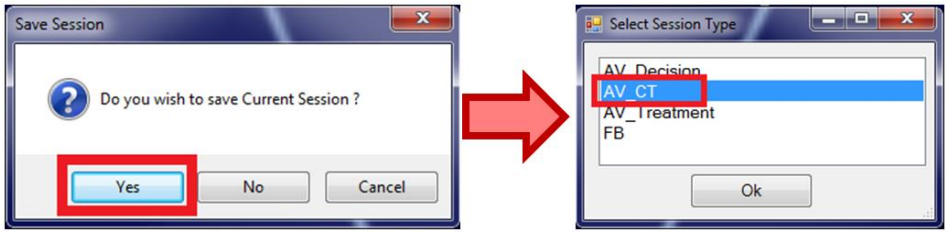


The purpose of AV Biofeedback is to not only facilitate regular breathing during imaging and treatment, but also across multiple imaging and treatment sessions, so it is important to **use the same Waveguide** as used in the 4 minute of AV biofeedback breathing in the Decision Session:



- Position patient as per department protocol in preparation for their CT sim

- Once in position, ensure patient is wearing display goggles and imaging and sound from AV Biofeedback computer is clear.
- Start a New Respiratory Session
    - **Select the correct Waveguide**
- After a brief moment to position the marker in the correct position, the breathing session will commence.
- Perform imaging as per department protocol.
- After imaging is complete, click 'Stop Session' and save data as 'AV_CT':

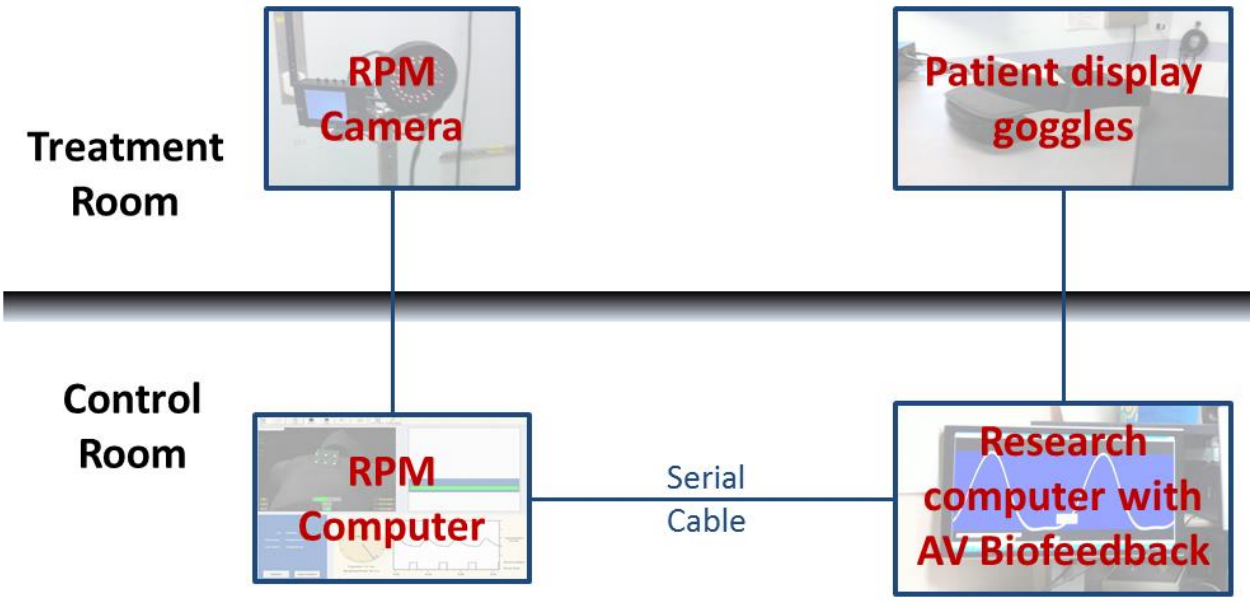


- Stop and save in the RPM software
- Also save:
    - CT sim images (DICOM data) [file location]
- It is important to save these files straight away, as they may be automatically deleted within days
- If Decision Session was performed on the same day as CT sim, have the patient and the staff member who operated the Breathe Well software complete the patient and staff surveys

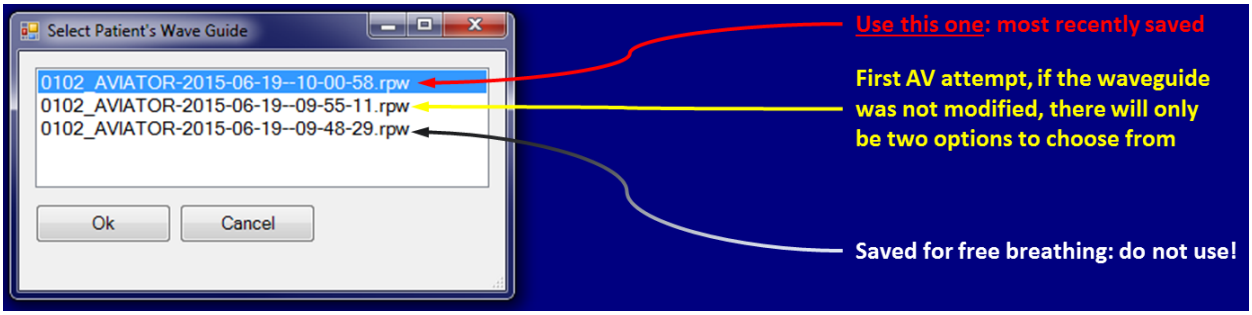
<u>This concludes the AV Biofeedback CT sim Session.</u>

2.2.2. Treatment Delivery with AV Biofeedback

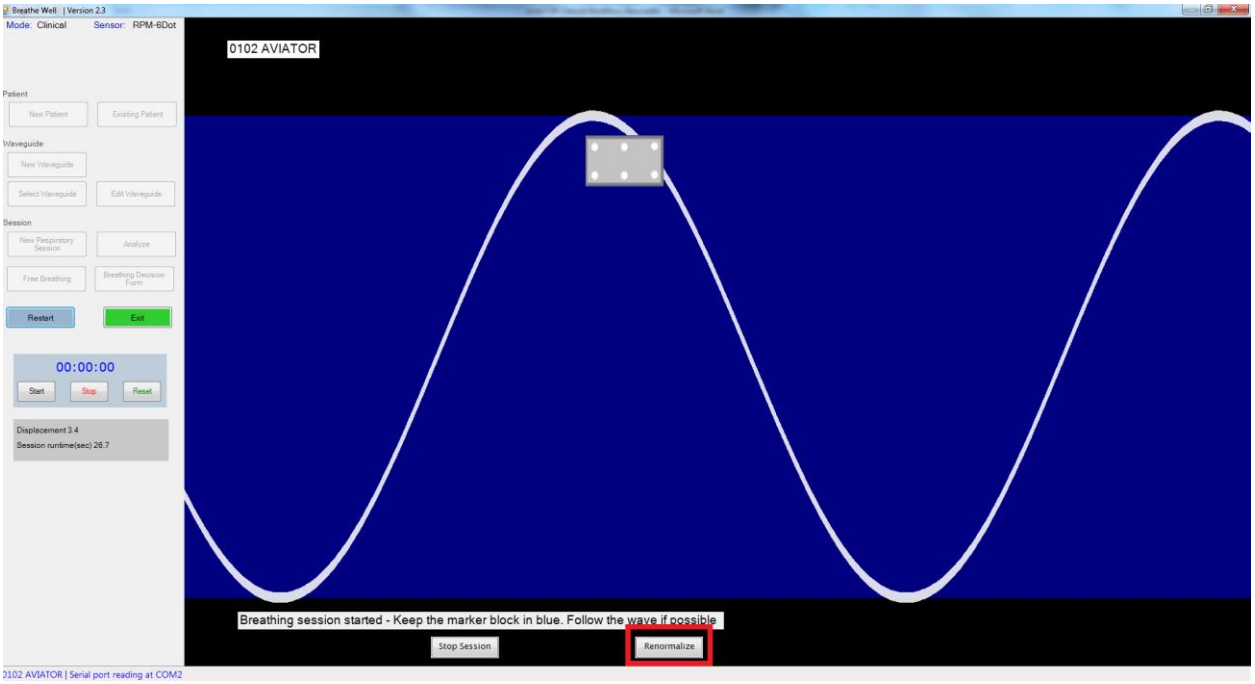
The setup here is similar to the setup used for the Decision and CT sim Sessions:



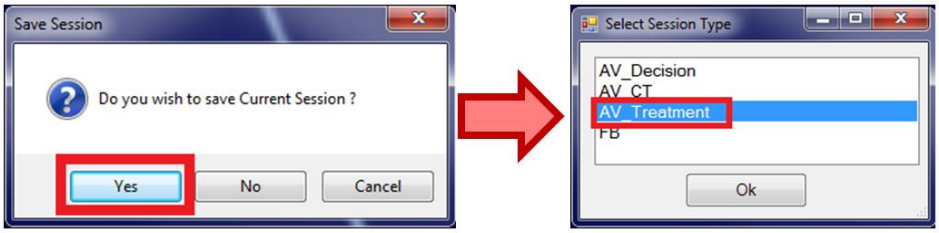
Use the same Waveguide as used in the 4 minutes of AV biofeedback breathing in the Decision Session, and then again in the CT sim Session.



- Position patient as per department protocol in preparation for treatment.
- Once in position, ensure patient is wearing display goggles and imaging and sound from AV Biofeedback PC is clear.
- Start a New Respiratory Session and select the correct Waveguide.
- After a brief moment to position the marker in the correct position, the breathing session will commence.
- Perform treatment delivery as per department protocol – ***regarding any couch shifts***:
    - After a couch shift, in the Breathe Well software click '***Renormalise'***, which repositions the marker-block at the centre of the AV biofeedback display because the couch shifts may have moved the marker-block off-screen
    - DO NOT click renormalise during any beam-on times
    - Renormalise will automatically save the breathing data, so after a treatment session and 'Renormalise' was clicked once, there will be two breathing data files for that one session.



- Once treatment is complete, click 'Stop Session' and save the data as 'AV_Treatment':



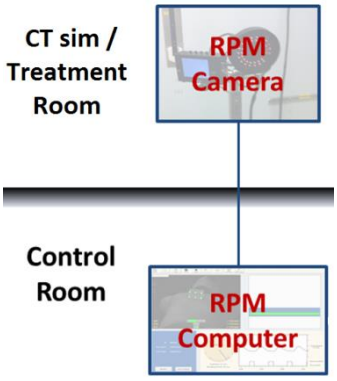
- Also save:
  - CBCT images (DICOM data) if used (if linac does not have on-board imaging, disregard this point)
  - RPM File [file location]
- It is important to save these files straight away, as they may be automatically deleted within days.

- If this is the final fraction of treatment, complete patient and staff surveys

<u>This concludes the AV Biofeedback Treatment Session</u>

2.3. Image and Treat with Free Breathing

In the event that the patient is randomised into the control arm, or in the event that 'RMSE Disp' for Free Breathing is less than the 'RMSE Disp' for AV Biofeedback in the Decision Session, then the AV Biofeedback system will not be used in their imaging and treatment, the setup will be as per department protocol, and it is important that the RPM system is used:



While AV Biofeedback will not be used, it is still important to save the following data for each CT sim and treatment fraction:

- RPM Breathing signals
- CT sim images
- CBCT images (if CBCTs are not acquired then disregard this point)

3. Control Group

Patients in the Control Group will have been identified as an eligible patient by the Radiation Oncologist, and then agreed to take part in the study. However, they have been randomised into the Control Group and will not be using AV Biofeedback. The setup, conduct of AVIATOR in the control group as well as the data to save will be the same as detailed in the previous section: '2.3. Image and Treat with Free Breathing'.

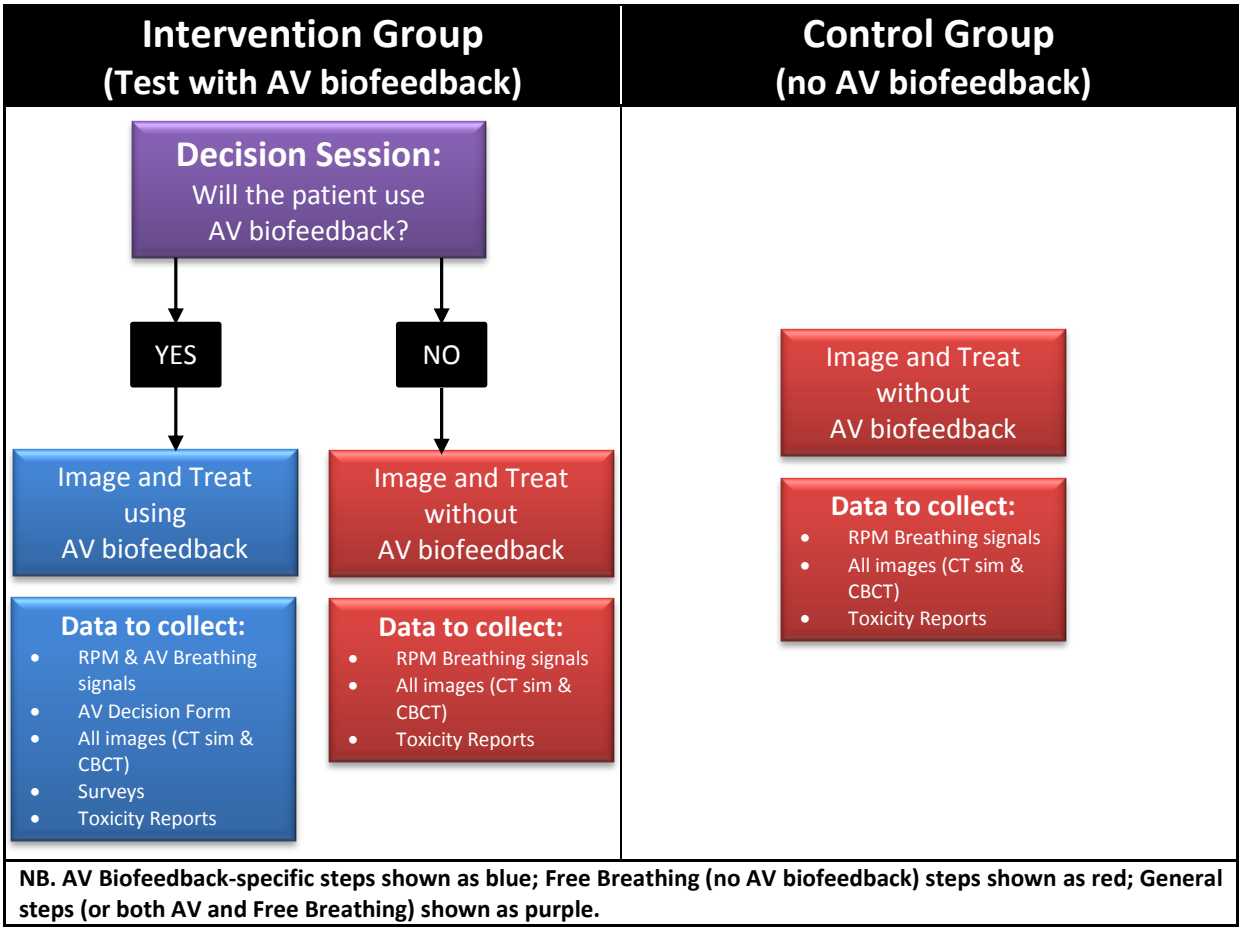
4. Post-Treatment Toxicity Report

As noted in the Flowcharts on page 1, a Toxicity Report is required for every patient regardless of their allocation to intervention or control groups.
With each patient follow-up visitation the Toxicity Report must be completed by the treating physician; this is done for each follow-up for up to 12 months after each patient has completed their treatment.
The completion of this Toxicity Report marks the conclusion of the AVIATOR trial for each patient.

AVIATOR Clinical Workflow

1. General Workflow

The AVIATOR study is a randomised clinical trial, as such, not all patients will be using the breathing-guidance system: audiovisual (AV) biofeedback. Once an eligible patient has been identified, Fiona Hegi-Johnson will contact the University of Sydney Randomisation group to know which study group each patient will be allocated to as well as receiving that patient's Trial ID number.
Below are the general workflows for two AVIATOR study groups:



NB. AV Biofeedback-specific steps shown as blue; Free Breathing (no AV biofeedback) steps shown as red; General steps (or both AV and Free Breathing) shown as purple.

What follows is an outline for each of these steps.
For more details on AV Biofeedback see documents:

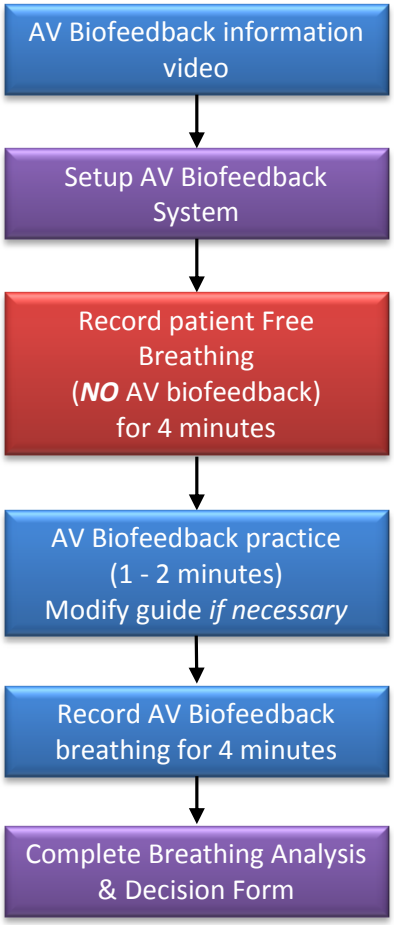
- User Guide (Version 4-1: Breathe Well)
- AVIATOR Protocol

2. Intervention Group

The AVIATOR trial is randomised in a 2:1 ratio meaning that for every 3 patients that are recruited into the study, 2 of them will be allocated to the intervention group to be tested with AV biofeedback while 1 in 3 are allocated to the control group. The advantage of using AV biofeedback is that their breathing becomes more regular; however, to ensure that this is the case, each patient will undergo a Decision Session prior to their CT sim and treatment to determine whether AV biofeedback is the best option for them. Once Randomisation has been performed the patient will receive a 'Trial ID', use this number to label and save the relevant AVIATOR trial data.

2.1. Decision Session

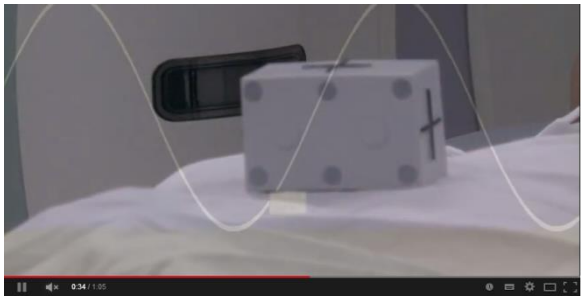
There are cases where patients naturally have regular breathing, or have difficulty following the AV biofeedback guide, so a Decision Session will be performed to determine whether it is best to use AV biofeedback for each patient. The general workflow of the Decision Session is below:



What follows are the details and user guide for each of the above processes.

2.1.1 AV Biofeedback information video

A brief (~1 minute) information video has been made to inform the patients about what AV Biofeedback is and what they will be required to do to follow it. Have the patient watch the video on the research computer before they go into the CT sim room and answer any question that they may have (video file should be on the research computer's desktop).



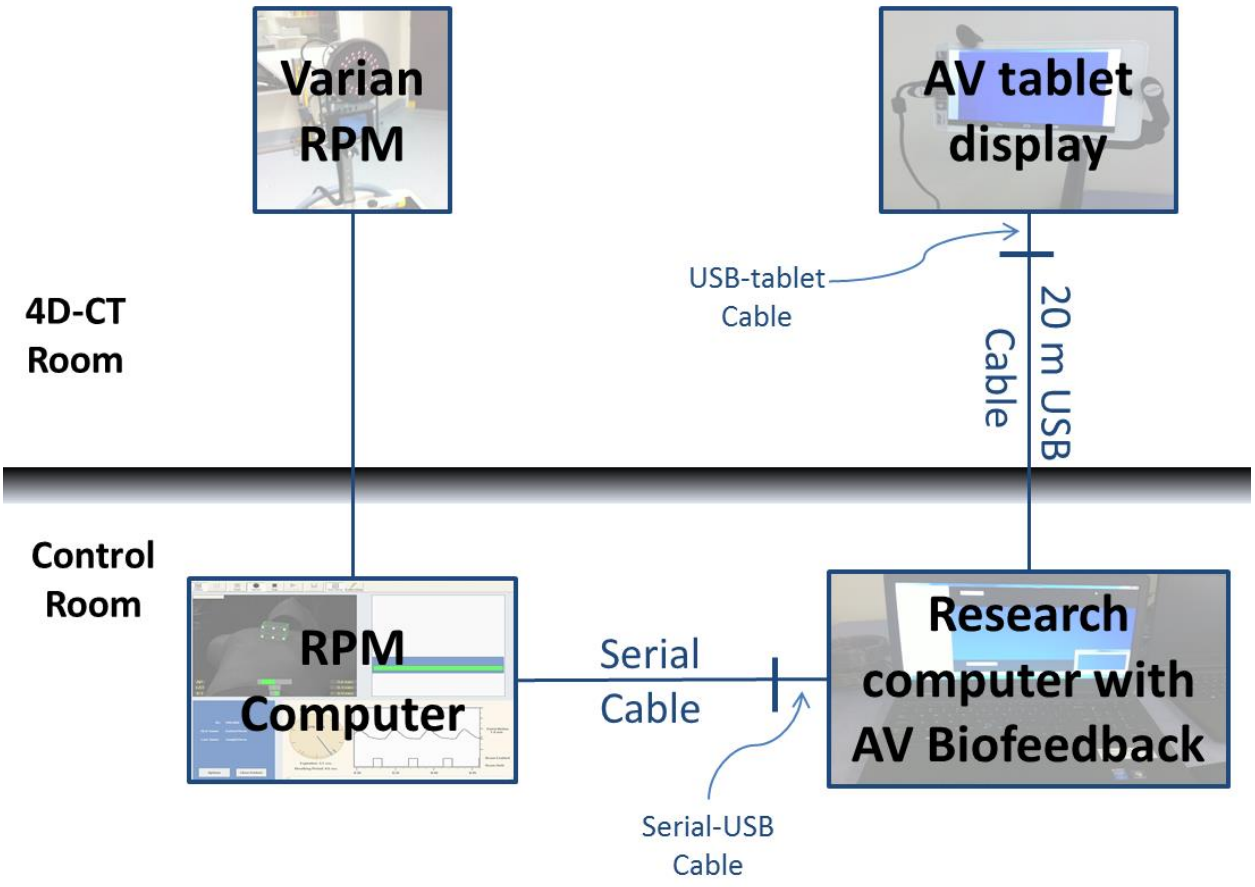
Screen shot from information video

2.1.2 Setup AV Biofeedback System

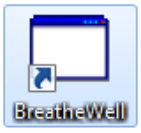
Equipment needed:

- Research laptop with AV Biofeedback software (called 'BreatheWell') installed
- Audio-visual (AV) screen/tablet
- RPM System
- Cabling:
    - Serial Cable
    - USB-to-Serial Cable
    - USB 20 m extension cable
    - USB-tablet cable

Schematic of the setup is shown below:



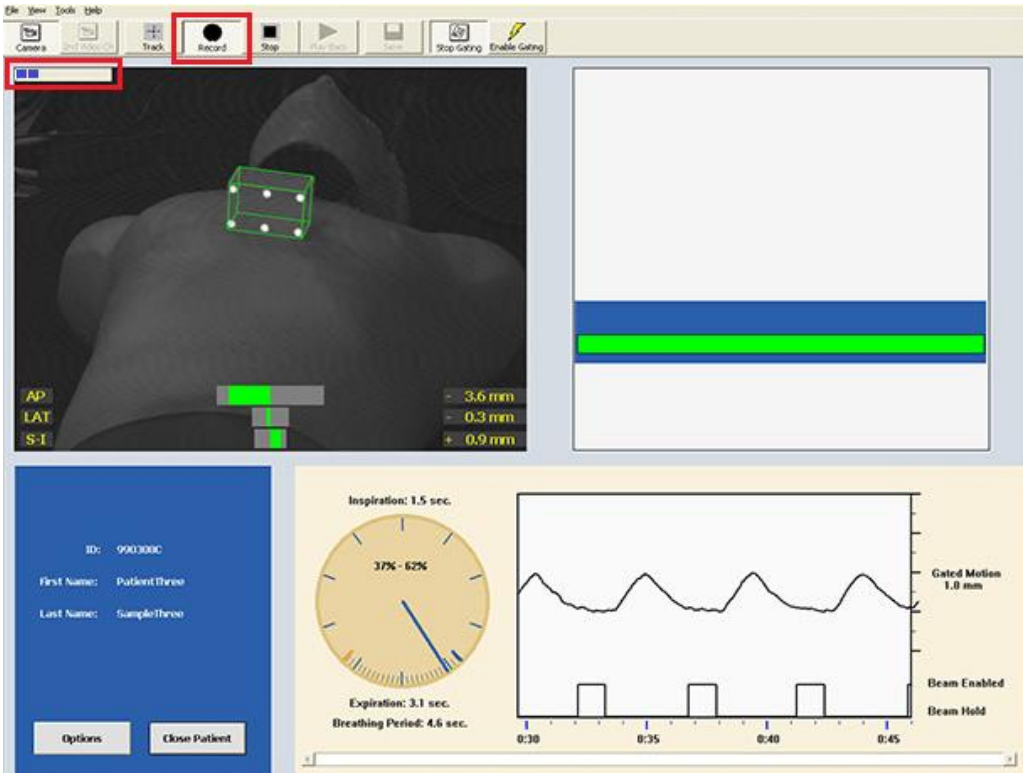
- Once connected, open iDisplay software on the research laptop: 

- Open up iDisplay on the tablet and press ‘connect via USB’, you should then see the laptop’s background on the tablet
    - Connecting the laptop to the tablet via iDisplay is quite sequence-sensitive. If an error occurs, the best solution is typically to close iDisplay on the laptop and tablet and try again.
- Open up AV Biofeedback software: ‘BreatheWell’ using the Desktop icon on the Research laptop: 

- You will see the initial AV Biofeedback screen:

- If the *Patient Display Preview* reads “No preview available” (like it does above) it means that the display goggles are not properly connected to the AV biofeedback computer.
- The functions to perform on the Breathe Well software (in order) in the Decision Session are:
    1) Connect to RPM
    2) Create New Patient / Load Existing Patient
    3) Create New Waveguide / Load Existing Waveguide
    4) New Respiratory Session
    5) Analyze
    6) Breathing Decision Form

- Once the patient is on the couch ensure that the RPM is both tracking ***AND*** recording the RPM marker block motion.
- In the RPM screenshot on the following page, the Record button is highlighted and a bar containing blue blocks is highlighted. Once the number of blue blocks on the bar is 3 or fewer, click ‘Record’.
- If there are more than 3 blue blocks it means that the phase calculation is not performing optimally, and errors can occur in the Breathe Well software if the number of blue blocks exceeds 3 for an extended period of time.

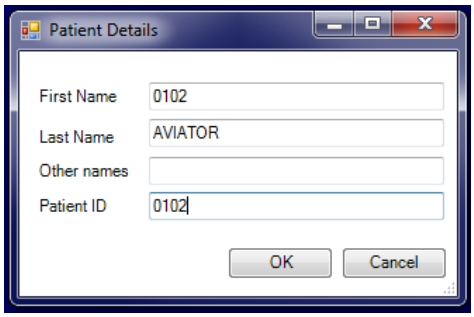


Screen shot of RPM. There are fewer than 3 blue blocks present on the highlighted bar, so it's good to Record.

- Once the RPM is recording the breathing signal, in the Breathe Well software click 'Connect' to start receiving the RPM breathing signal
    - If unsuccessful, try a different COM# from the dropdown menu in the Breathe Well software and click 'Connect' again

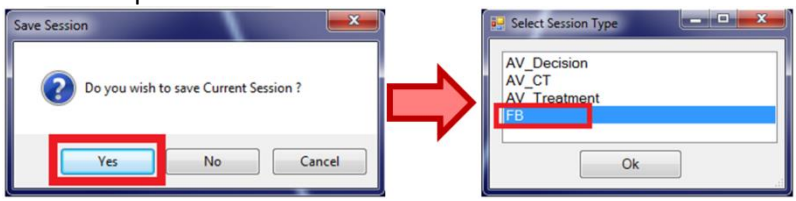
2.1.3. Record Patient Free Breathing

Once connected to the RPM, click 'New Patient' and enter Trial ID (received with the Randomisation call) as their first name, 'AVIATOR' as their last name, and their Trial ID again as the Patient ID:

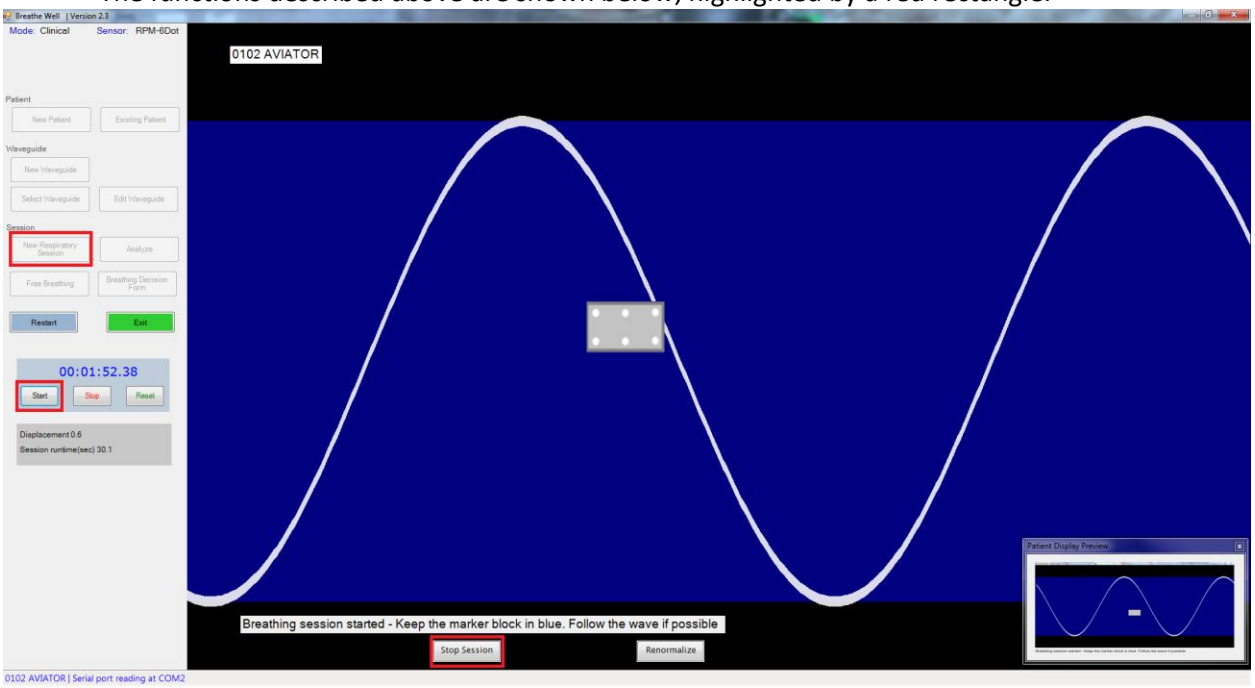


Turn off the tablet at this point and ensure that the music is ***muted***. It is important that they breathe as naturally as possible without instruction.

- After you have created a New Patient file, click 'New Waveguide', this will acquire 10 breaths to and calculate the average of these to create the waveguide, and save it without any modifications.
- Click 'New Respiratory Session' and once the wave appears on the screen click 'Start' on the stopwatch panel:
- At 4 minutes click 'Stop Session' and save the data as 'FB':



- The functions described above are shown below, highlighted by a red rectangle.



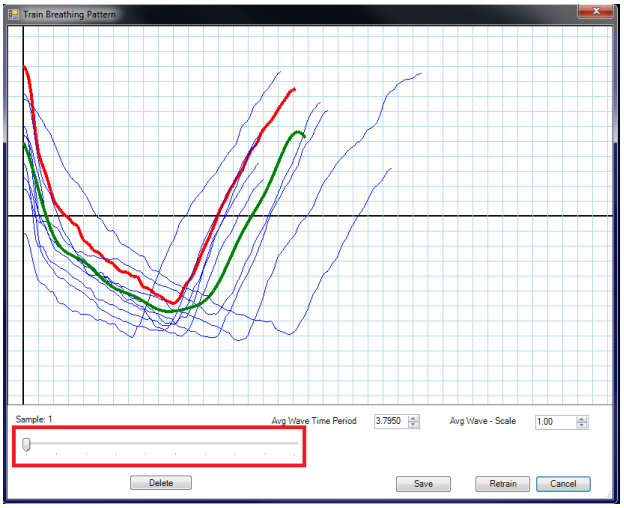
- After the session has been saved, click ‘Analyse’, this will analyse the session you just saved
- In the analysis screen, click ‘Save’ and then close the analysis screen.
- Click ‘Reset’ in the Breathe Well software
- Stop and save in the RPM software, then re-track and record in preparation for the AV biofeedback session.

This concludes the Free Breathing Session.

2.1.4. AV Biofeedback Practice

With the RPM tracking and recording the signal, turn on the tablet (and double-check iDisplay is still running properly, extending the laptop screen to the tablet) and unmute the audio.
In the Breathe Well software:

- Connect to RPM
- Click 'Existing Patient' and select the correct 'Trial ID AVIATOR' patient
- Click 'New Waveguide', AV Biofeedback will acquire 10 breaths before displaying them to you:

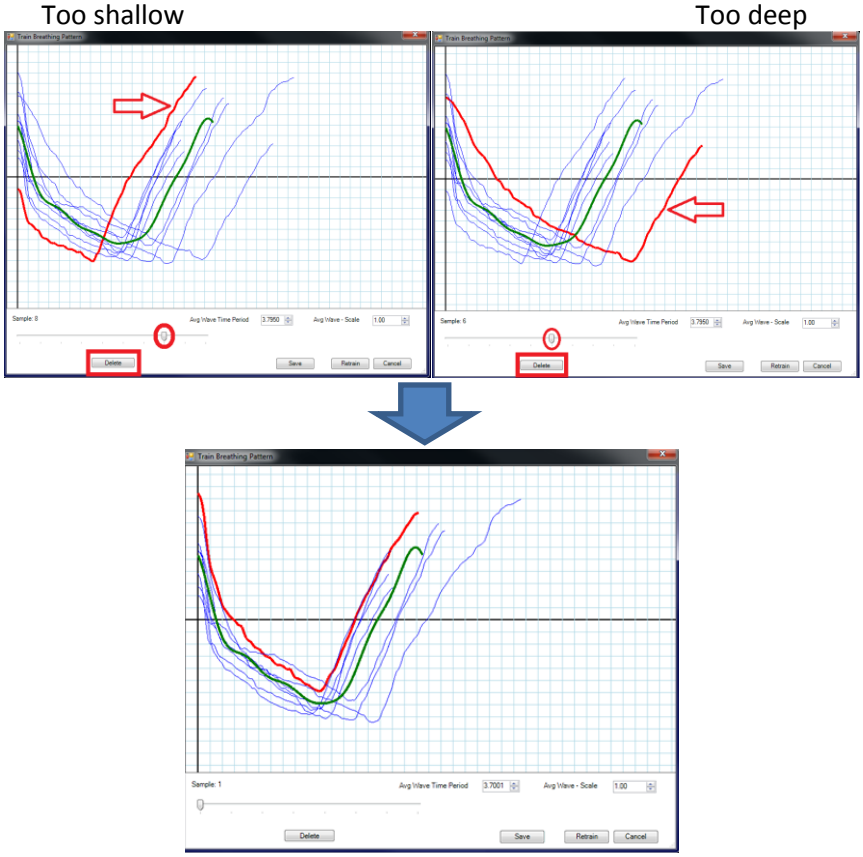


Blue curves: each of the 10 acquired breathing cycles
Red curve: a selected blue curve
Green curve: the average of the blue curves, which will be displayed as the waveguide
The slider-bar (highlighted by the red rectangle) underneath the curves scrolls through each of the 10 cycles.

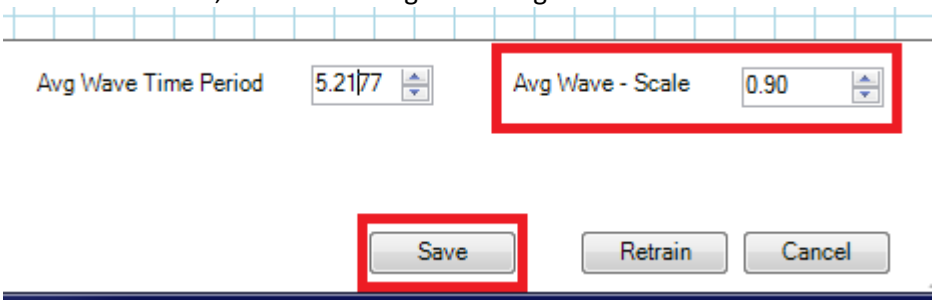
If there are any outlier breathing cycles not representative of their "normal" breathing (e.g. overly-deep breaths, coughs, yawns, etc.) select them using the slider-bar and delete them:

Too shallow

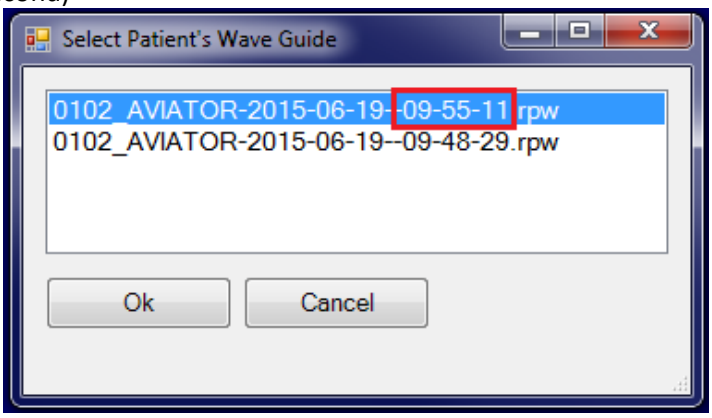
Too deep



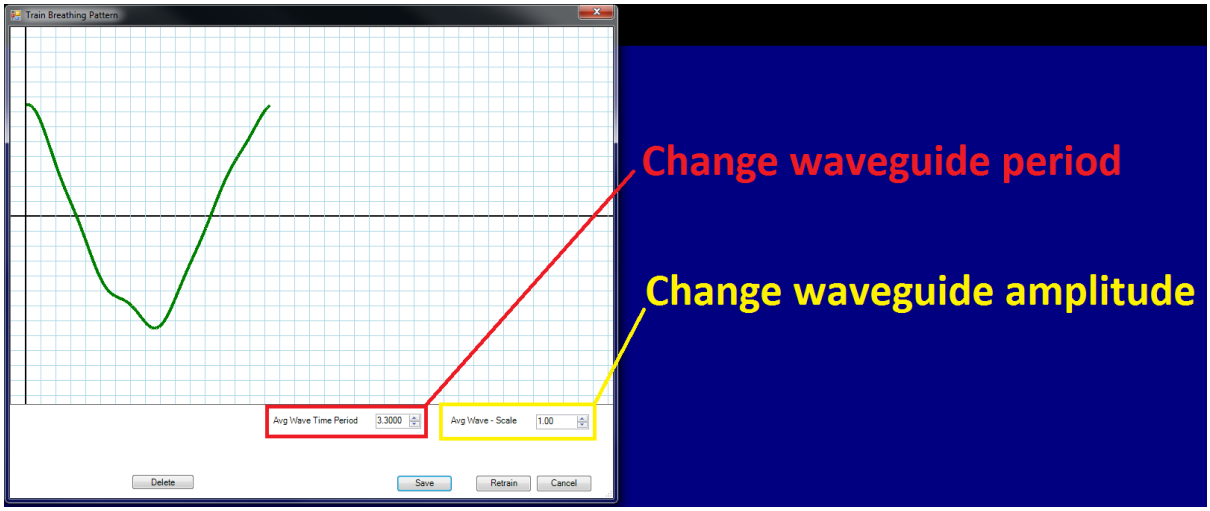
- An issue with making patients conscious of their breathing is that they tend to put more effort into their breathing, inadvertently breathing slightly more deeply than they usually would.
    - To counter this, scale the waveguide's 'Avg Wave – Scale' from 1.0 down to 0.9



- The 'Avg Wave Time Period' (shown above as 5.2177 seconds) can also be modified if it exceeds the limits of 4D-CT reconstruction (e.g. 10 breaths per minute: 6 seconds).
- Save this waveguide
- Next click 'Select Waveguide' and select the one you just saved (most recently saved files appear at the top of the list – time the file was created highlighted with red rectangle: hour-minute-second)

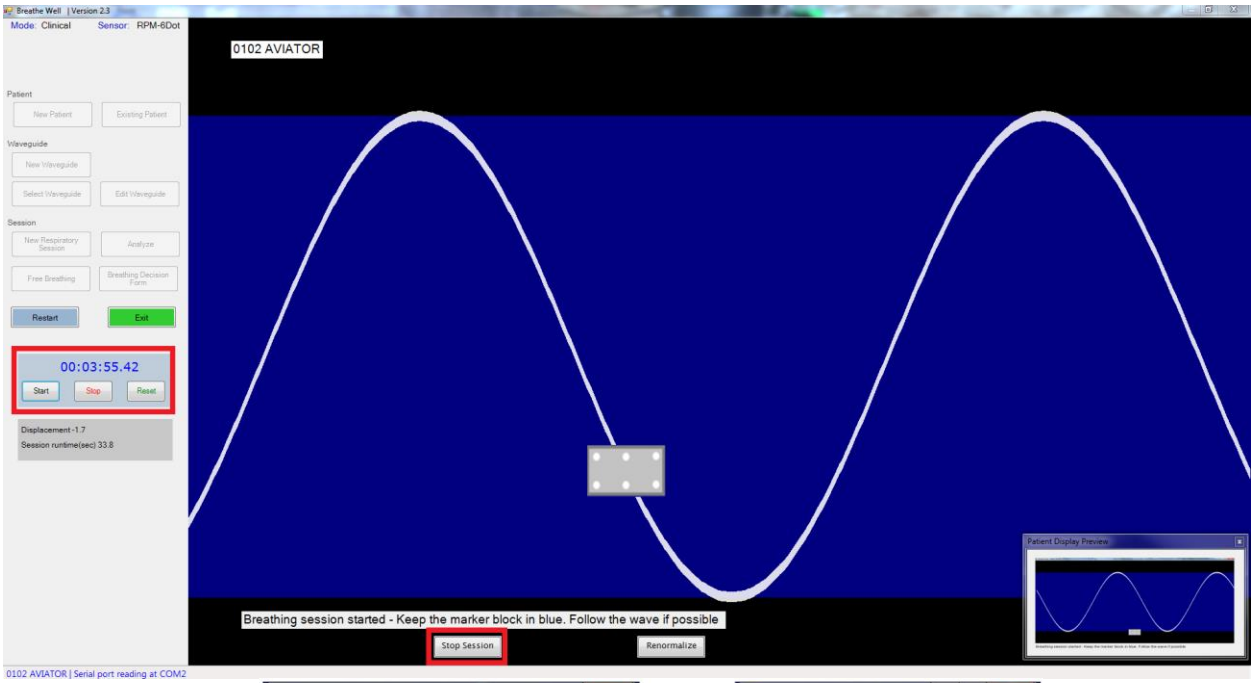


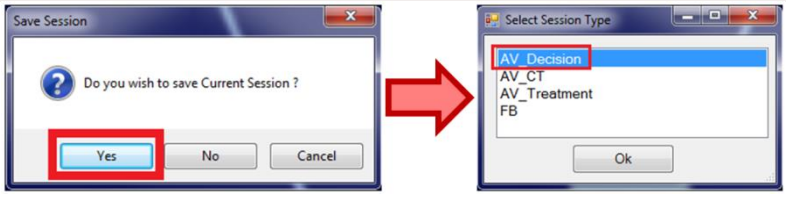
- Click 'New Respiratory Session', this will commence AV biofeedback guided breathing. After a brief calculation of mean position the waveguide will appear and the music will begin to play.
- Give the patient 1 minute to attempt the AV biofeedback guidance (use the sidebar stopwatch if necessary). Are there any issues?
    a) Is the patient having difficulty staying within the blue region?
    b) Is the patient having difficulty following the waveguide? (Is it too fast? Too slow?)
- If points a) and/or b) are issues, then a modification of the waveguide may be necessary: click Reset → Existing Patient → Edit Waveguide and select the recently acquired Waveguide you wish to modify
- This will bring up the selected waveguide and options to modify it:



- Avg Wave Time Period: period of the waveguide in seconds
- Avg Wave - Scale: Amplitude of waveguide scale:
  - More than 1.0: Increasing amplitude size
  - Smaller than 1.0: Decreasing amplitude size
- Only minor modifications to these numbers should achieve the desired result.
- Save modified waveguide

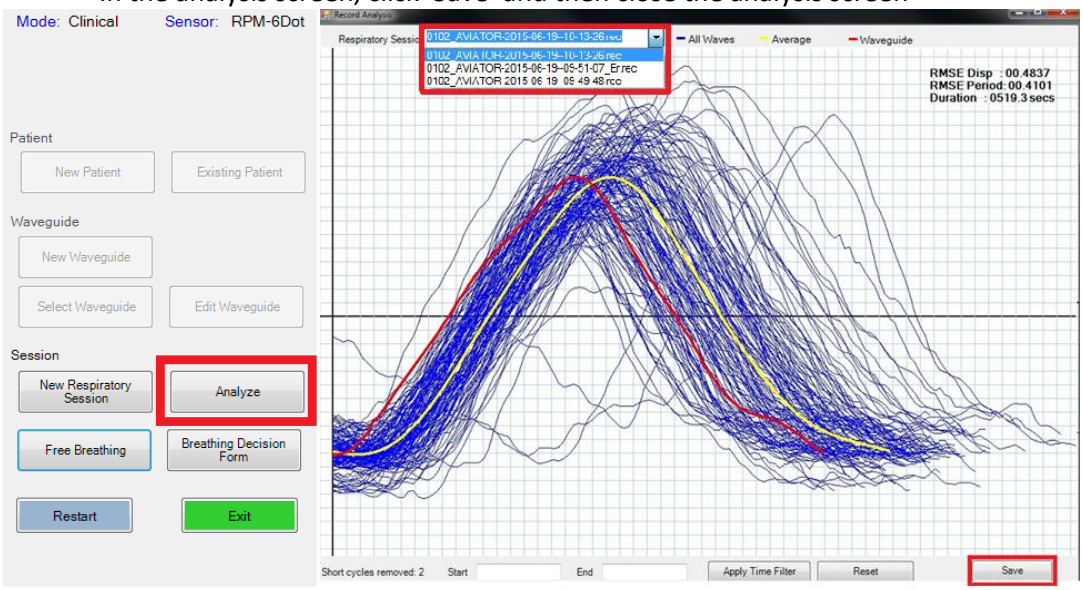
- Click ‘New Respiratory Session’; after a brief moment to position the marker in the correct position, the breathing session will commence.
- Once the white waveguide appears on the screen (and the music commences) click ‘Start’ on the sidebar stopwatch.
- After 4 minutes ‘Stop Session’ and save it as ‘AV_Decision’:





- After the session has been saved, click ‘Analyse’, this will analyse the session you just saved

- In the analysis screen, click ‘Save’ and then close the analysis screen

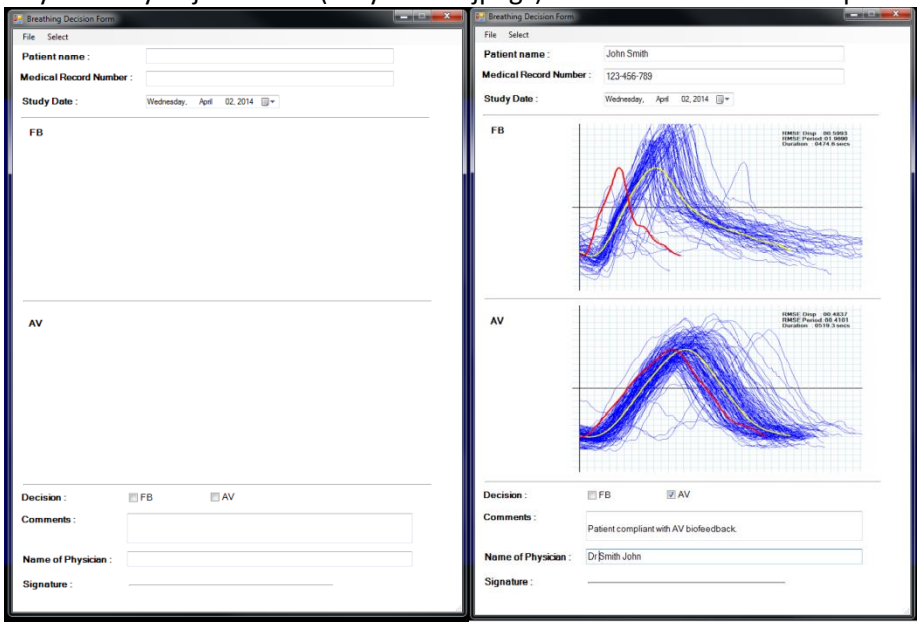


- Stop and save in the RPM software
- Aside: in the analysis form, the blue curves are each individual breath, the red curve is the waveguide, and the yellow curve is the average curve based on all the blue breaths
    - RMSE Disp is a measure of how much all the breaths vary from this average curve

This concludes the AV Biofeedback Session

2.1.5. Breathing Decision Form

- Now that both breathing sessions have been performed and both sessions have been analysed and saved click 'Breathing Decision Form'
- This will bring up the Decision Form window, select the AV biofeedback (AV) and Free Breathing (FB) analysis files you just saved (they will be jpegs) and fill in the rest of the patient details:



Breathing Decision Form.
Left: Unfilled. Right: Complete.

Note: Enter the same patient name and ID information here as you did in creating a new patient file (Trial ID and AVIATOR).

Decisions are made by which breathing session has the **lower 'RMSE Disp'** value. In this instance, the AV biofeedback session was more regular (RMSE Disp (AV) = 0.48, less than RMSE Disp (FB) = 0.59).

There is no threshold for how much less the RMSE value needs to be to make the decision (e.g. if RMSE Disp (AV) = 0.48, and RMSE Disp (FB) = 0.49, then AV would still be the decision).

Save the Decision Form as a PDF.

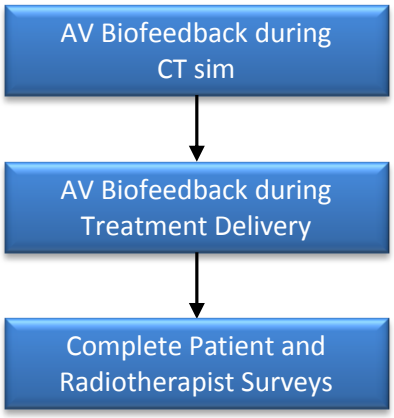
The entire Decision Session takes approximately 20-30 minutes to complete.

- If Decision Session is being performed on a different day to the CT sim, have the patient and the staff member who operated the Breathe Well software complete the patient and staff surveys
    - If Decision Session and CT sim session are being performed on the same day, wait until the CT sim is completed to perform the surveys.

This concludes the Decision Session.

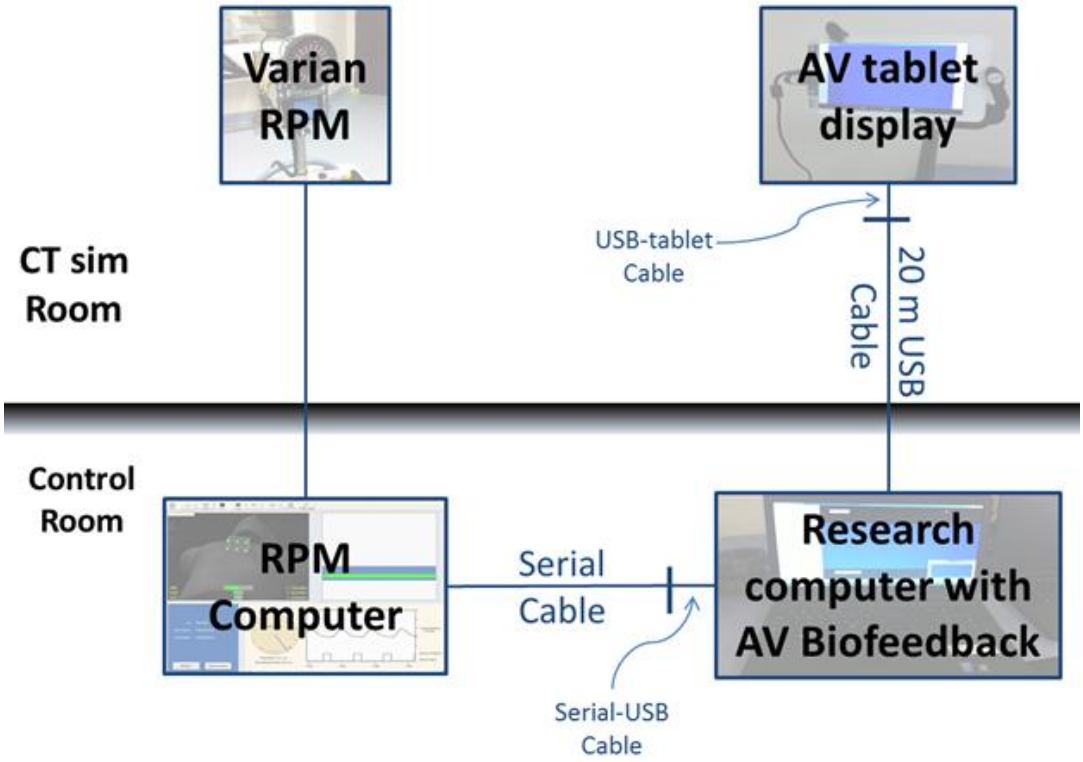
2.2. Image and Treat Using AV Biofeedback

Continuing on from the previous section, we will first address those patients for whom, based on the Decision Session, AV Biofeedback was selected to remain in their imaging and treatment.

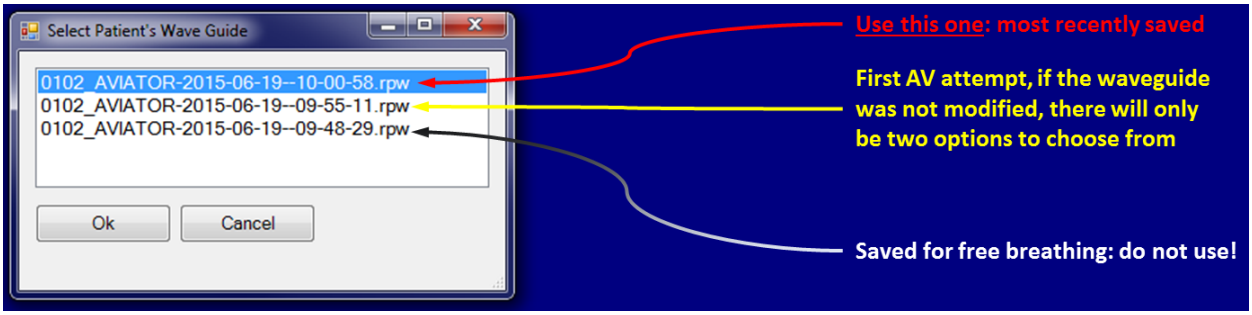


2.2.1. CT sim with AV Biofeedback

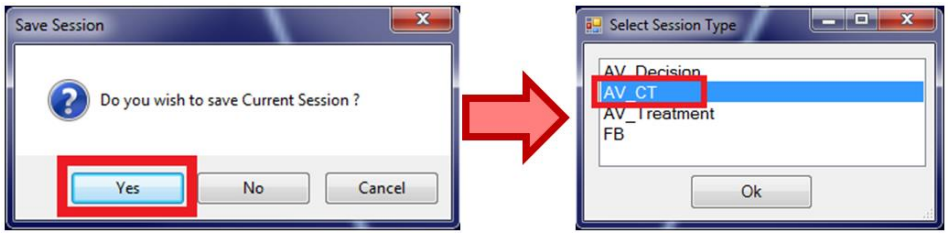
The setup here is the same as used for the Decision Session:



The purpose of AV Biofeedback is to not only facilitate regular breathing during imaging and treatment, but also across multiple imaging and treatment sessions, so it is important to **use the same Waveguide** as used in the 4 minute of AV biofeedback breathing in the Decision Session:



- Position patient as per department protocol in preparation for their CT sim
- Once in position, ensure the tablet is on and iDisplay is correctly extending the laptop's screen.
- Select the correct patient and waveguide
- Start a New Respiratory Session
- After a brief moment to position the marker in the correct position, the breathing session will commence.
- Perform imaging as per department protocol.
- After imaging is complete, click 'Stop Session' and save data as 'AV_CT':

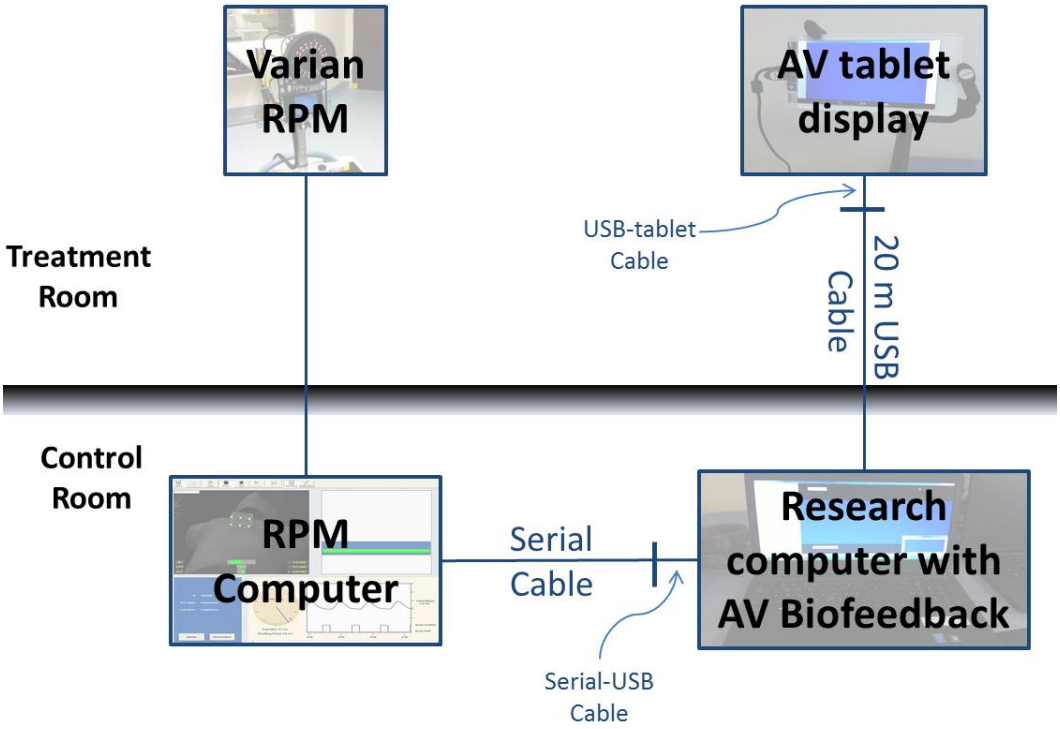


- Stop and save in the RPM software
- Also save:
    - CT sim images (DICOM data) [file location]
- It is important to save these files straight away, as they may be automatically deleted within days
- If Decision Session was performed on the same day as CT sim, have the patient and the staff member who operated the Breathe Well software complete the patient and staff surveys

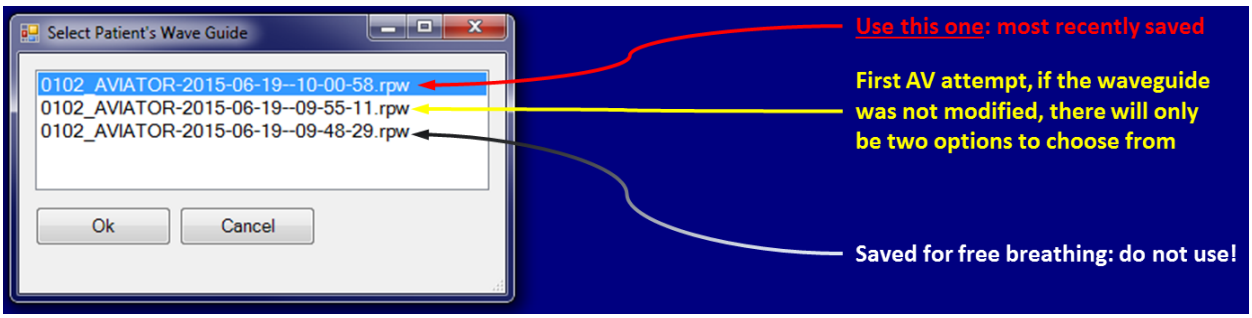
<u>This concludes the AV Biofeedback CT sim Session.</u>

2.2.2. Treatment Delivery with AV Biofeedback

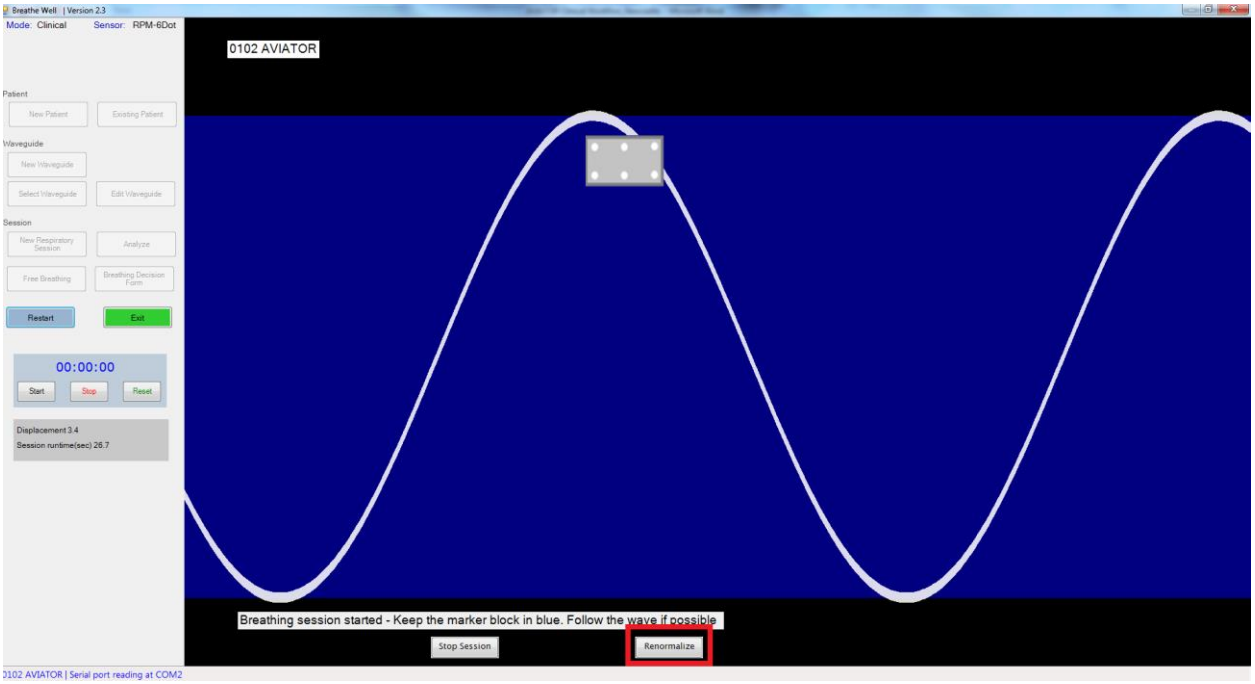
The setup here is similar to the setup used for the Decision and CT sim Sessions:



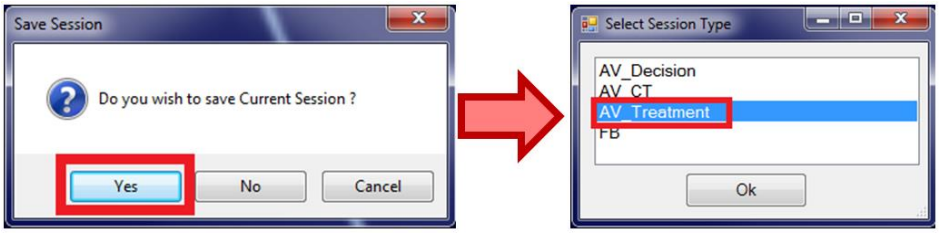
Use the same Waveguide as used in the 4 minutes of AV biofeedback breathing in the Decision Session, and then again in the CT sim Session.



- Position patient as per department protocol in preparation for treatment.
- Once in position, ensure the tablet is on and iDisplay is correctly extending the laptop's screen.
- Select the correct patient and waveguide
- Start a New Respiratory Session
- After a brief moment to position the marker in the correct position, the breathing session will commence.
- Perform treatment delivery as per department protocol – ***regarding any couch shifts***:
    - After a couch shift, in the Breathe Well software click '***Renormalise'***, which repositions the marker-block at the centre of the AV biofeedback display because the couch shifts may have moved the marker-block off-screen
    - DO NOT click renormalise during any beam-on times
    - Renormalise will automatically save the breathing data, so after a treatment session and 'Renormalise' was clicked once, there will be two breathing data files for that one session.



- Once treatment is complete, click 'Stop Session' and save the data as 'AV_Treatment':

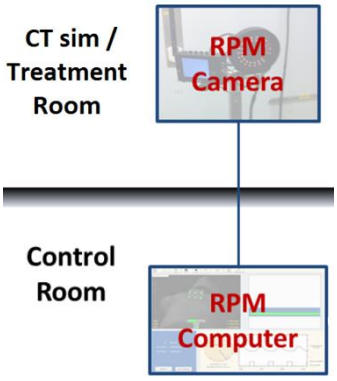


- Also save:
    - CBCT images (DICOM data) if used (if linac does not have on-board imaging, disregard this point)
    - RPM File [file location]
- It is important to save these files straight away, as they may be automatically deleted within days.
- If this is the final fraction of treatment, complete patient and staff surveys

This concludes the AV Biofeedback Treatment Session

2.3. Image and Treat with Free Breathing

In the event that the patient is randomised into the control arm, or in the event that 'RMSE Disp' for Free Breathing is less than the 'RMSE Disp' for AV Biofeedback in the Decision Session, then the AV Biofeedback system will not be used in their imaging and treatment, the setup will be as per department protocol, and it is important that the RPM system is used:



While AV Biofeedback will not be used, it is still important to save the following data for each CT sim and treatment fraction:

- RPM Breathing signals
- CT sim images
- CBCT images (if CBCTs are not acquired then disregard this point)

3. Control Group

Patients in the Control Group will have been identified as an eligible patient by the Radiation Oncologist, and then agreed to take part in the study. However, they have been randomised into the Control Group and will not be using AV Biofeedback. The setup, conduct of AVIATOR in the control group as well as the data to save will be the same as detailed in the previous section: '2.3. Image and Treat with Free Breathing'.

4. Post-Treatment Toxicity Report

As noted in the Flowcharts on page 1, a Toxicity Report is required for every patient regardless of their allocation to intervention or control groups.
With each patient follow-up visitation the Toxicity Report must be completed by the treating physician; this is done for each follow-up for up to 12 months after each patient has completed their treatment.
The completion of this Toxicity Report marks the conclusion of the AVIATOR trial for each patient.

Introduction

This document describes the quality assurance tests that should be performed after any software or hardware change of the Audiovisual biofeedback (AV) system or before each simulation and gated treatment with the AV system. For background see Cui *et al*. *Commissioning and quality assurance for a respiratory training system based on audiovisual biofeedback* JACMP 11(4) 2010.
The QA presented in this document is relevant for Breathe Well software version 2.3 or higher.

Daily QA or prior to each simulation and treatment if used less frequently than daily

1. Visual inspection of the hardware

Is there any visible damage to the AV control computer, cables and the screen or goggles?

- ❑ Yes (Report)
- ❑ No

2. Visual display and auditory sounding tests for the screen or video goggles

Connect the screen or goggles to the AV computer. Play a sample video. Is the video displayed properly and the sound volume comfortable and is sound coming from left and right speakers (goggles only)?

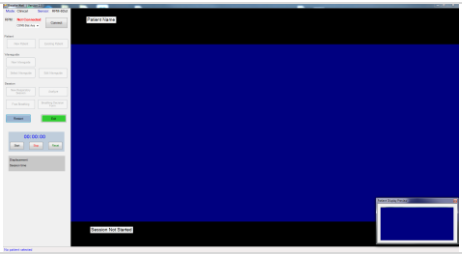
- ❑ Yes
- ❑ No (Report)

Potential issue: If 'no' for video display:
Goggles: go to 'Screen Resolution' (Control Panel\All Control Panel Items\Display\Screen Resolution) to ensure display is extended to the screen/goggles and that the resolution for the screen/goggles is correct (800 x 600).
Tablet: Ensure that, in Settings, in Developer Options, USB debugging is ticked. If video problems persist, there may be an issue with the tablet drivers on the laptop not being installed.

3. Initialization of the Breathe Well software

a) Start the BreatheWell software first. Is the AV computer showing the operator interface, as shown in Fig. 1(a), while the screen/goggles showing the patient interface with a welcome instruction as in Fig. 1(b)?

- ❑ Yes
- ❑ No (Report)



(a)

(b)

Fig. 1. (a) The operator interface

(b) Patient display as shown on the screen/goggles (intentionally blank).

b) On the operator interface, does the in-screen patient display match what is shown on patient screen/goggles?

- ❑ Yes
- ❑ No (Report)

Monthly QA. Also to be performed after a software change.
Details of test

_____	_____	_____
Centre name	Breathe Well Software Version**	RPM Software Version (Help->About)*

**see Breathe Well software top-bar for version number

1. AV computer-RPM computer Connectivity

AV computer connects to RPM computer via serial cable. Once connected, ensure RPM computer is tracking RPM marker block. On AV computer select correct COM# from the 'RPM dropdown menu' in Breathe Well software and click 'Connect'. If unsuccessful, try a different COM# from the dropdown menu. Successful?

- ❑ Yes
- ❑ No (Report)

If unsuccessful, refer to User Guide 'Appendix A: Troubleshooting' for further options to address AV-RPM connectivity issues.

2. Create an unmodified New Waveguide Session

Use the RPM test phantom. In the Breathe Well software create New Patient (First Name: 'AVQA'. Last Name: (the date) 'DDMMYYYY'), then create New Waveguide. With the RPM phantom in motion acquire sample respiratory traces, and save it without any modification. Successful?

- ❑ Yes
- ❑ No (Report)

3. Play a New Respiratory Session for the unmodified waveforms

Still using the RPM test phantom. Click Load unmodified waveguide by clicking 'Select Waveguide' (file to select will be the only option available in the menu). Now click 'New Respiratory Session. After calculating the mean, the audio patch should be toggled automatically and the music should sound synchronous and harmonious. Is the block tracing the motion magnitude, shape and time period of the background wave?

Note: small variations in period may be observed, <0.1s per cycle, causing a small drift out of synchronisation (the phantom is not performing biofeedback!) and are acceptable.

- ❑ Yes
- ❑ No (Report)

Is the exhale (bottom) period longer than the inhale (top) period on the AV screens?

- ❑ Yes
- ❑ No (Report)

Stop Session. Do ***not*** save file.

4. Create a modified New Waveguide Session

Still using the RPM test phantom. Click 'Restart', click 'Existing Patient' and select the patient name you created in Step 2. Click 'New Waveguide'. Remove one sample; adjust the average wave time period and scale. Are all of these operations successful and the modified waveforms saved?

- ❑ Yes
- ❑ No (Report)

5. Play a <u>New Respiratory Session</u> for the modified waveforms

Still using the RPM test phantom. Click 'Select Waveguide', there should now be two files to choose between. Select the top one (top option is always the most recent). Begin another New Respiratory Session for the modified waveform. The block should be immediately out of synch with respect to the background waveguide. Observed successfully?

- ❑ Yes
- ❑ No (Report)

Stop Session. Do ***not*** save file.

6. Audio synchronization test & Randomization – Out-of-bounds respiratory pattern

a) Still using the RPM test phantom. Load the original unmodified guiding waveform such as the one in Step 2 (second file option in 'Select Waveguide' – if you are uncertain, the timestamp is written into the file name - select the earlier option). Start 'New Respiratory Session'. Once session is started, slightly raise the motion phantom itself (by ~2 cm) by placing something beneath it, producing a partially out-of-bounds respiratory pattern. When the block moves outside the blue region the music should fade to silence, and when the block returns within the blue region, the music volume should increase back to normal. Successful?

- ❑ Yes
- ❑ No (Report)

Press 'Renormalize'. After the mean had been calculated, the block should be continuously within the blue region and music should be playing continuously, not fading in and out.
Stop Session. **<u>SAVE FILE</u>**.
Successful?

- ❑ Yes
- ❑ No (Report)

b) On the AV computer, open folder: 'C:\ProgramData\UniversityofSydney\BreatheWell' and open the folder with the correct patient name you created in Step 2. There should be two 'REC files', these are the breathing files. Renormalizing the data creates an additional breathing file.
Successful?

- ❑ Yes
- ❑ No (Report)

7. Changed range of motion function test

Turn off RPM test phantom, and add tape (4-5 layers) to the widest point of the rotating disc. This will increase the range of motion of the phantom. Turn test phantom back on. It is best to slightly elevate the RPM test phantom for this as the added layers of tape may scrape across the couch surface.

a) Using the original unmodified wave, begin another New Respiratory. The block should NOT trace the background wave and should move above and/or below the ranges of the background wave. Successful?

- ❑ Yes
- ❑ No (Report)

b) Then click the Renormalize button and the ball/block should still NOT trace the background wave. Successful?

- ❑ Yes
- ❑ No (Report)

Stop Session. Do ***not*** save file. Remove tape from test phantom.

Attestation

_____	_____	_____
Physicist name	Signature	Date

Notes

*There are known problems with RPM v1.7.5 3D option and a Varian Medical Device Correction Notice has been issued.

Reporting

Report any problems electronically to the Chief of Clinical Physics and Sean Pollock (sean.pollock@sydney.edu.au).

Revision History: Do not print this with QA document

2008-09-29	PJK	Initial draft
2008-12-08	PJK/SG/GC	Modified after actual test
2009-03-02	PJK/SG/GC	Add the audio function into the feedback system and test the synchronization between the audio patch and the video patch.
2009-04-03	PJK/SG/GC	Run a QA procedure and found the audio patch is still not stable.
2009-04-07	PJK/GC	Test the video goggles.
2009-04-08	SG/GC	Run another QA procedure and passed. Need a phantom that has an irregular breathing pattern.
2009-04-13	SG/GC	Run the QA procedure using the motorized programmable phantom and passed.
2009-05-22	PK/GC	Test updated A/V patches, which did not work properly. Switch back to older version and they worked fine, with PK and GC as volunteers simulating real clinical setting.
2009-06-05	PK/GC/SG	Test the updated A/V patches with Renormalization function. Successful.
2009-10-08	GC	Update the QA worksheet.
2009-12-15	GC	After redefine the session names.
2011-06-07	PK/THK	Applied to Sydney
2012-02-09	THK	Modified with the latest version of Breathe Well
2012-05-25	THK	Modified with the latest version of Audiovisual biofeedback software
2012-08-30	PJK	Modified to add larger motion
2012-10-02	PJK/EE	Added test for sound coming from both speakers.
2013-03-25	SP	Added resolution info for goggles (Point 2).
2013-05-10	PK	Added directionality test based on EE/EC/JK observation from RPM
2013-05-10	PK	Added version number for RPM due to Device Correction Notice and above observation
2013-05-17	DL	Removed offset test from Point 3 and 4.
2013-06-21	SP	Goggles resolution dimensions (800 x 600) added to Point 2.
2013-06-16	PK/DL	Added allowable variation in period (<0.1s).
2013-10-14	PK/SP	General revisions for screen and V2.0.
2013-10-15	SP	General revisions for V2.0. Point 6 in Monthly QA separated into a) and b).
2013-10-15	SP	'Potential issue' added in to point 2 in Daily QA and points 1 & 2 for Monthly QA to counter potential problems user may come across for those steps.
2014-04-02	SP	Amended sections pertaining to 'music speeding up' as this is no longer a function in Breathe Well v2.1.0 – Previous Step 5 (Audio synchronization test – irregular respiratory pattern) in Monthly QA replaced with Step 5 (Audio synchronization test – out-of-bounds respiratory pattern).
2014-11-4	SP/PK	SUAVE -> Breathe Well and improved clarify in several sections.
2015-01-14	SP	Updated for Breathe Well v2.3: • Screenshots updated for latest version in Daily QA. • New first step in Monthly QA: 'AV computer-RPM computer Connectivity' ○ This negates a previous 'Potential issue' comment. • Step added for testing 'Free Breathing' function. • Out-of-bounds respiratory pattern & Renormalization steps merged into one • Step added to check whether Renormalzing created an additional .rec file.

Appendix V

User guide documentation provided to study sites participating in audiovisual biofeedback studies

Sydney Regular Respiration Software
User Guide

This User Guide is for Breathe Well software version 2.5

Contents

1. Setup

1.1 Breathe Well Software Initialization and Setup

After Breathe Well software has been installed it will auto-save patient data to folders in the location: *C:\ProgramData\UniversityofSydney\BreatheWell*

If this location does not show up, it means the folder is hidden; type the file location into Windows Explorer and you will see it there.

IMPORTANT: Breathe Well software is compatible with a number of different motion sensor cameras, it is important to specify which sensor is being used in the *config.txt* text file located in C:*ProgramData**UniversityofSydney**BreatheWell*:

- If the Intel Realsense is being used, ensure the line in config.txt reads: Clinical,Realsense,COM4,30,1
- If the Microsoft Kinect is being used, ensure the line in config.txt reads: Clinical,Kinect,COM4,30,1
- If the Varian RPM (6-dot) is being used, ensure the line in config.txt reads:
- Clinical,RPM-6Dot,COM4,30,1
- If the Varian RPM (2-dot) is being used, ensure the line in config.txt reads:
- Clinical,RPM-2Dot,COM4,25,1

Start the Breathe Well software

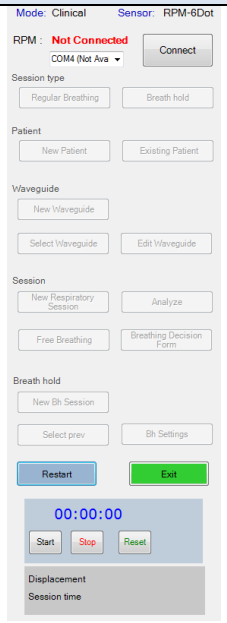
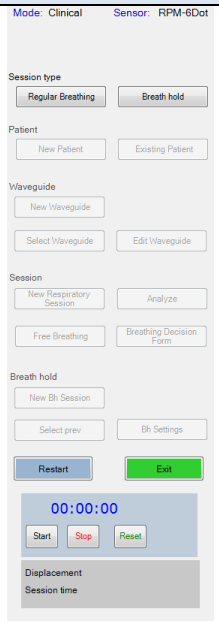
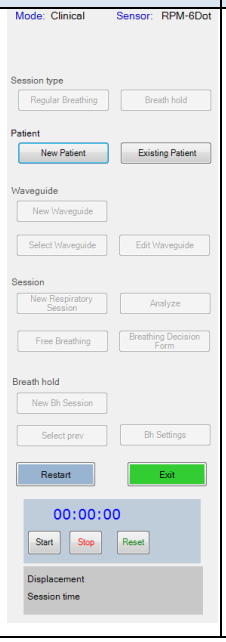
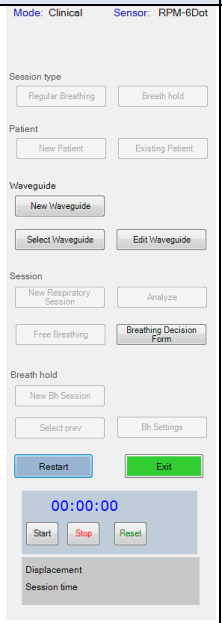
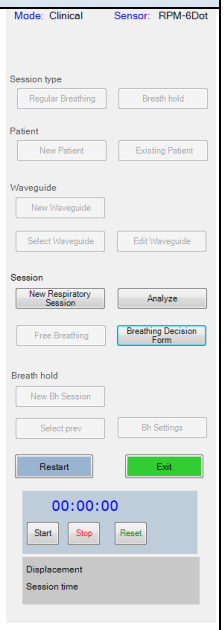
i. Run the BreatheWell executable file
ii. The initial screens on the Breathe Well computer are shown below.

Operator Display | **Patient Display (intentionally blank)**

Figure 1. *Screenshot of the video patch of the Breathe Well audiovisual biofeedback system for operator and patient displays.*

1.2 Breathe Well Operator Bar

As shown on the Operator Display in Figure 1, there is an options bar to the left of the screen. Various options will become active once certain actions are completed; this is illustrated below in Figure 2.

ACTION	Initial Display – Not connected to motion sensor	Connected to Motion sensor – Perform Regular Breathing *or* Breath Hold	Create New Patient file or select Existing Patient	Waveguide options (Regular Breathing)	Breathing Session options (Regular Breathing)
OPERATOR BAR					

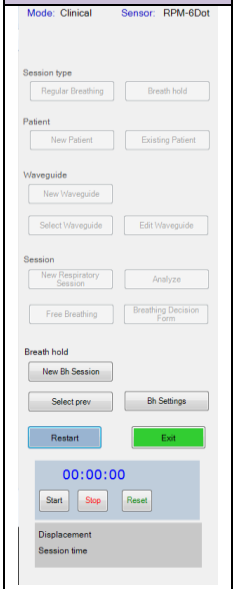
Breathing Session options (Breath Hold)


Figure 2. *Breathe Well options becoming activated as workflow actions are completed.*

2. Breathe Well Patient Session

2.1. Audiovisual Biofeedback Session

2.1.1 Create a Waveguide

Setup the Breathe Well software as well as the RPM software (see Section 1.SETUP).
Select **New Patient** and enter patient details (if patient has already been entered into Breathe Well, select **Existing Patient** and select correct patient).

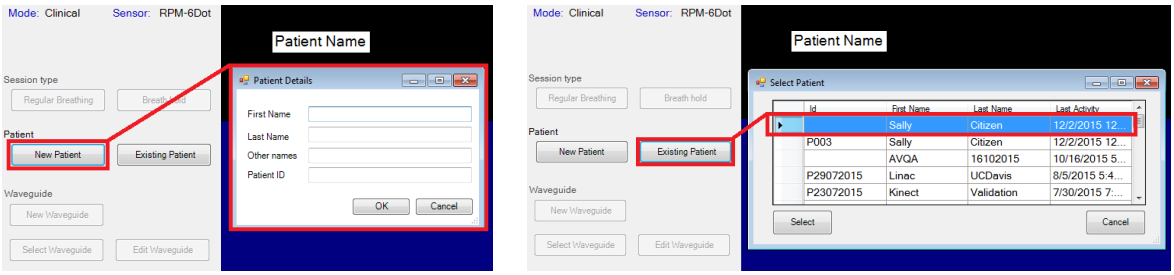


Figure 3. *Selecting either a New Patient or an Existing Patient.*

Select **New Waveguide**, the software will start obtaining ten breaths to construct the waveguide for the patient to follow.
When the program has completed collecting samples, the waveforms for each sample will be displayed on the screen along with options to edit the waveforms (see Figure 4 below).

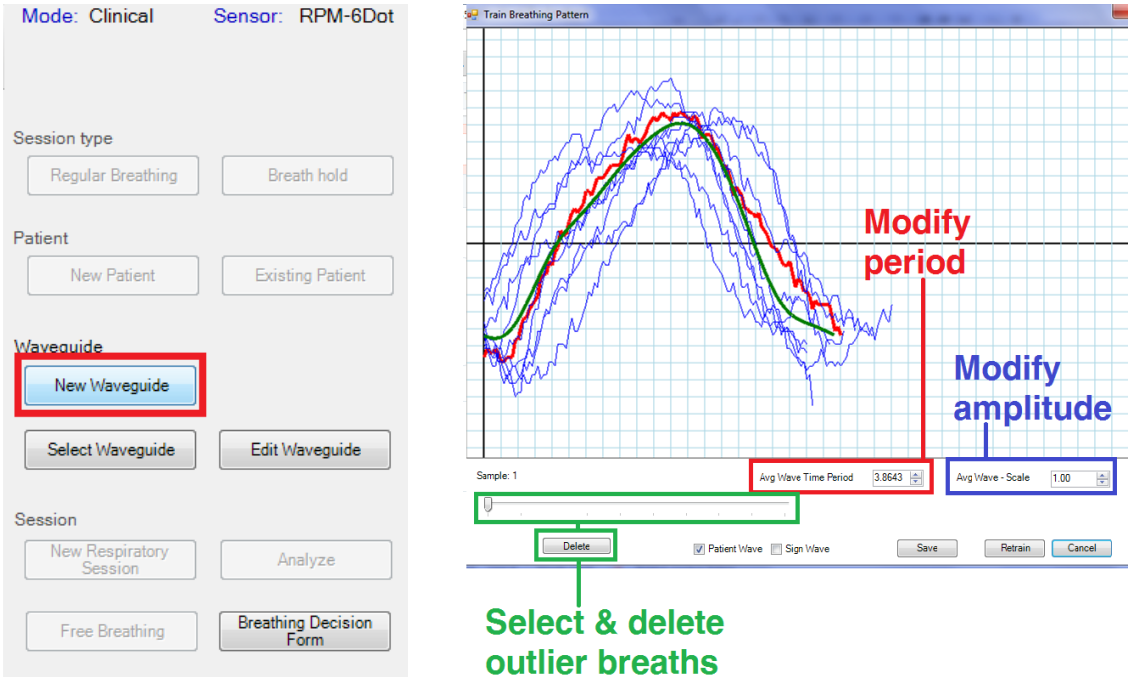


Figure 4. *Screen to determine patient's waveguide. The blue curves are sampled from the patient (each individual breath). The green curve is the average waverform for the remaining samples (to be used as the waveguide). The red curve is the selected breath that can be deleted. Move the arrow at the lower left to change the selected blue patient curve. The period and scale of the average waveform can be modified using the options on the bottom-right.*

Select individual curves and delete outliers if necessary. No threshold is available on when to delete/keep waveforms – it is up to the personal judgment of the operator as to what is an 'outlier' breath is.
Click **Save** to save the waveguide.
Select **Select Waveguide** and select the waveguide files created for your patient (see Figure 5).

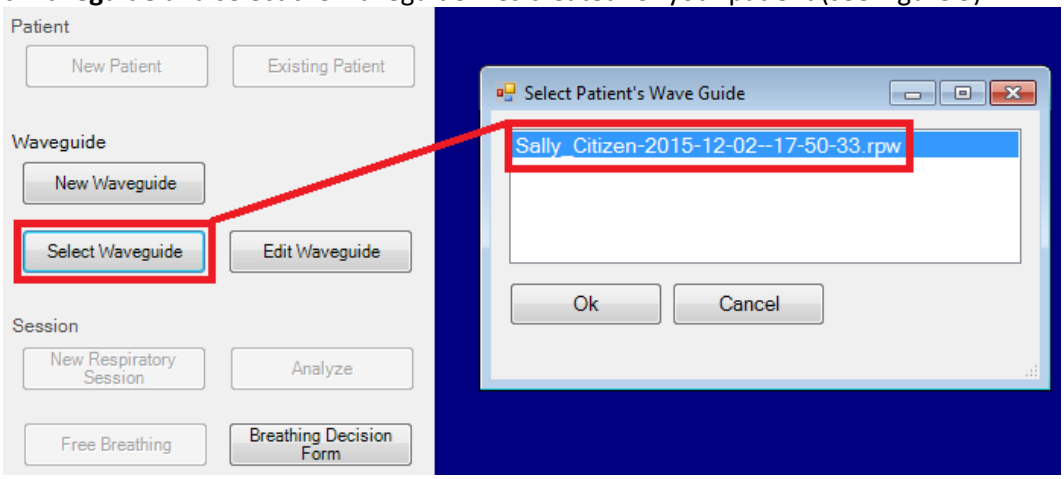


Figure 5. *Screen to select a created waveguide. If multiple waveguides have been created, the most recently saved waveguide will be at the top of the list.*

If the patient is having difficulty following the waveguide, modifying the waveguide may be necessary. Click **Edit Waveguide** and adjust the average wave time period and scale using the respective controls (see Figure 4).

2.1.2. New Respiratory Session

Ensure correct patient and desired waveguide have been selected.
Select **New Respiratory Session**. The session will commence automatically.

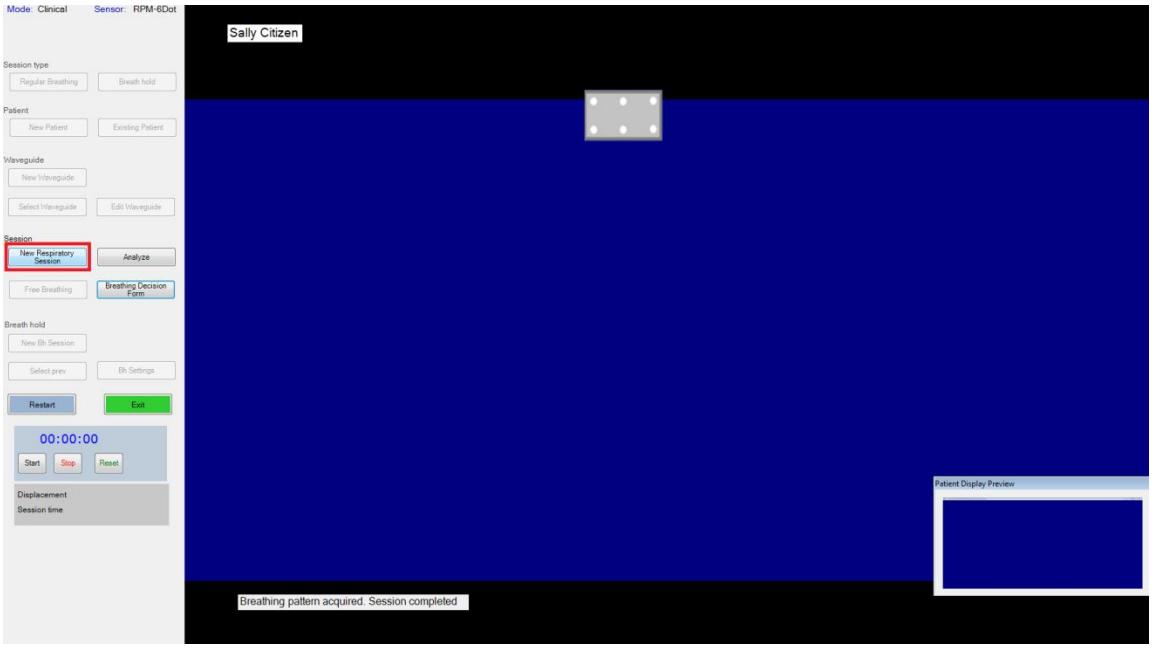


Figure 6. *Starting a new respiratory session.*

The software will start calculating the mean marker-position to correctly position it on within the breathing limits (within the blue region).

Figure 7. *Breathe Well software calculating marker mean position (from 4 breathing cycles) to correctly position marker on guiding interface.*

Once the mean marker-position has been calculated, the session will start automatically.
The waveguide is displayed as a white wave moving from left-to-right while the real-time respiratory breathing of the patient is displayed as a grey marker-block.

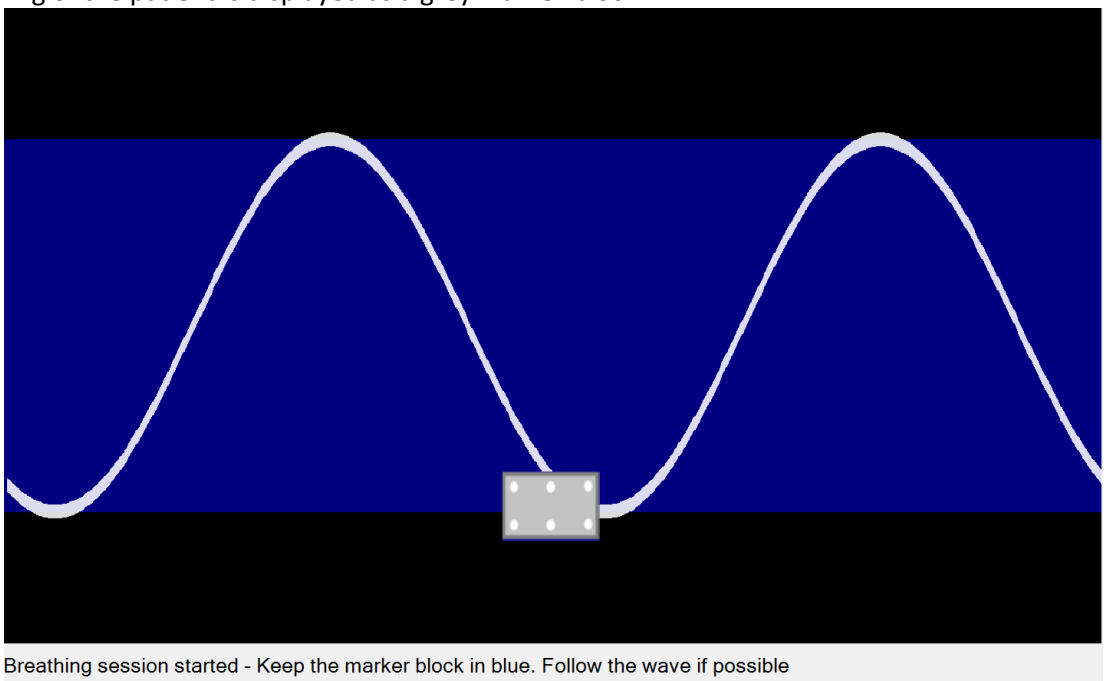


Figure 8. *Patient Display: showing their waveguide (white) and their current breathing position (block).*

It is important that the patient uses exactly the same waveguide throughout their course of treatment to minimize inter-fraction breathing motion variations.

If the couch is shifted/moved or patient shifts position, this will move the marker, potentially off-screen. When couch/patient shifts occur, click the '**Renormalize'** button to renormalize the baseline of the marker block; it readjusts the mean position of the marker block to be in the middle of the display. Only click **Renormalize** before imaging and treatment procedures, not during beam-on time. Clicking Renormalize will also prompt you to save the file for the pre-renormalize data.

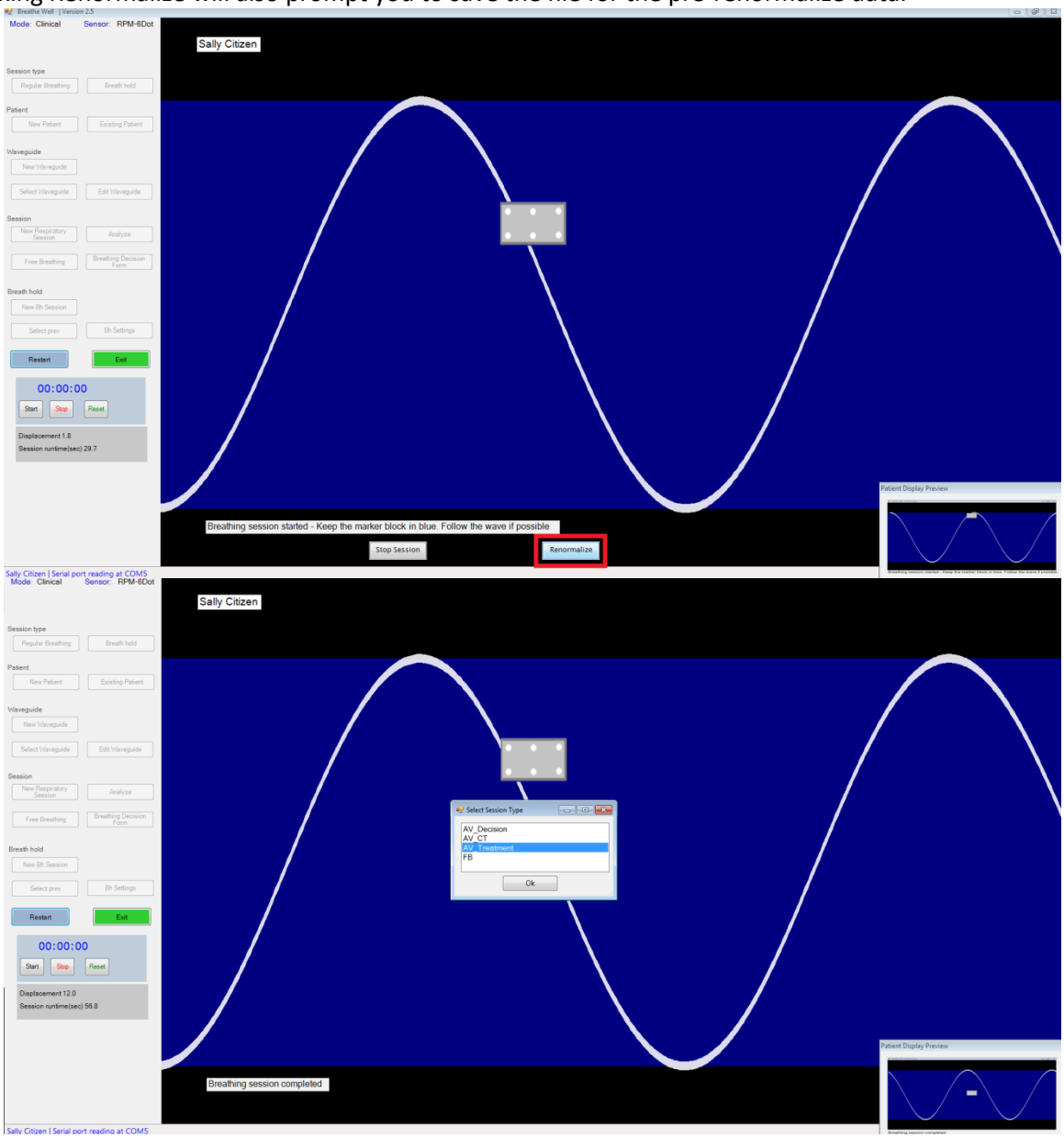


Figure 9. *Location of Renormalize function (top), and save the file (bottom).*

N.B. By renormalizing, this will save a data file of the breathing session up until to the point **Renormalize** was clicked and then commence a new file from the point after renormalization. i.e. there will be two data files for the one session if **Renormalization** is used once. This should not discourage the use of the

Renormalize function, it is especially important to use after couch-shifts, just note that there will be multiple breathing data files associated with its use.

When the session is over, click **Stop Session** and select **Yes** when you are prompted to Save Current Session and select the appropriate option for the session (AV_Decision, AV_CT, or AV_Treatment):

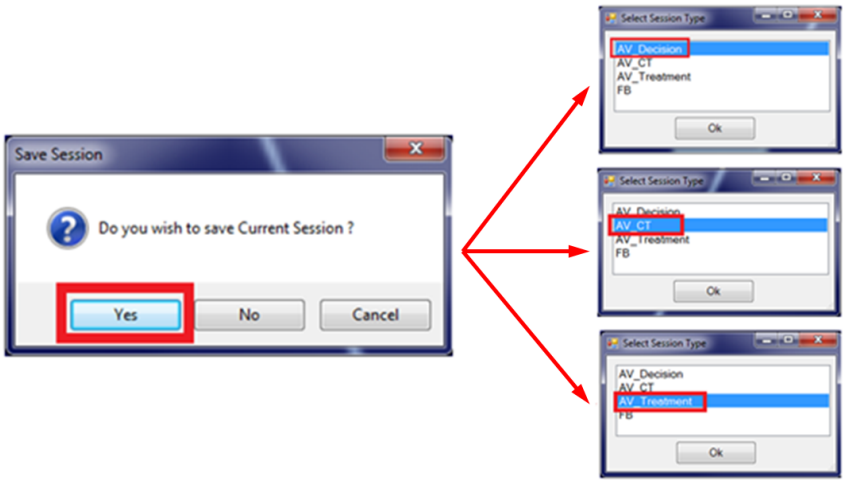


Figure 10. *Pop-up options when you click 'Stop Session' for AV biofeedback sessions.*

Data will be saved automatically into that patient's folder

If using goggles - Discard the hygiene covers and wipe down the goggles using sani-wipes after use (thanks to Diana Browder's input, 10/28/2009).
Place the goggles/tablet carefully away in the appropriate storage place.

2.1.3. Audiovisual Biofeedback Operator's Display

The Operator's Display presents information pertaining to the current Respiratory Session, illustrated and explained below:

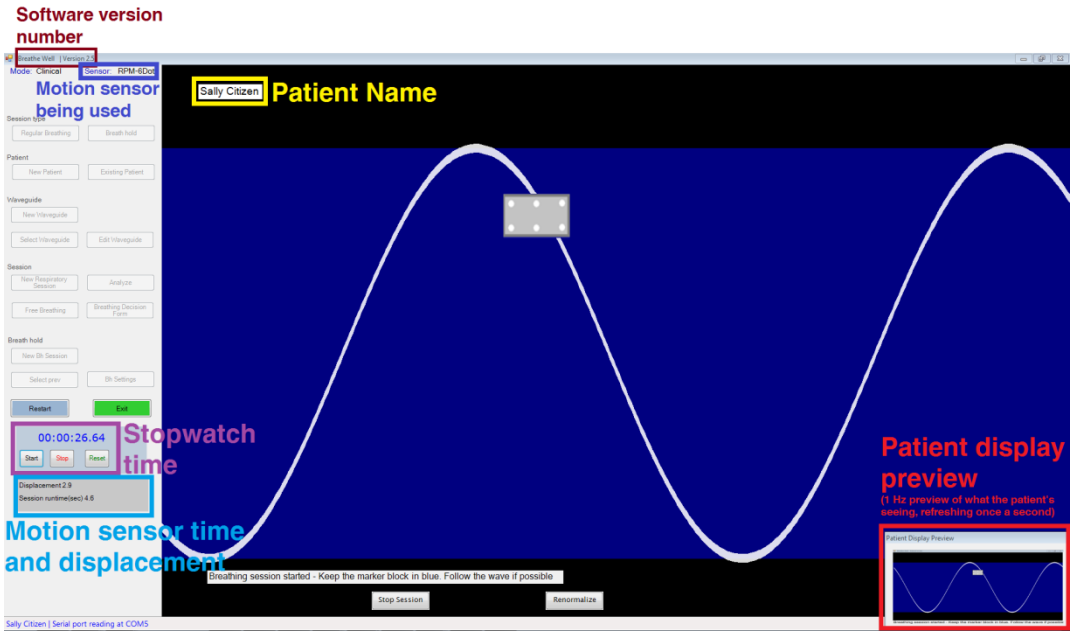


Figure 11. *Operator's Display with session information highlighted*

Brown box: Breathe Well software version number
Dark blue box: The sensor being used
Yellow box: Patient name.
Purple box: Stopwatch. To time length of breathing sessions in minutes and seconds if needed.
Light blue box: Time and displacement information from the motion sensor being used.
Red box: An in-screen display of the patient display which refreshes at a rate of 1 Hz (hence it may appear out of synch, but it isn't, it's just a slow refresh-rate). This informs the operator if the Patient Display is not properly connected, or not displaying the correct information.

2.2. Free Breathing Session

A Free Breathing session is performed when a Screening Procedure is required, i.e. when a decision needs to be made as to what the more regular breathing condition is, either (1) unguided (Free Breathing), or (2) guided (audiovisual biofeedback) breathing.
Setup the Breathe Well software as per Section 1. SETUP.

Important: Ensure that the patient display is **turned off**.

Following the selection of the correct **Existing Patient**, select **New Waveguide**. Immediately save the waveguide without modification, click **Select Waveguide** and select the one you just saved (it will be at the top of the option list), and then click **New Respiratory Session**. Record the patient's free breathing for 4 minutes.

Click **Stop Session** and select **Yes** when you are prompted to Save Current Session and select **FB** from the options presented.

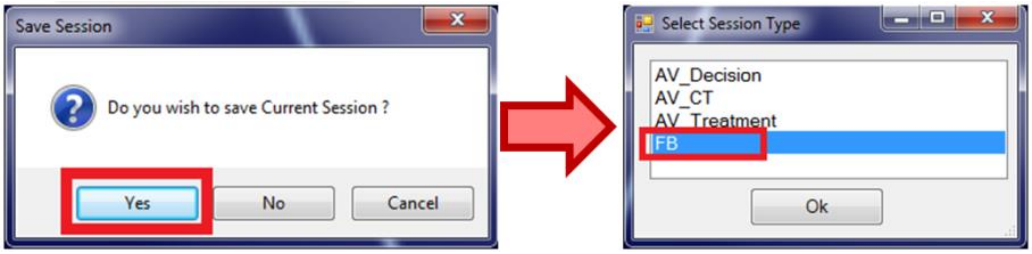


Figure 12. *Pop-up options when you click 'Stop Session'.*

Data will be saved automatically into that patient's folder with 'FB' tagged at the end of the file name for Free Breathing.

3. Respiratory Analysis & Decision Form

If a screening procedure is being utilized to determine whether or not to use the Breathe Well software audiovisual biofeedback guidance, then a comparison of breathing regularity between guided and unguided breathing will need to be performed. The Breathe Well software has a function that allows this decision to be made *in situ*. ***This section will only need to be performed once per patient prior to CT sim.***

3.1. Analyse Respiratory Sessions

Once respiratory session has been saved for unguided breathing (see **Section 2.2. Free Breathing Session**) and guided breathing (see **Section 2.1 Audiovisual Biofeedback Session**) select **Analyse**, this will bring up the Analyse window, shown below in Figure 13:

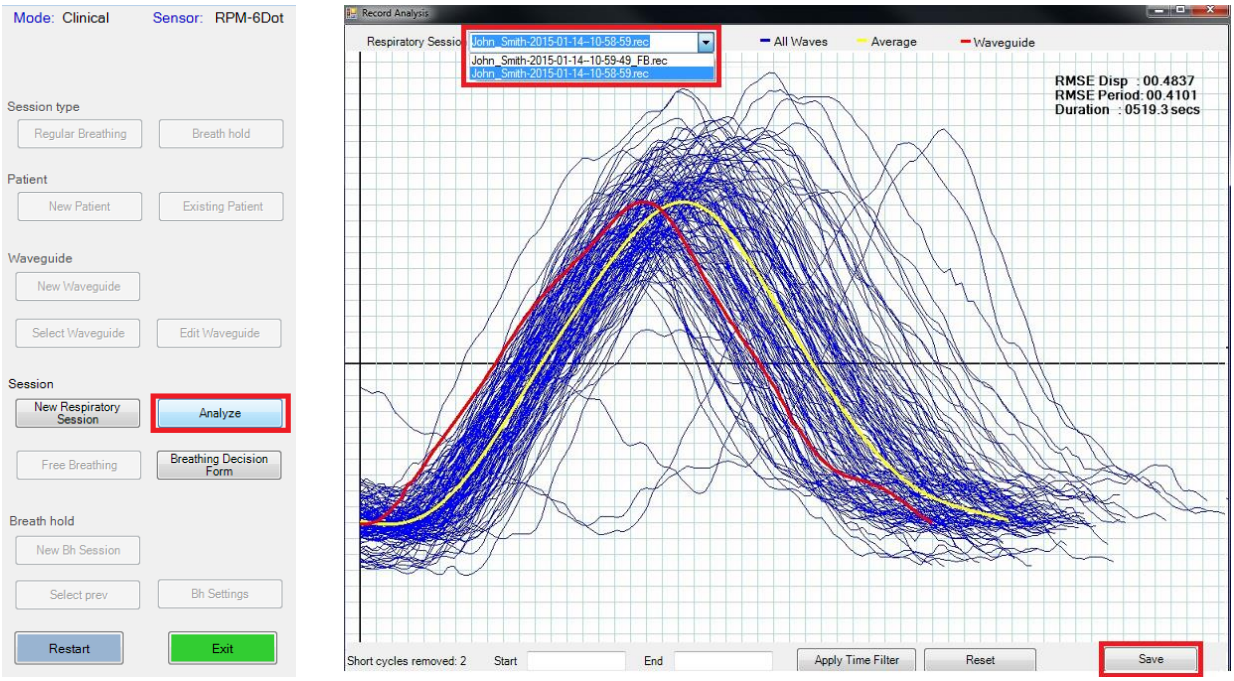


Figure 13. *Analyse option and Analysis window. Blue curves: each individual breath. Yellow curve: average breath. Red curve: selected waveguide (later versions of the software may not display the red curve).*

The analysis for most recently saved session will automatically be brought up. However you can select another breathing session from the dropdown menu. Files with 'FB' tagged on the end is the Free Breathing file, the file with 'AV_Decision' tagged on the end of the AV biofeedback file.

Save each analysis for these two sessions.
N.B. Analysis window saved as a jpeg. A new jpeg is saved each time you click 'Save', so best not spam the 'Save' button.

Also present on the Analyse window are metrics for measuring regular-breathing: the root-mean-square-error (RMSE) of displacement and period.

3.2. Breathing Decision Form

Bring up the Decision Form by selecting **Breathing Decision Form**.

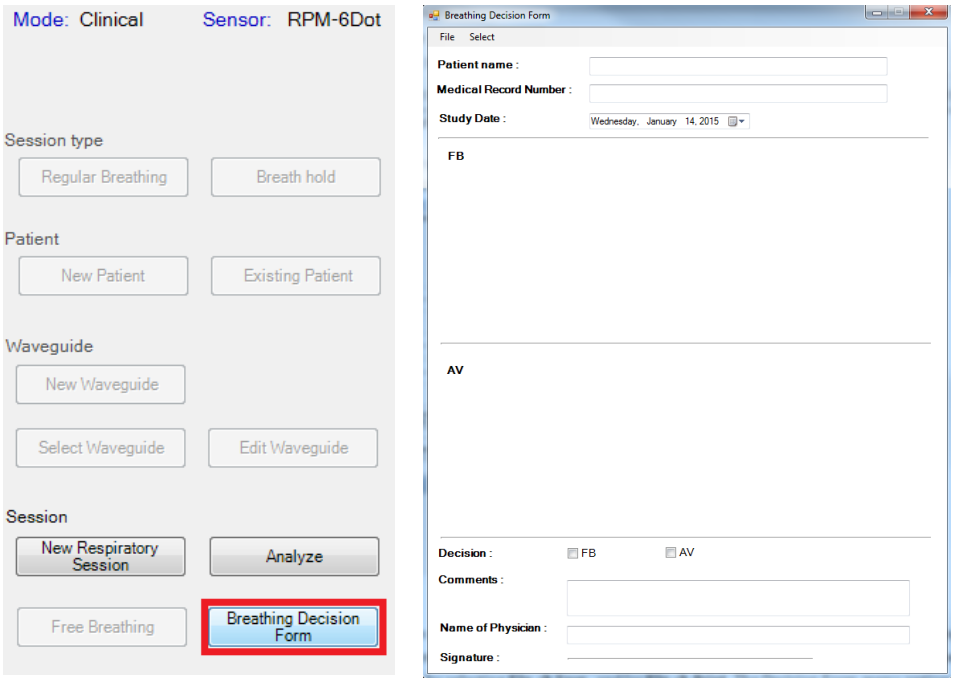


Figure 14. *How to bring up Breathing Decision Form*

Complete the Decision Form by selecting each of the saved 'Analyse Respiratory Session's, by selecting on the Decision Form menu **Select →FB/AV Image**. Once the Decision form has been completed, save and/or print the Form by selecting **File → Save**, and/or **File → Print**. The Decision Form menu options are shown below in Figure 15.

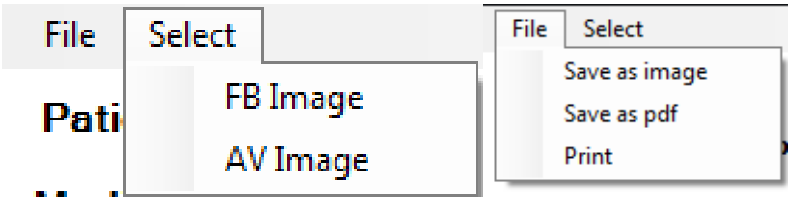


Figure 15. *Decision Form menu options.*

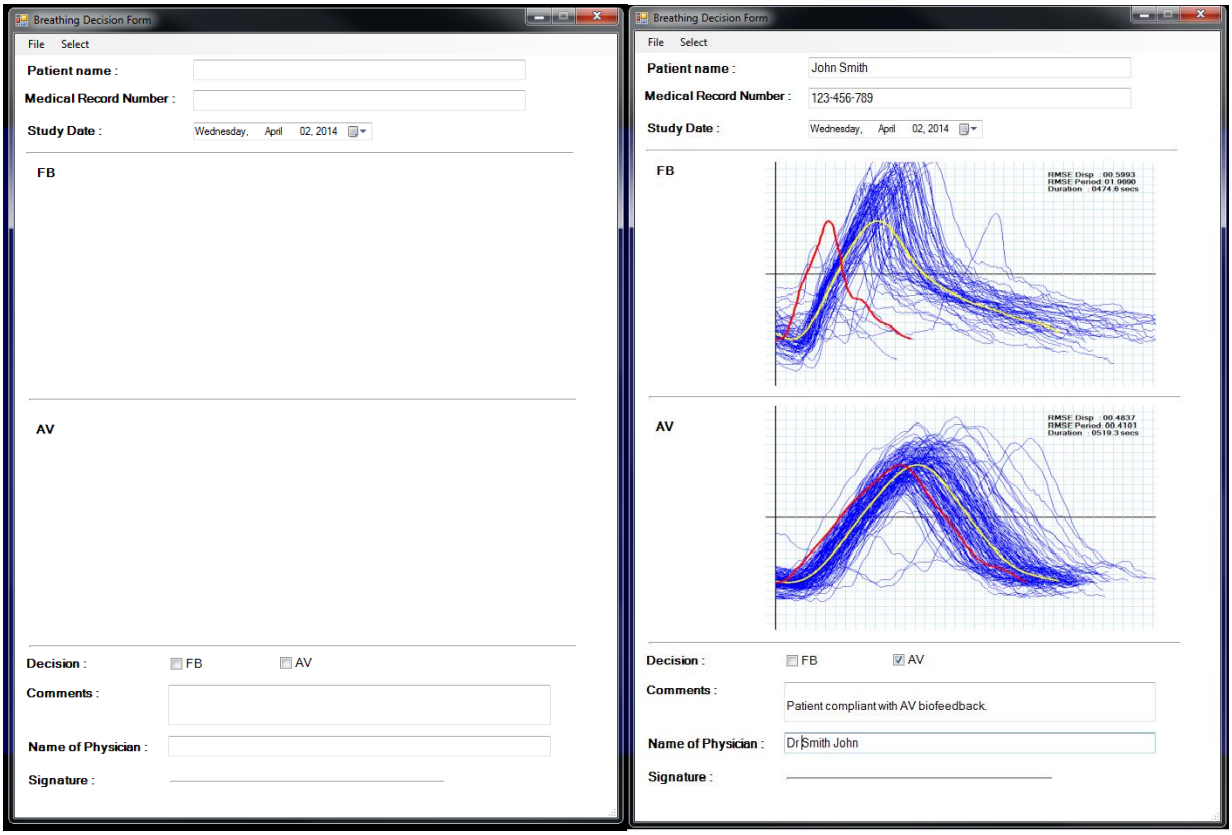


Figure 16. *Breathing Decision Form.*
Left: Incomplete. Right: Complete.

Decisions are made based on which breathing session has the lower '**RMSE Disp**' value. In this instance, the audiovisual biofeedback (AV) session was more regular (RMSE Disp (AV) = 0.48 compared to RMSE Disp (FB) = 0.59). So for patient 'John Smith', audiovisual biofeedback breathing guidance with the Breathe Well software will remain in his treatment planning and treatment delivery utilizing **THE SAME WAVEGUIDE** as was acquired here.

This screening procedure (if utilized) with Free Breathing, Analyse, and Decision Form will only need to be completed once per patient prior to their treatment planning.

Appendix A: Troubleshooting

If the system is working at all after trying the options below the fallback position is to use no training and contact the developers.

If audio is causing problems or not easy to understand by the patient, turn audio off using computer volume control.

If system is not working it may be that 'record' on the RPM software is not depressed, or a loose/wrong connection. The RPM connects to the audiovisual through a serial port.

If after learn respiratory session the green line is not a smooth curve similar to the blue curves then reacquire the respiratory session.

If necessary enable serial output in RPM program itself. View → System Configuration → General tab → Advanced. Check "Enable Serial Protocol" and select Format = Extended and COM port = COM1. (Password RespGate needed). Restart RPM 1.7 in order to make the change take effect.

a. If serial still does not work, (in the standard RPM installation, serial protocol options are disabled by default) then: close RPM, - open RPMSetup.ini in the Program Files\Varian\RPM 1.7 folder, under [Misc] section change "Serial" value to 1. [Misc] Serial=1
b. If serial output is still not reappearing even after updating rpmSetup.ini then may need to adjust regiustry. Use regedit change My Computer→HKEY_LOCAL_MACHINE→SOFTWARE→Varian Medical Systems→RPM Respiratory Gating System→Settings: SerialComm from False to True (enable serial protocol) and SerialProtocolNum from 1 to 2 (IAS to extended).

For the Dell desktop setup at Stanford, there is an issue with detecting the LCD screen display in order to have a dual-screen setup. It was only possible to clone the screen (same display on both screens). However, restarting the computer after connecting the monitor cables fixed the problem.

Another possible issue with having different screens on the dual displays could be the cables to which the display monitors are connected. The Dell desktop setup at Stanford has two VGA cables coming from the desktop computer. The cable with the white tag attached should be connected to the primary monitor. The other cable should be connected to the patient display. When the computer is restarted, the initial boot-up screen will be displayed to the primary monitor – make sure that this is the operator monitor.

If the Research computer is not receiving data from the serial port, make sure that the "Enable Serial Port output" checkbox is set in the RPM configuration screen.

Patient may hear the windows 'beeps'. If they exist, turn off in control panel→sounds

If patient has irregular phase, then ball motion will pause. Either reduce by changing predictive filter? Could also hide ball.

If not using RPM, could have smoothness issues at less than 30 Hz framerate (per Diana's experience).

Error message may appear on patient screen. Patient/therapist should be aware of this. Check for error message programs running in task bar and close. If fails close in windows task manager (ctrl-alt-delete).

You may need to adjust the resolution of the BREATHE WELL LCD screen

i. Adjust the resolution to 800x600 before running the BREATHE WELL software. If the display settings are changed while the program is running, the waveforms disappear.
ii. The following steps to change the resolution are specific to the Dell computer system used at Stanford:
    a) Right-click on the desktop and select **NVidia Control Panel**.
    b) On the left-hand navigation panel, select **Set up Multiple Displays** under the **Display** category.

Appendix B: Revision History

Date	Name	Reason for Changes	Version
01/07/2009	Siddharth (sgopalan)	Updated to reflect new AVFeedback version	1.1
02/03/2009	Siddharth (sgopalan)	Merged with existing AVFeedback guide	1.2
03/17/2009	Siddharth (sgopalan)	Added instructions for the audio patch	1.3
06/16/2010	Paul	Added executive instructions	1.4
01/27/2011	Taeho Kim	Instruction in Sydney	1.5
7/5/2012	Taeho Kim	Instruction for AV biofeedback _v 1.0.8.1	2.0
10/29/2012	Taeho Kim	Breath-hold guidance included	2.1
17/05/2013	Sean Pollock	Mentions of STARR changed to SUAVE	2.1
21/06/2013	Sean Pollock	Resolution info for goggles added.	2.1
21/10/2013	Sean Pollock	Modified for AV v2.0. Additional sections added for Display Options and DIBH.	3.0
02/04/2014	Sean Pollock	Modified for SUAVE v2.1.0. Display options amended & Offsets description added. 'Respiratory Analysis & Decision Form' section added.	3.1
24/07/2014	Sean Pollock	Updated DIBH section for SUAVE v2.1.0.0	3.2

13/01/2015	Sean Pollock	Updated document for Breathe Well v2.3:
		- Footer added to track software and document versions
		- Updated interface and workflow details
		- Removed:
		  o Section on customizing interface (colours, etc)
		  o BH & DIBH (re-insert once functionality added back in)
			4.0

04/02/2015	Sean Pollock	Updated to include stopwatch function	4.1
30/06/2015	Sean Pollock	Updated for version 2.3.2. which included the option to tag saved .rec files with session name	4.2
02/12/2015	Sean Pollock	Updated for version 2.5. New options, additional motion sensor options. V2.5 sidebar updated in Figures.	5.0

Sydney RealSense Software and Hardware User Guide

This User Guide is for Breathe Well software version 2.5

Contents

1. Hardware setup

1.1. Hardware components

The provided hardware components for audiovisual (AV) biofeedback are as follows:

1) 2 × aluminium rods
2) 2 × rod connectors
3) 1 × table clamp
4) 1 × Intel RealSense
5) 1 × Patient display
6) 1 × Intel NUC computer
7) Cabling

The cabling should already be correctly connected to its relevant components. The NUC computer should already be fixed to one of the rods.

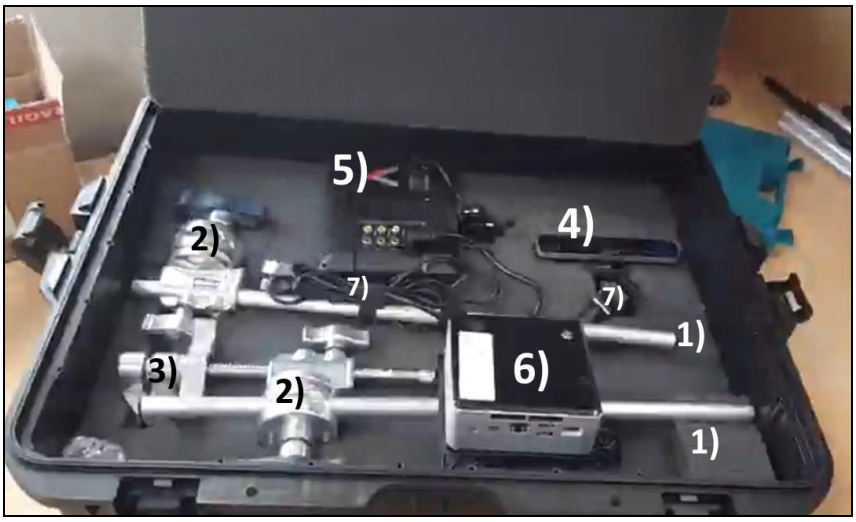


Figure 1. *Hardware components in delivery case.*

The assembled hardware setup for the Intel Realsense AV biofeedback setup is shown below in Figure 2.

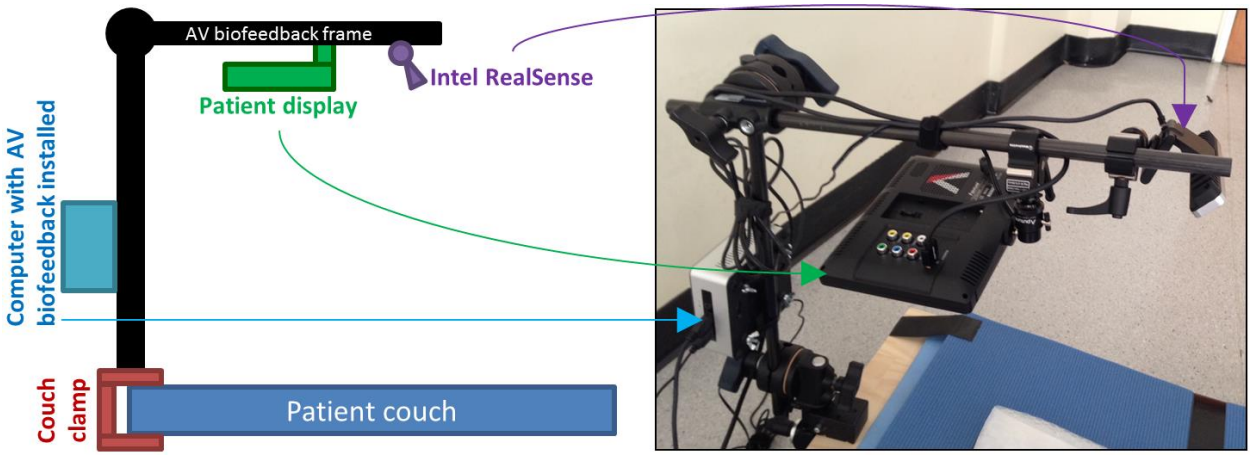


Figure 2. *AV Biofeedback setup schematic (left) and hardware components (right). N.B. rods shown in Figure 2 are made of a different material to those shown in Figure 1.*

Required components for AV biofeedback NOT provided with the delivered package are as follows:

1) Monitor display with VGA input
2) Keyboard with USB connector
3) Mouse with USB connector
4) Display Port to VGA cable
5) VGA extension cable
6) 2 × USB extension cables (1 for mouse, 1 for keyboard)

A schematic of all the connected components is shown below in Figure 3.

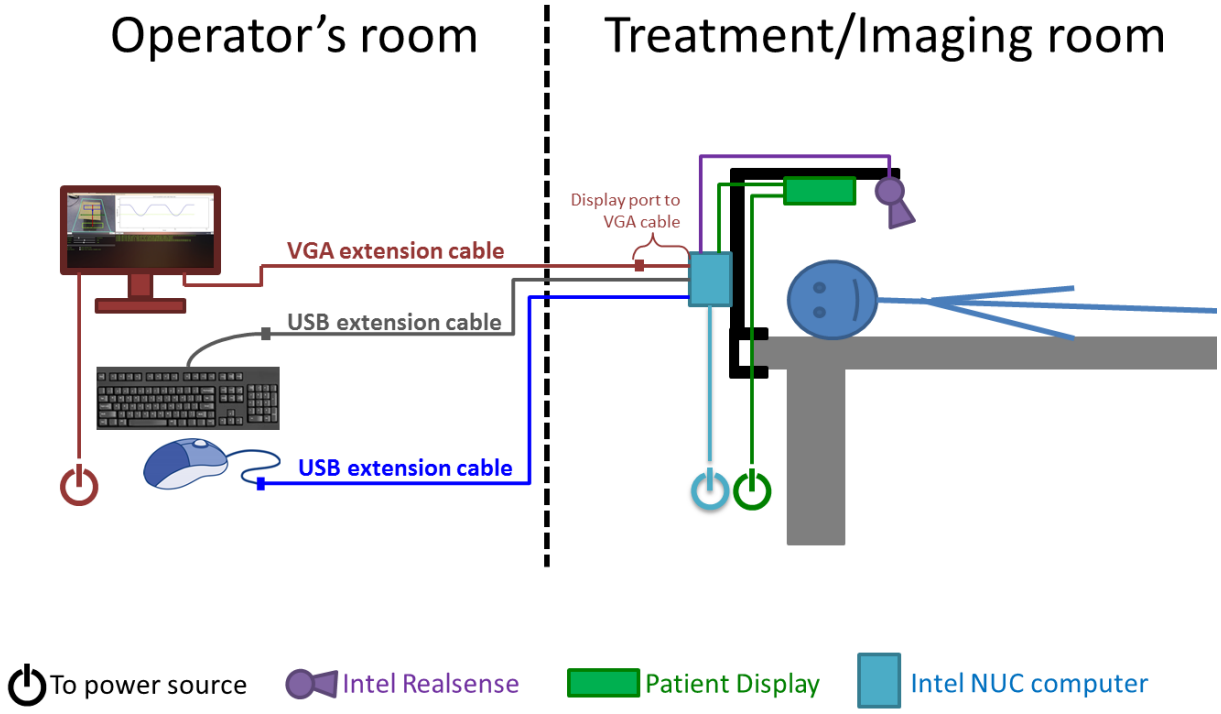


Figure 3. *Schematic of full AV biofeedback system setup from CT/Treatment room to the operator's room*

Where to connect the cabling to the NUC computer is shown below in Figure 4.

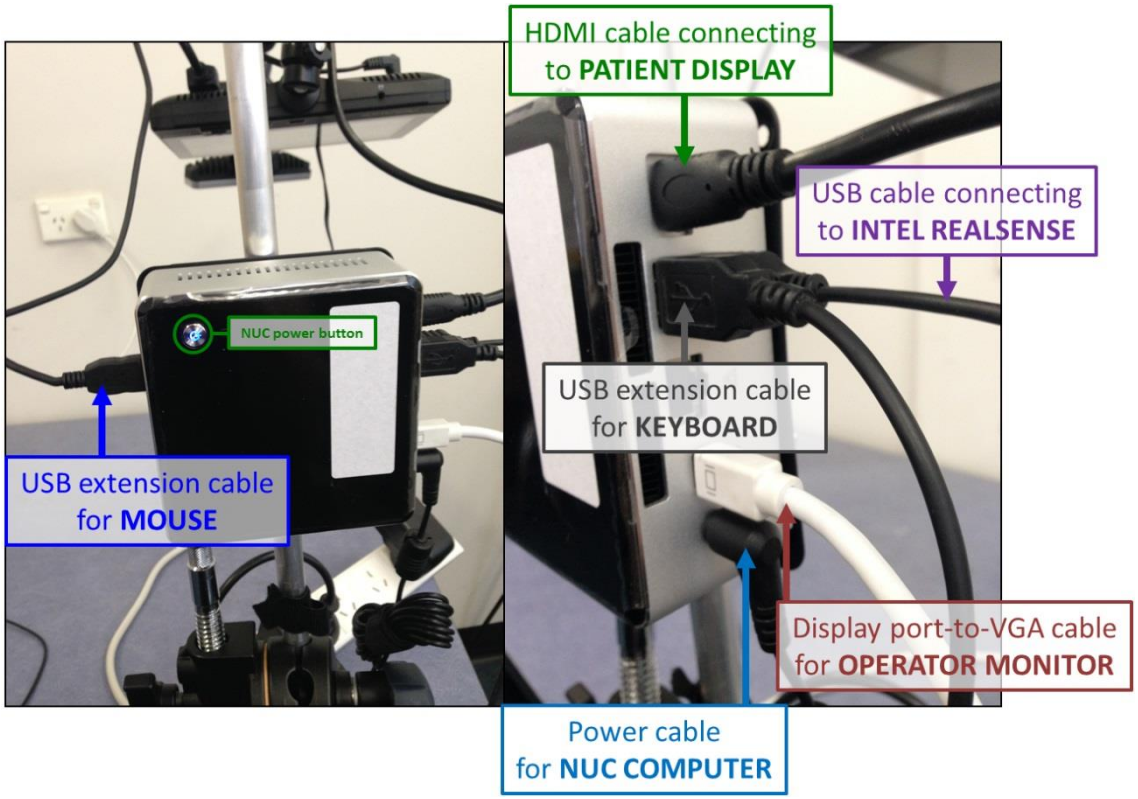
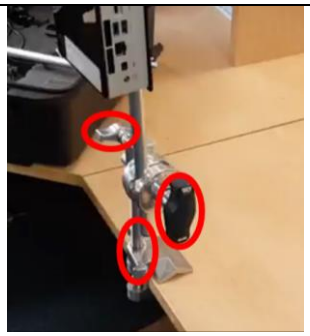


Figure 4. *Cables plugged into the NUC computer and their purpose*

1.2. Component assembly

1. Remove table clamp and rod with NUC computer attached (components 1, 2, 3, 6 from Figure 2) 2. Attached to a table and adjust handles (highlighted in figure to the right) such that the stand is fixed upright.	
3. Attach the Intel RealSense to the remaining rod, on the opposite end to the rod connector 4. Attached the Patient display such that the screen is approximately mid-way down this same rod	 
5. Attach the rod with RealSense and Patient display to the upright rod such that the RealSense and display are facing downwards	
6. Ensure any lose caballing is connected to the NUC computer in accordance with Figure 4. 7. Connect a display and keyboard to the NUC computer in accordance with Figure 3 and Figure 4	

2. RealSense software

Open “Breathing Coach” software from the Desktop: 

On initial Breathing Coach screen click “Patient” and select either “New” or “Open”.

Figure 5. *New or existing (Open) Patient options*

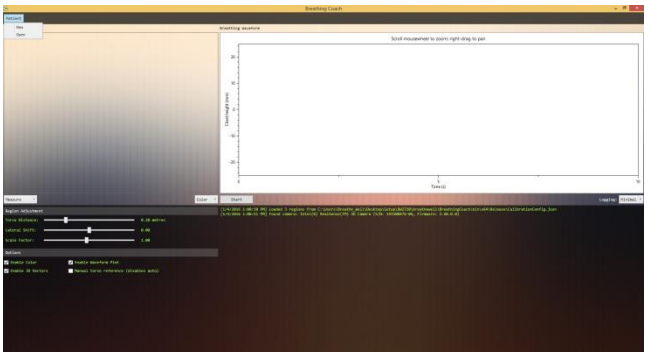


Figure 6. *Breathing Coach Realsense software initial display*

2.1. New or Existing Patient

If this is the patient’s first use of AV biofeedback, then select “New” under the Patient menu shown in Figure 5 and enter the patient’s name or Study ID:

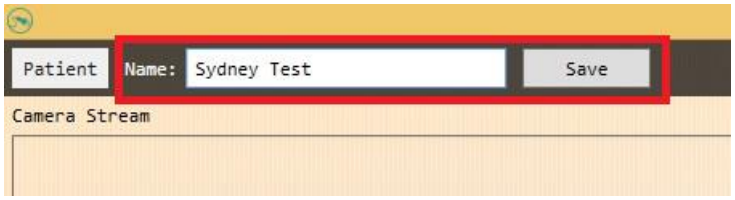


Figure 7. *Enter name/Study ID of new patient*

If this is NOT the patient’s first use of AV biofeedback, then select “Open” under the Patient menu shown in Figure 5 and select the patient’s name or Study ID. This will load this patient’s “Breathing Coach” options (these options will be explained in the next section).

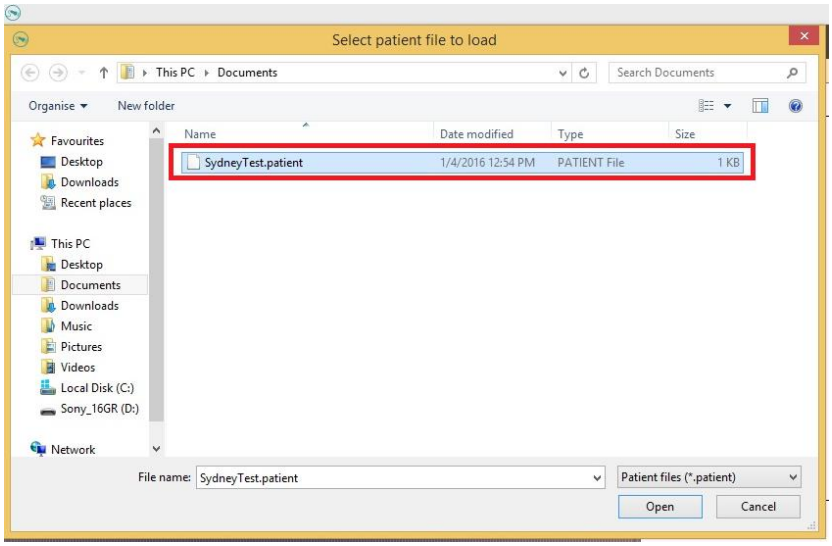


Figure 8. *Select name/Study ID of existing patient*

2.2. Tracking Patient Respiratory Motion

The “Breathing Coach” software has been optimized for patient use and may not operate optimally with a motion phantom. The operational distance of the Intel RealSense depth sensor is 20cm to 120 cm.

The Breathing Coach software does not require markers. Clicking “Start” will commence the tracking of the patient’s respiratory motion. Figure 9 shows the Breathing Coach software under default options after clicking “Start”. The respiratory motion of the region being monitored is what is used as the input for the audiovisual biofeedback software.

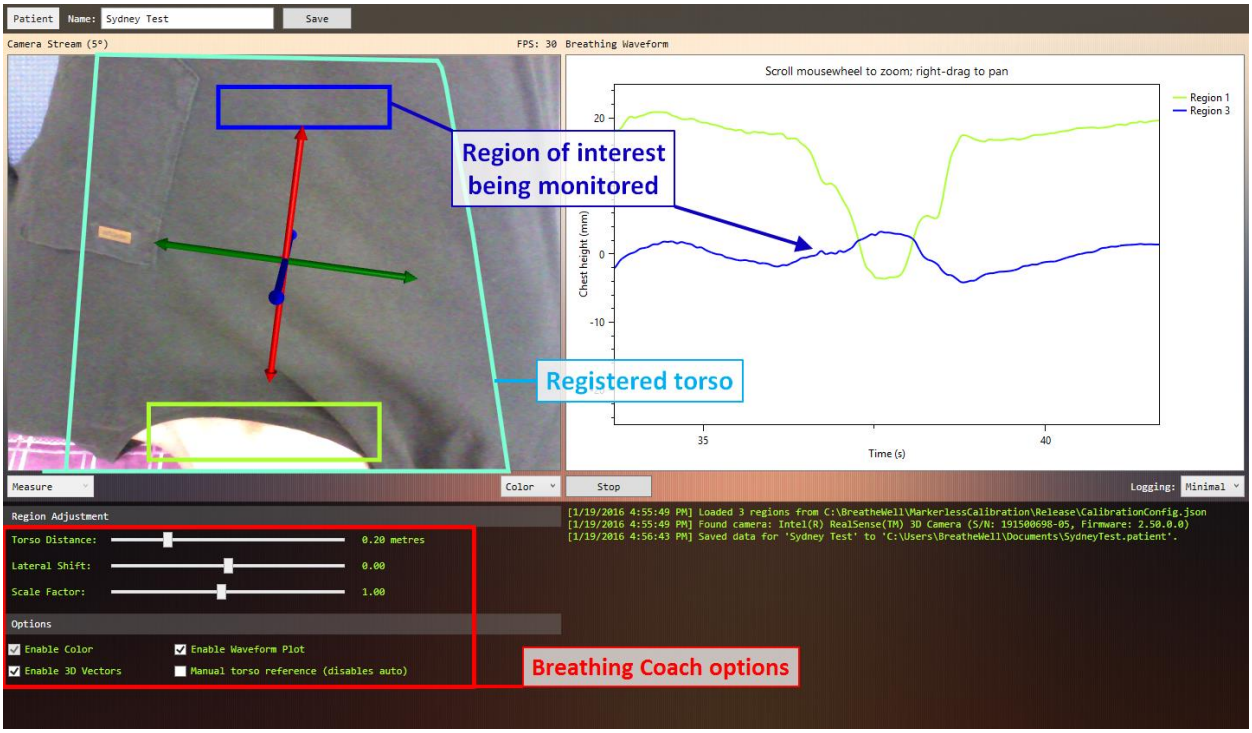
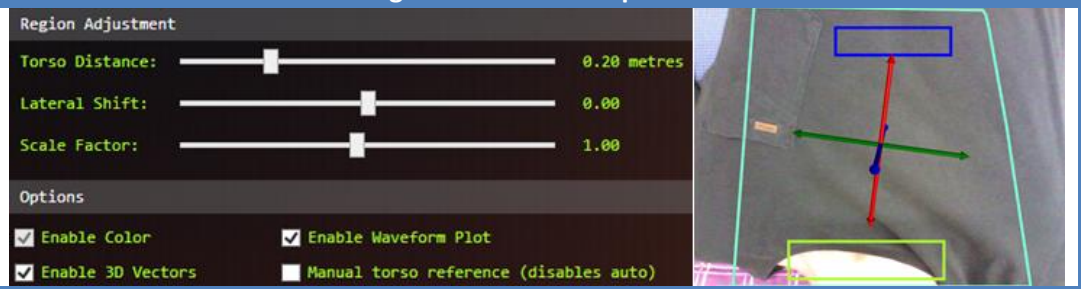


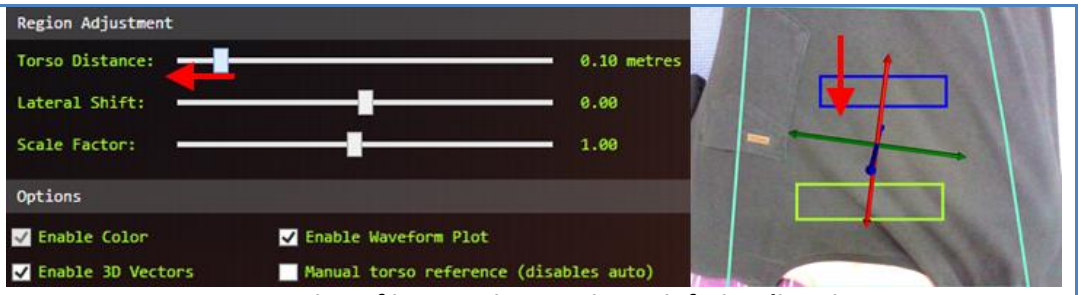
Figure 9. *Left: Optical image with overlaid region of interest, registered torso, and AP, LR, SI vectors. Right: Respiratory signal of the region of interest. Bottom: Breathing Coach options.*

Table 1 demonstrates the Breathing Coach options in detail.

Table 1. Breathing Coach software options

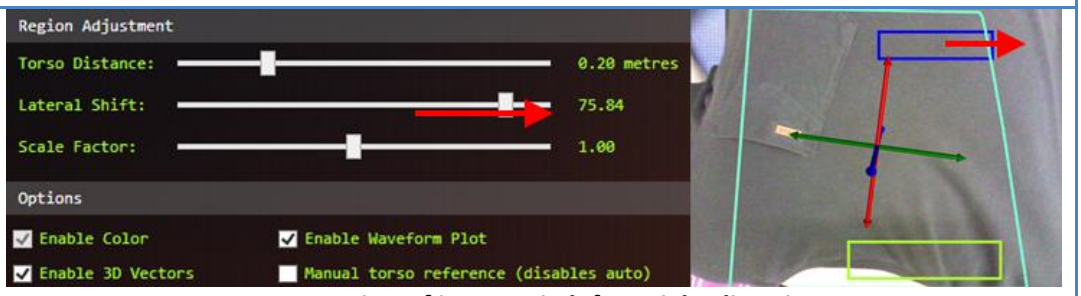
Default options	

Adjust 'Torso Distance'



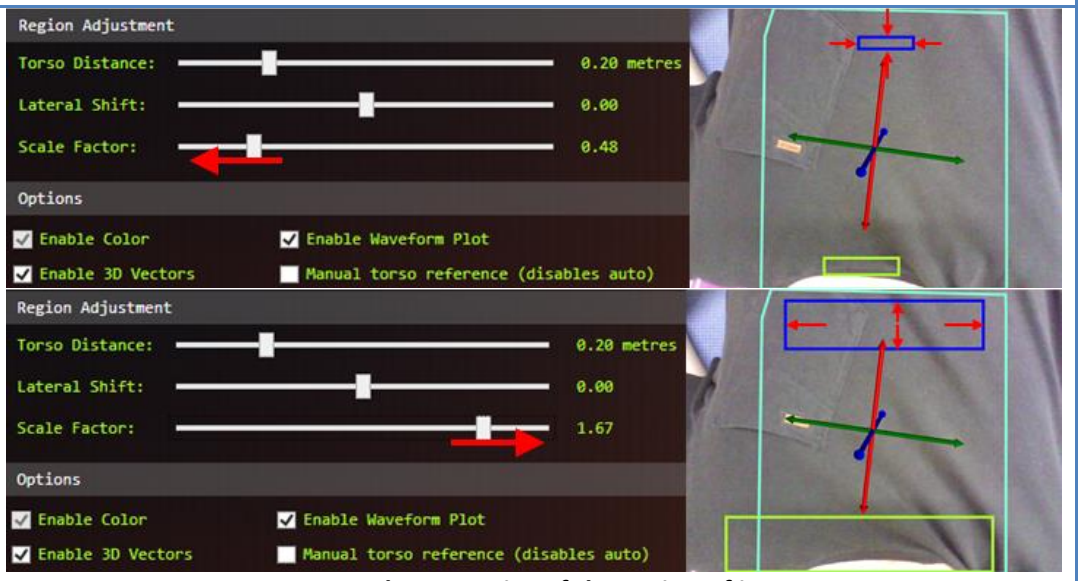
Move region of interest in superior or inferior direction

Adjust 'Lateral Shift'



Move region of interest in left or right direction

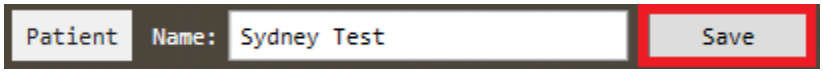
Adjust 'Scale Factor'



Increase or decrease size of the region of interest

It shouldn't be necessary to adjust the Breathing Coach options for most patients, however, for patients with sufficiently large or small torsos, it may be necessary to adjust some options.

Clicking "Save" will save the Breathing Coach options (NOT the respiratory signal, that is done in the audiovisual biofeedback software). This is to ensure consistent positioning of the region of interest interfractionally.



Having the Breathing Coach software and audiovisual biofeedback Breathe Well software running simultaneously can slow the sampling-rate of the Breathing Coach software. To maximize the sampling-rate whilst audiovisual biofeedback is also running, switch from “color” to “depth mode” and disable the “Enable color”, “Enable Waveform Plot”, and “Enable 3D Vectors” options. These options are shown in Figure 10.

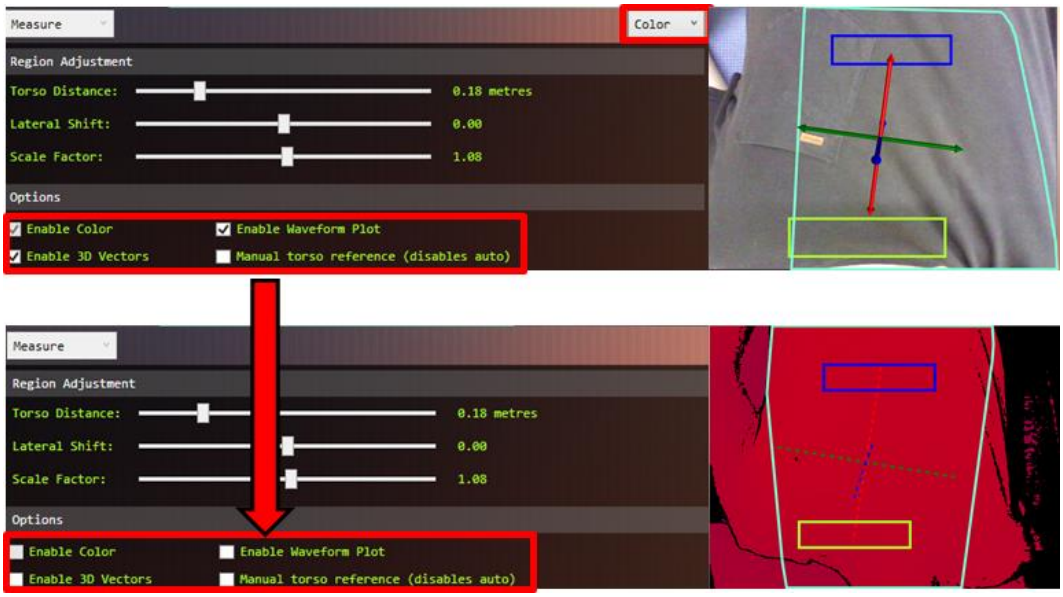


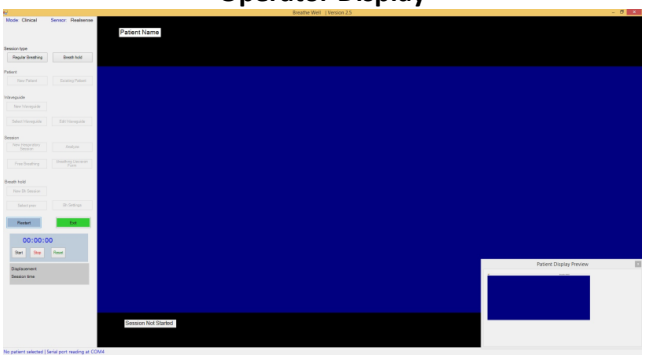
Figure 10. *Disabling options to maximize sampling-rate of the Breathing Coach software.*

With these options disabled, the respiratory signal of the region of interest will no longer refresh, appearing frozen, rest assured, as long as “Start” has been clicked it is tracking the respiratory signal.

With the motion signal tracking in the Breathing Coach software, open the AV biofeedback software: Breathe Well 

This will open up the AV biofeedback software on both the operator’s desktop and on the patient display:

Operator Display



Patient Display (intentionally blank)

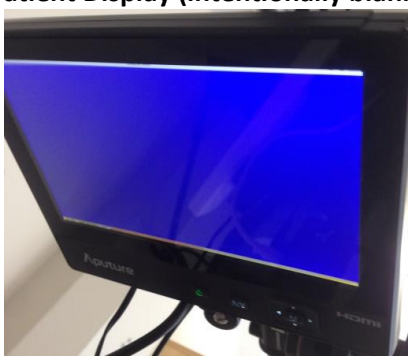


Figure 11. *Screenshot of the initial audiovisual biofeedback display and the initial patient display (intentionally blank to begin with)*

Please refer to document "AVFeedbackUserGuide_v5 Breathe Well" for further instructions on how to operate the AV biofeedback Breathe Well software.

2.3. Stop Session

AFTER saving the breathing session in the Breathe Well software, stop the session in the Breathing Coach software. If the Breathing Coach software is stopped before Breathe Well an error will occur in the Breathe Well software.

2.4. Adjusting the Signal Axis

Should the magnitude of respiratory signal exceed the limits of the y-axis in the Breathing Coach software, it can be adjusted using the scroll-wheel of the mouse. Having the signal going off axis will not compromise the signal input to Breathe Well software, but it may be desirable to see it nonetheless.

Figure 12. *Adjusting the displacement y-axis using the mouse scroll wheel*

Appendix A: Revision History

Date	Name	Reason for Changes	Version
04/01/2016	Sean Pollock	Version 1 completed	1.0
15/01/2016	Sean Pollock	Additional details for 'Breaching Coach' software added	

Appendix VI

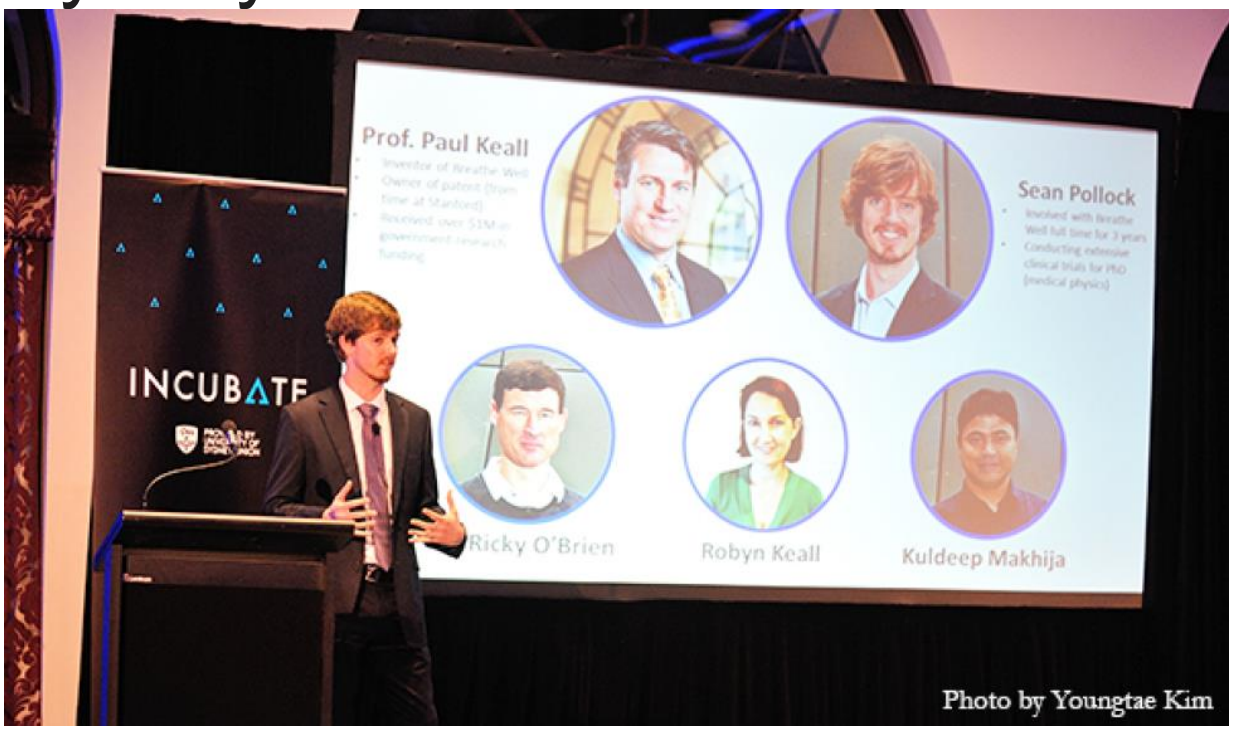
Media reports on the audiovisual biofeedback commercialisation process

Sources of media articles:

- “SYDNEY GENESIS: BREATHE WELL”
    - http://www.insideenterprise.org/sydney-genesis-breathe-well/
- “THIS STARTUP JUST LANDED $400,000 IN SEED FUNDING TO HELP CANCER TREATMENTS”
    - http://www.businessinsider.com.au/this-medtech-startup-just-landed-400000-in-seed-funding-to-help-cancer-treatments-2015-8
- “THE NEXT GENERATION OF MEDICAL DEVICE INNOVATORS”
    - http://atp-innovations.com.au/2015/11/next-generation-of-medical-device-innovators/

Inside ENTERPRISE

Sydney Genesis: Breathe Well



POSTED BY: MEGAN ENGARD FEBRUARY 18, 2015

Sydney Genesis is the longest running entrepreneurship program at the University of Sydney. The program is founded on the idea that when innovative new businesses, technology startups, and social entrepreneurs work side by side, a truly unique exchange of knowledge and inspiration flourishes. Each year Genesis opens its doors to students and alumni from any background who are passionate about their ideas in business, technology or social entrepreneurship. Over the course of the program participants are encouraged to bring their ideas to life with the assistance of workshops, mentoring, networking, funding and prizes.

Sean Pollock was a participant of the Sydney Genesis program during the first semester of 2014 and was one of the 8-10 finalist teams to pitch their ideas before a panel of industry experts at the Final Pitch Event in May. He is a current University of Sydney student who completed his Masters in Medical Physics in June, 2012 and is now working on his PhD in Medicine. Sean and his PhD supervisor Prof. Paul Keall have created a start-up company around a medical device at the centre of their research called Breathe Well, which provides breathing guidance for cancer patients for better quality imaging and radiotherapy.

How did you come up with your idea?

The technology behind Breathe Well was actually developed by my PhD supervisor, Paul Keall, while he was working in the United States in 2003. I first became involved in the project while working on my masters here at USYD when I received an email inviting students to volunteer for an imaging study that was investigating the Breathe Well device. That was my first contact with the project and eventually led me to join the project as part of my Masters' research before continuing on with a PhD. The business is now run by Paul Keall as the company director, myself as co-founder, two software developers and a company secretary.

What prompted you to get involved with Sydney Genesis?

Back when we started, my advisor and I were both coming from the research side of things. We had a research device and we had spoken to a few colleagues about commercialising it, but we had no real business model. We first reached out to ATP Innovations about possibly working on the business plan and they directed us to Sydney Genesis as a starting point. Genesis was great for us because we hadn't really thought about things from the perspective of customers. We had a research point of view, which was simply "We've researched it, we have a great product and you should want it, too." Going through the Genesis program really helped us understand the other point of view and how to create a business around your buyer's needs.

What is your business model?

We have created two possible revenue streams with Breathe Well. The first comes from a larger prototype device we have developed, which would be sold to hospitals. We have also developed a smaller, compact version of the device that would go to patients to practice on before using the larger device with their doctors. A prototype of the smaller tablet sized device is what we used during our Genesis Final Pitch to the panel of judges. After doing quite a bit of research into the competitive landscape we have set a price of $30,000 for the direct purchase of the device as well as an additional 20% per year service charge which covers systems upgrades, maintenance, breakages, etc. Existing devices on the market monitor patient breathing but don't provide feedback to the patient, and cost between $40,000 and $50,000. Our first market would most likely be Australia, though we have looked at the United States as well.

What are some of the biggest challenges you've faced?

For us, the biggest challenges were around learning the important business skills that were very different to our research mentality. The Genesis workshops were great for this because they are run by people who are leaders in their field. To be able to pick their brains during the workshop sessions and get their feedback on our ideas was incredible. Another challenge for us was to create a more streamlined version for the

product we had going in. We wanted to be able to offer this to clinicians, and luckily we started with a bit of wiggle room so we were able to make the adjustments we needed.

Where to now?

After finishing the Genesis program we applied to work with INCUBATE and we are now in their winter program. INCUBATE is a great follow up from Genesis; it is more intensive. While Genesis was more of a learning experience, INCUBATE provides more of a push to get things done towards regular set milestones. We formed a private company at the start of INCUBATE called Respiratory Innovations and are looking at recruiting the first patient in one of our largest clinical trials in the next few weeks, so things are very exciting at the moment. We are aiming to have our first sale in the next twelve months. That time frame allows us time for regulatory approval, clinical trials, etc. After Genesis, I am much more aware of the many opportunities on the business side of things so there are a lot of possibilities for what I can do next. I've been involved with Breathe Well for almost three years now, so I'd love to see it taken to the next level.

BUSINESS INSIDER AUSTRALIA

This medtech startup just landed $400,000 in seed funding to help cancer treatments

ALEX HEBER AUG 14 2015, 2:16 PM

Medtech startup Breathe Well just landed a $400,000 investment from Sydney Seed Fund to help develop improved cancer radiotherapy treatments.

Invented by Paul Keall, a professor in the School of Medicine at the University of Sydney, Breathe Well assists cancer patients in breathing predictably during a course of radiotherapy.

Keall came up with the idea while working in a teaching hospital at Virginia Commonwealth University, USA, while focusing his research and clinical activities on breathing motion during cancer imaging and radiation.

One of the key technical challenges during treatment was breathing irregularity.

“We could either develop complex imaging and treatment solutions to accommodate irregular breathing, or we could simply develop a system to help patients breathe more regularly,” he said.

“Breathing guidance improves efficiency, image quality and targeting accuracy. What this means is that with breathing training more patients can be treated, with higher cure rates and a better quality of life.”

Keall was involved in a study at Stanford University reviewing images from 50 lung cancer patients. It found significant errors for at least one image series in 90% (45/50) of the patients.

“Reducing these errors has benefits to the patient’s health, but also for the economy as the costly burden of managing treatment side effects is reduced,” he said.

By providing visual feedback of their breathing patterns, Breathe Well helps patients overcome the damaging consequences of irregular breathing.

“The problem of irregular and unstable breathing motion is widespread across the radiology and radiation oncology, affecting some of the most common forms of cancer such as lung, breast, and liver cancer. Errors caused by respiratory-related motion have been reported to be present in up to 90% of medical images used to plan the patient’s radiation treatment,” PhD medical candidate Sean Pollock who is also on the team, told Business Insider.

The startup secured a $588,000 grant from the National Health and Medical Research Council earlier this year, allowing it to conduct a series of clinical

trials around Australia. It has also applied for several additional grants including one from the NSW Health's Medical Device Fund.

Keall has also recruited software engineers Kuldeep Makhija and Dr Ricky O'Brien, and commercialisation expert Daniel Zafir, who recently joined as Managing Director.

"Apart from ground-breaking Breathe Well technology, we were impressed by its remarkable team led by Professor Keall," Sydney Seed Fund partner Benjamin Chong said.

Pollock says the simplicity of the design is why he joined the startup.

"Rather than spend millions on a better treatment machine, you can improve the accuracy of existing facilities at a fraction of the cost by providing breathing guidance to the patient," he said.

THE NEXT GENERATION OF MEDICAL DEVICE INNOVATORS

Nov 27, 2015

Health Minister Jillian Skinner tonight congratulated 12 outstanding medical researchers as they graduated from the 2015 Medical Device Commercialisation Training Program.

Presenting certificates at a ceremony at ATP Innovations, Eveleigh, Mrs Skinner said the graduates represent the next generation of medical innovators.
"These entrepreneurial graduates come from medical, biomedical engineering, mechatronics and biological science research backgrounds," Mrs Skinner said.
"Their research includes a templating system to develop patient-customised implants, a new method of heart valve repair and a home diagnostics kit for medical testing."

The Medical Device Commercialisation Training Program (MDCTP) was set up following a review of the first round of the NSW Government's Medical Devices Fund. It aims to address a gap between the skill base in the development of medical device research and the skills required to commercialise emerging innovative technologies.

As part of the 2015 program, ATP Innovations provided a three-month intensive training course aimed at early-to-mid-career, post-doctoral and other researchers. Mrs Skinner awarded four members of the graduating class with scholarships to further develop their research:
· **Professor Stephanie Watson, Kleer-i – $50,000** in seed funding for the Kleer-i patch, a sutureless wound sealing device for cataract surgery;
· **Dr David Yeo, Royal Prince Alfred Hospital – $25,000** in seed funding for Pivot Sphincterotome, a procedure for the management of bile duct pathology;
· **Dr Dharmica Mistry, BCAL Diagnostics Pty Ltd – $10,000** international engagement scholarship for higher accuracy breast imaging and screening tests;

· **Dr Robert Gorkin, University of Wollongong – $10,000** international engagement scholarship for new condoms utilising an advanced hydrogel material with anti-STI agents.

“It takes a breadth of skills to get an innovative medical research concept off the ground and our graduating researchers are now equipped with the skills required to bring their fantastic ideas into the marketplace,” Mrs Skinner said.

The first group of MDCTP trainees graduated in late 2014.
For more information visit: http://www.health.nsw.gov.au/ohmr/pages/default.aspx
Or visit the Medical Device Commercialisation Training Program page at ATP Innovations and apply: http://atp-innovations.com.au/mdctp/

Medical Device Commercialisation Training Program 2015: Graduates
Aiden O’Loughlin
University of Western Sydney
Stabilyzer: One in three people in Australia die of cardiovascular disease. The underlying process causing the majority of these deaths is atherosclerosis. Atherosclerosis is a disease where fatty material is deposited in sections of the wall of the artery. Deaths occur when local atherosclerotic lesions rupture, stimulating clot formation, leading to occlusion of the artery. These lesions are termed ‘vulnerable plaques’. Both heart attacks and strokes can be caused by vulnerable plaques rupturing. Recent research has shown that vulnerable plaques can be identified prior to their rupture. The Stabilyzer device provides treatment that will prevent future heart attacks and strokes with the development of a locally applied treatment to stabilise these plaques.

Annabelle Chan
University of Sydney
Rapid Templating System: The rise in rapid prototyping technologies has presented a unique opportunity for the creation of custom made implants. However, the logistical shift from generic high volume production systems to individually customised implants prevents its widespread usage. The Rapid Templating System aims to form patient specific implants quickly and effectively. The system involves the production of a 3D-printed guided mould, based on patient scans, to shape terminally sterilised generic materials into patient-customised implants. The generation of custom implants within packaged materials allow implants to be immediately ready for use,

avoiding treatment delays due to sterilisation post production. This approach has the capacity to significantly reduce inventory costs for medical device companies, as abundant implant-size ranges are no longer required to accommodate all patient cases. Further developments in regenerative medicine may allow further customisation material properties, allowing the implant to be patient specific anatomically as well as a biomechanically.

David Yeo
Royal Prince Alfred Hospital
Pivot Sphincterotome: Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopic procedure that allows access into the biliary system and has revolutionised the management of bile duct pathology. However, it is a notoriously difficult procedure to learn and even in experienced hands, this procedure is associated with complications including pancreatitis, bleeding, perforation and in rare cases, death. Cannulation of the bile duct remains the most challenging step of the procedure even with current sphincterotome technology. The Pivot Sphincterotome has been developed to facilitate easier, faster and ultimately safer biliary access. The ERCP sphincterotome US market alone is worth approximately $USD150 million and with an increasingly elderly population requiring less invasive procedures, it is expected to increase. Developed by an ERCP practitioner, the Pivot Sphincterotome aims to accommodate the shortcomings of current technology making the ERCP experience more user-friendly, efficient and safe.

Dharmica Mistry
BCAL Diagnostics Pty Ltd (BCAL Dx)
BCAL Diagnostics: To develop and commercialise a novel universal screening test for the detection of breast cancer that is highly accurate, safe, cost effective, and available to all women regardless of age, race and geographic location.
Breast cancer is the most common cancer amongst women, therefore, the effectiveness of the screening and diagnosis technology used is a high priority. The current model relies on a woman being physically present at a clinic for breast imaging which is not always convenient. While the present technologies are currently state of the art, there is a high cost involved. There are also well known performance limitations that result in only a small subset of women who are actually eligible for screening.
BCAL Diagnostics aims to shift the paradigm in breast cancer screening and diagnosis by introducing a blood test for detection of the disease. The implication of such a

technology could revolutionise the way breast cancer is managed by allowing a blood sample to be taken remote from the site of analysis. This technology will allow access to more women, anywhere in the world, who could provide a blood sample, at a time and place convenient to them. Such a test would fit into a woman's routine health regime and be incorporated into their personal lifestyle. In addition, with such high levels of accuracy, this technology would provide greater peace of mind between annual checks. The BCAL Diagnostics technology could utilise a single blood test on multiple levels for disease prevention, diagnostic mass screening and post-intervention.

James Otton
Liverpool Hospital
SeCure Beating Heart Repair: Mitral regurgitation is a condition caused by a leaking heart valve and affects more than four million individuals in the USA. The standard method of fixing valves is with open heart surgery, a complex operation performed on cardiopulmonary bypass. The operation is expensive, and recovery time from the operation is measured in weeks or months. The SeCure Beating mitral heart repair device enables heart valve repair while the heart is still beating, with no need for bypass or long anaesthesia time or surgical scars. Patients can recover in hours or days and the cost of surgery can be dramatically reduced. The heart repair can be repeated if necessary and conventional surgery can also be performed at a later date. With the new technology many patients who have been deemed unfit for surgery could be given lifesaving treatment.

Robert Gorkin
University of Wollongong
Geldom: Backed by experts at the University of Wollongong and Swinburne University of Technology, Geldom is helping make condoms more wearable by replacing latex with better feeling materials called tough hydrogels. These tough hydrogels are superior to latex and can improve the experience by offering more tissue like sensation. They also have other revolutionary benefits – no bad odours or tastes, no latex allergies, inherent self-lubrication, and can even be embedded with anti-sexually transmissible infections agents or stimulants. These new options have the potential to dramatically increase condom use. The impact – not only redefining what safe sex should feel like – but the added social benefits of improved family planning and disease prevention. This work is geared towards disrupting the $6 billion condom industry desperate for innovation. This patent pending work has been supported by

the Bill & Melinda Gates Foundation and has featured on ABC's Catalyst.

Josef Goding

University of New South Wales

CardioFlex: is the next generation of cardiac pacemaker leads. Conventional pacemaker leads are comprised of a long, coiled metal wire running from the neurostimulator to the electrode implanted in the heart. These conventional leads are prone to infection, dislodgement and mechanical failure. They are also incompatible with MRI because they act as antenna and generate unsafe amounts of heat in the body under MRI. CardioFlex leads do not use metal wires but are instead fabricated from conductive elastomers, a novel material being developed at UNSW. Conductive elastomers allow the CardioFlex lead to be soft, flexible and totally MRI compatible. This means recipients are less likely to require a surgical lead extraction and they do not need to worry about their pacemaker interfering with ongoing or future medical treatments. Other applications of conductive elastomers being investigated include flexible electrode arrays and nerve cuffs for neural interfacing.

Sandra Ast

AusSI Systems

AusSI Systems: This product allows for simple medical testing remotely from home. The home diagnostics kit consists of a small device attachable to a smartphone and together with an app, it allows for the analysis of the same urine dipsticks that are commonly used in the GP's office. The medical results can then be shared with the GP online instead of going to the doctor, when unwell or busy. This will assist in a comprehensive assessment of the patient's health problem currently not possible via online consultations. This smartphone diagnostics device also features recording of the test results over time opening up numerous additional applications, ranging from personalised healthcare to new testing methods for diseases.As the healthcare sector is moving towards a digital platform, these internet connected devices will be essential in the generation of digital medical records as well as the successful implementation of online medical services.

Sean Pollock

Respiratory Innovations

Breathe Well: is an interactive medical device that allows breast cancer patients to help improve their own cancer treatment, simply by breathing. In breast cancer radiation therapy, nearby healthy tissues like the heart and lungs are at risk of

receiving unnecessary, and potentially fatal, radiation damage. Breathe Well shows patients how to hold their breath to put as much distance possible between the heart and radiation beam to achieve the most accurate breast radiation treatment possible.

Stephanie Watson
Save Sight Institute
Kleer-i: One in twenty cataract surgery wounds leak, causing infection and blindness to occur. Sutures cause scarring, are time- consuming to apply, require great skill, and distort vision. In addition to this, patients have poor compliance with postoperative eye drops. Cataract surgery is the most common operation and has the longest waiting list in NSW. Eye surgery costs are rising as the population ages. Kleer-i is a next-generation "patch", bonded over an eye wound by a low-powered laser. It falls off once the wound heals. Surgeons will use Kleer-i to rapidly seal eye wounds without sutures, while simultaneously delivering drugs. Kleer-i will save 25% to 40% of operating time and promote faster wound healing, reducing vision loss from scarring, distortion and infection.
Kleer-i is unique in combining drug delivery with suture-less wound closure. It avoids the toxic side-effects and high failure rates associated with existing therapies: sutures, histoacryl glue and fibrin sealant.

Stephen Bradford
CSIRO/Garvan Institute of Medical Research
MethylC&Me: Obesity is a growing global health problem with direct costs estimated at $21 billion annually (Australian Diabetes, Obesity and Lifestyle Study). Current therapeutic and policy intervention is not working. Evidence suggests that early directed intervention for individuals with a predisposition to obesity and related co-morbidities is more effective at maintaining long term positive health outcomes. This technology measures the levels of specific modifications to a person's DNA (DNA methylation marks) that are associated with current or future health status. The core IP is in panels of such DNA methylation biomarkers that could be used to identify an individual's risk and likely trajectory for obesity and Type 2 diabetes mellitus. This would help direct clinicians, such as endocrinologists and dietitians, in the clinical management of patients and identify at risk people early – reducing the health burden of chronic disease.

Yang Chen
Woolcock Institute

Scintilla Electrostatic Inhaler: Metered dose inhalers (MDI) are a commonly used device to deliver aerosolise medications for the treatment of pulmonary diseases. The emitted aerosols from MDI contain millions of fine particles that carry intrinsic charge that is imparted on them during the atomisation phase. These static charges can cause variations in particle aerosolisation and dosage. Moreover, the MDI requires manual actuation force to operate and its efficacy relies on patient's co-ordination between actuation and inhalation, which can be difficult for elderly patients with chronic obstructive pulmonary diseases (COPD). The Electrostatic Metered dose inhalers (EMDI) is a novel electrostatic metered dose inhaler, which utilises electronic force and electrostatic charges to generate inhalable aerosol. It will reduce the need of excipients in the drug formulation to help with the aerosolisation process, and also minimise the difficulties that can occur when using conventional MDIs. EMDI can provide more efficient treatment to people with respiratory diseases, especially for the 65 million patients who currently suffer from COPD around the world.

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Appendix VII

Videos recorded and produced over the course of this thesis

Dropbox link to videos:

https://www.dropbox.com/sh/8ac7ee2aumaehqq/AAC138HtW8jSA618KObiZ2Axa?dl=0

a) Patient information video
    - "AV biofeedback info video.mp4"
b) Medical Device Commercialisation Program 2015 Showcase presentation
    - "MDCTP_Sean Pollock.mp4"

YouTube link to videos:

c) Animated 3 Minute Thesis presentation: produced by 99 Scholars as a part of my runner-up prize
    - https://youtu.be/JmaSVupp2-w
d) Invited keynote Genesis final speech one year after first completing the Genesis program
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